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Myocardial Dysfunction and Heart Failure in Rheumatoid Arthritis

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Abstract

Rheumatoid arthritis (RA) patients have almost twice the risk of heart failure (HF) of patients without RA, even when adjusting for presence of ischemic heart disease. Moreover, RA patients remain at two-fold higher risk of mortality from HF compared to non-RA patients. These observations suggest that RA specific inflammatory pathways are significant contributors to this increased risk of HF. We summarize the epidemiology of HF in RA patients, the differences in myocardial structure or function between RA vs non-RA patients without clinical signs of HF, and data on the role of systemic and local inflammation in RA HF pathophysiology. We also discuss the impact of subduing inflammation thorough the use of RA disease modifying therapies (DMARDs) on HF and myocardial structure and function, emphasizing gaps in literature and areas needing further research.

Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory disease affecting approximately 0.5-1% of the population. RA patients have almost twice the risk of heart failure (HF) of patients without RA, even when adjusting for conventional cardiovascular (CV) risk factors and coronary artery disease (CAD)[1,2]. This observation suggests that RA specific immune/inflammatory pathways are significant contributors to this increased risk of HF. This review will: 1) summarize the epidemiology of clinical HF in RA; 2) in RA patients without clinical HF, delineate differences in myocardial structure and function compared to non-RA patients; 3) examine data in RA patients supporting the pathophysiologic roles of systemic and local inflammation in driving HF and subclinical myocardial dysfunction; 4) review available data on the effect of RA disease modifying therapies (DMARDs) on HF and subclinical myocardial structure and function in RA and 5) discuss future areas for additional research.

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Epidemiology of Heart Failure in Patients with RA

RA patients are at an almost 50% higher risk for incident CV disease (CVD) than non-RA patients (pooled Relative Risk (RR) of 1.48)[3]. In table 1, we summarize the incidence rates of HF specifically, revealing hazard ratios (HR) in RA vs non-RA of 1.21 to 1.87[2,4–6]. While several of the more recent epidemiologic studies[7–9] suggest declining overall CV event rates, and CV associated mortality rates, in RA patients diagnosed after 2000 vs those diagnosed prior to 2000, these studies did not include or clearly distinguish HF as an outcome. HF associated mortality is also increased two-fold, and time to onset of HF is shorter, in RA vs non-RA groups[1,5,10] (Table 1). However despite the higher incidence of HF, RA patients were less likely to report orthopnea and paroxysmal nocturnal dyspnea than non-RA controls [10]. These data raise the possibility that RA associated HF may be underdiagnosed and that aggressive screening for abnormalities in myocardial structure and function, while RA patients are still without HF symptoms, could present an opportunity for early intervention and prevention of HF.

The etiology of the increased risk of HF in RA has not been well delineated. While higher rates of CAD pose a large risk for HF in RA[4], the relative contribution of CAD to HF is attenuated in RA compared to non-RA patients (HR 3.25 [95% CI 2.35-4.51] vs HR 4.94 [95% CI 3.30-7.38], respectively)[1] . Likewise, the attributable risk of HF due to conventional CV risk factors was only 54% in RA, compared to 77% in non-RA patients ($p<0.01$)[1]. This suggests that CAD and CV risk factors cannot solely account for the increased risk of HF in RA. Of note, most cohort studies[1,2,4,6,11,12] in Table 1 do not distinguish ischemic vs. non-ischemic HF. However, Mantel et al[5] recently found similar hazard ratios in RA vs non-RA patients for incident ischemic and non-ischemic HF of 1.27 (95% CI 1.07-1.51) and 1.22 (95% CI 1.04-1.42), respectively. Taken together these data suggest that a significant proportion of RA patients develop HF independently of CAD.

HF comprises a heterogeneous group of disorders that may be primarily cardiac in nature or secondary to systemic disease. HF can be stratified by left ventricular (LV) ejection fraction (EF), as reduced (EF < 40%), midrange (EF 40-49%), or preserved (EF ≥ 50%)[13]. HF with reduced EF (HFrEF) is characterized by systolic dysfunction, often with chamber dilation and eccentric remodeling, and is most commonly associated with ischemia, hypertension and valvular disease. In contrast, HFpEF (previously ‘diastolic HF’) is characterized by normal EF and LV volumes, but concentric remodeling or LV hypertrophy[14]. HFpEF is commonly associated with systemic proinflammatory states such as obesity, aging and diabetes [14]. With regard to RA, Davis et al[10] reported that in patients with clinical HF, the mean EF in RA patients was higher than that of non-RA patients (50% vs 43%, respectively, $p=0.007$) and the RA group was *twice* as likely to have preserved EF (OR 1.90 [95% CI 0.98–3.67]). Schau et al[15] reported that of 38 RA patients with clinical HF, nearly all (n=36, 95%) had a diastolic phenotype with preserved EF. These observations suggest that RA may be added to the list of chronic inflammatory states that predispose to HFpEF.

Due to the retrospective nature of most of the HF studies in RA, limited data are available on the relationship of RA associated factors to the risk of developing HF, particularly HFpEF. However, in the Mantel[5] study, non-ischemic HF was associated more potently than ischemic HF with erythrocyte sedimentation rate (ESR) > 40 and with RA disease

activity score with 28 joints (DAS28) > 5.1 (HR 3.03 [95% CI 1.69-2.73] for ESR>40; HR 3.35 [95% CI 1.84-6.09] for DAS28>5.1). Moreover, rheumatoid factor (RF)-positive RA patients had a 40% higher risk of incident HF than RF-negative patients. Investigators at the Mayo Clinic[2,4,16] also observed an elevated risk of HF with RF positivity (HR 1.6 [95% CI 1.0-2.5]), as well as with elevated ESR (HR 2.1[95% CI 1.2-3.5]), and extraarticular disease (HR 3.1 [95% CI 1.9-5.1]). Taken together, these data suggest that rheumatoid inflammation represents an independent risk factor for incident HF, and perhaps more strongly for the HFpEF phenotype.

Traditional diagnostic and prognostic CVD biomarkers include N-terminal pro B-type natriuretic peptide (NT-proBNP), BNP and troponin. BNP, released with atrial contraction, has long been heralded as a biomarker for predicting systolic, decompensated HF risk and all-cause mortality[17]. And a gradient increase in cumulative incidence of CV death per every unit increase of troponin was noted in a large population of stable CAD patients in the general population[18]. However, diagnostic/prognostic biomarkers for HF in RA patients are understudied. An association between NT-pro BNP level and all-cause mortality in RA (HR 2.36 [95% CI 1.42-3.94]) was reported, but HF associated mortality was not separately identified[19]. The elevated mortality of HF in RA adds urgency to the identification of sensitive measures to detect early myocardial dysfunction in patients with RA.

Measures of Myocardial Structure and Function in RA Patients without Clinical HF

It is useful to examine whether echocardiographic parameters, known to predict the development of clinical HF, are overrepresented in RA patients *without* clinical HF compared to non-RA patients.

LV Structure—In the general population, values of LV mass above defined cut-offs have been linked to an increased risk of composite CV endpoints, including HF[20] . In RA patients *without* symptoms of HF, LV mass has been compared to non-RA controls in cross-sectional transthoracic echocardiographic (TTE) studies, summarized and analyzed in two meta-analyses (Table 2). In these meta-analyses comprising 25 and 16 individual studies[21,22], respectively, higher mean differences in LV mass index (LVMI) of +6.2 g/m^2 and +0.47 g/m^2, respectively, were reported in the RA compared to non-RA groups. In contrast, two more recent TTE studies reported lower average LVMI[23] in the RA group, or no significant difference in LVMI[24] between groups.

Other studies have utilized cardiac magnetic resonance (CMR) imaging to measure LV mass in RA. In three cross-sectional CMR studies of RA patients vs non-RA controls[25–27], all *without* clinical HF, RA patients had *lower* LVMI (differences of −14.7 g/m2, −4.558 g/m^2 and −14.7 g, respectively), while a fourth CMR study [6] showed no significant group difference (Table 2). CMR is considered the gold standard for assessing LV mass and volumes[28] because of its high spatial and temporal resolution that is not limited by body habitus or ventricular geometry and thus, the ventricles can be imaged in their entirety without having to make geometrical assumptions. Yang et al[29]showed that adequate visualization of LV wall segments could be obtained in 97% of patients using CMR vs only 38% with TTE[29]. Thus, observed differences in LVMI may be attributable to technology.

Other considerations include lack of statistical adjustment for potential confounders in the TTE meta-analyses, and differences among all studies in levels of severity or duration of RA. Indeed, positive associations of CRP and RA disease duration with LVMI, and current corticosteroid use with lower LVMI, have been reported[27].

Additional insight might be gained from investigating differential rates of change in LVMI in RA vs non-RA groups over time. However, in a prospective observational TTE study[30] in RA patients without clinical HF, while LVMI in both RA and non-RA groups declined significantly over 4-5 years, rates between groups were not statistically different. In the Plein[27] CMR study, early untreated RA patients had a lower mean LVM at baseline than non-RA controls, but after a year of treatment, mean LVM increased in the RA group from 78.2g to 81.4g ($p=0.01$). These CMR studies suggest that RA itself may be associated with a decline in LVM, perhaps similar to the sarcopenia seen in peripheral muscle in RA, and that treatment of RA may facilitate re-gain of some muscle mass. However, proof of this hypothesis will require longer followup with carefully performed sequential MRI or TTE, and adjustment for treatment effect and CV risk factors. Until then, cross-sectional studies reporting associations of lower or higher LV mass with RA therapies are difficult to interpret.

Other descriptions of LV geometry[31] such as concentric remodeling (normal LVMI and relative wall thickness (RWT)>0.42 cm), concentric hypertrophy (increased LVMI and RWT>0.42 cm), and eccentric hypertrophy (increased LVMI and RWT ≤0.42 cm), have been used to categorize phenotypes of LV remodeling. Descriptions of LV geometry in RA vs non-RA patients have been reported in three TTE studies. Rudominer et al[32] observed that of 16 RA patients without clinical HF but with LV hypertrophy, 15 had eccentric hypertrophy. In contrast, Myasoedova et al[23] reported that among individuals without HF, concentric remodeling was more prevalent in the RA compared to non-RA group (44% vs 19.2%; $p<0.001$). Cioffi et al[33] also reported a significantly higher prevalence of concentric geometry in RA vs non-RA (47% vs 10%; $p<0.001$) groups without HF. Thus, the evidence currently points to a concentric geometry phenotype in the RA patients without clinical HF which would be in keeping with the presumed non-ischemic nature of RA associated HFpEF.

LV Function

Systolic Function.: In RA vs non-RA individuals without clinical CVD, the conventional measure of systolic function, EF, does not differ significantly by either TTE [21,24,34,35]or CMR[36]. However, systolic strain, assessed by speckle tracking echocardiography or by tagging in CMR, is a more sensitive predictor of systolic dysfunction and of CV clinical endpoints including mortality[37] in general population studies. While EF reflects change in LV volume only, systolic strain is an assessment of myocardial deformation during systole coupled to LV volume. GLS is reported as a negative value, reflecting shortening of the LV axis during contraction; a more negative value reflects greater contraction with normal values in the −15.9% to −22.1% range[38]. Systolic strain has been examined in RA patients without clinical HF (Table 2). All three TTE studies[34,35,39]and one CMR study[36] reported lower GLS (i.e., less negative, worse function) in RA vs non-RA patients. In an RA cohort

without clinical CVD[35], low GLS predicted future CV hospitalizations for CHF, MI, limb ischemia, or atrial fibrillation (HR 4.50[95% CI 1.40-13.70]].

Diastolic Function.: LV diastolic dysfunction (DD) is a characteristic finding in HFpEF and is manifested by increased myocardial stiffness, impaired relaxation and impaired systolic reserve[40]. DD is assessed by Doppler echocardiography by measurement of transmitral blood flow velocities in early (E) and late (A) diastole, septal and/or lateral mitral valve annular velocities (e'), and tricuspid regurgitant jet velocity[41]. Twenty-five case-control studies of DD in RA patients vs non-RA controls, all without clinical HF, were analyzed in a meta-analysis [21] (Table 2). DD (≥ 2 abnormal diastolic parameters) was reported in 26-36% of the RA vs 15-21.7% of the non-RA group. In the prospective TTE study of Davis et al[30] comparing RA (n=160) vs. non-RA (n=1391) patients without HF, more rapid decreases in E/A, E/e,' and deceleration time [DT]), and a more rapid increase in left atrial volume index (LAVI), all reflecting decline in diastolic function, occurred in the RA group (in contrast to no difference in rate of change in LVMI). Whether these changes in diastolic function herald the onset of HFpEF in RA is as yet unknown.

Biomarkers of Myocardial Dysfunction.: There are few reports of CVD biomarkers in RA patients without clinical HF. BNP, as a screening tool for asymptomatic DD in RA patients, had low positive predictive value (25%), sensitivity of only 40%, and specificity of 89%[42]. BNP and troponin levels may both be confounded by systemic inflammation. In fact, although there are no reports in RA evaluating associations of troponin T or I levels with subclinical LV remodeling, RA patients were reported to have higher levels of high sensitivity troponin I (cTn-I) than non-RA, and DAS28-CRP was independently associated with cTN-I levels in RA patients[43]. The paucity of work and potentially limited utility of conventional CV biomarkers in detection of subclinical LV dysfunction in RA underscores the need to incorporate novel biomarker studies into prospective studies of the natural history of LV remodeling in RA patients.

Pathophysiologic Roles of Systemic and Local Inflammation in HF and Subclinical Myocardial Remodeling in RA

There is substantial evidence of an association of RA characteristics, such as RA duration, disease activity and seropositivity[44–46], and baseline biomarkers of inflammation (interleukin-6 [IL-6] and CRP), with both baseline and longitudinal changes in LV structure and function[30,44–47] (see Table 3). However, investigations of specific molecular mechanisms that drive these changes in RA are few. In this section, we consider the following: 1) what is the body of evidence suggesting that circulating inflammatory molecules critical to synovial inflammation and joint destruction also *cause* LV dysfunction in RA; 2) can local (myocardial) inflammation be demonstrated and does it contribute to LV dysfunction in RA; 3) does endothelial dysfunction occur locally in the RA myocardium, is it associated with systemic and/or local myocardial inflammation, and does it contribute to LV remodeling and dysfunction. We also represent these hypotheses in graphic form in Figure 1.

Systemic inflammation and LV structure/function in RA—Several inflammatory molecules that play a key role in RA synovitis and joint destruction, such as tumor necrosis factor (TNF), IL-1, IL-6, and matrix metalloproteases (MMPs), have also been implicated in the pathogenesis of HF in the general population. Inflammatory cytokines critical to HF pathophysiology can be broadly categorized into those implicated in negative LV inotropy (TNF, IL-1, IL-6, IL-18)[48] or in LV remodeling (TNF, TIMP-1, MMP-3, MMP-9, MCP-1, IL-8, IL-17)[49,50].

Given the limited number of studies in RA patients and in experimental RA models, we focus on TNF, IL-1 and MMPs. Higher levels of TNF have been reported in both blood and myocardia of patients with HF in the general population compared to those without HF.[51] Animal studies further support a direct role for TNF in HF pathophysiology. Infusion of TNF causes acute hemodynamic collapse and inflammatory infiltrates in the LV which are reversed with cessation of infusion[52]. In mice with cardiac-restricted overexpression of a human TNF transgene, depression of LV function, LV dilatation, marked myocardial inflammation, and ultimately myocardial fibrosis, HF and death were observed[50].

IL-1 levels are also elevated in patients with chronic HF[53]. IL-1 acutely depresses myocyte contractility, due in part to impairments in cytoplasmic calcium handling and β-adrenergic receptor signaling[53]. At the histologic level, IL-1 is implicated in cardiac myocyte hypertrophy via NF-kB, JAK/STAT and PI3K pathways and ultimately in myocardial fibrosis[53]. Although evidence is lacking in RA, it can be hypothesized that TNF and IL-1, circulating in high levels in RA patients, bathe the myocardium and engage cognate receptors on myocardial cells, inducing the types of deleterious effects outlined above.

Myocardial inflammation and LV structure/function in RA—Just as the RA synovium becomes infiltrated with inflammatory/immune cells including monocytes/macrophages, T cells and B cells, there has been interest in whether a similar process occurs in RA myocardia. In early autopsy studies[54], higher prevalences of inflammatory cell infiltrates and myofiber degeneration were reported in RA vs non-RA hearts. However, there is almost no modern literature on histopathology of RA hearts. Moreover, given the risks involved in endomyocardial biopsy and its potential diagnostic inaccuracy due to sampling error (as myocarditis tends to be patchy), the research field has turned to non-invasive cardiac imaging, including CMR and cardiac PET/CT scanning, as alternative methods to identifying myocardial inflammation and fibrosis.

Several studies in RA patients have utilized CMR with late gadolinium enhancement (LGE) to identify myocardial fibrosis/inflammation (Table 3). In RA patients without clinical CVD, Kobayashi et al[55,56] reported a prevalence of LGE of up to 38.9%. Moreover, LGE was associated with DAS28 in a multivariable model adjusted for CV risk factors. Ntusi et al[57]reported a significantly higher prevalence of LGE in RA vs non RA patients without HF (46% vs. 0%, respectively) on CMR, and confirmed an association of LGE with disease activity in the RA patients. Moreover, they demonstrated moderate correlation between DAS28-CRP and LV extracellular volume (ECV) estimation, a quantitative measure that is postulated to reflect the extent of myocardial fibrosis (R = 0.61, $p<0.001$). A limitation to the interpretation of LGE is that it can represent inflammation, edema, necrosis or fibrosis or

any combination thereof. Use of 18-fluorodeoxyglucose positron emission tomography with computed tomography (FDG PET-CT) has emerged as a potentially more specific method for detecting myocardial inflammation. That myocardial FDG uptake reflects inflammation is supported by studies demonstrating accumulation of ^{18}FDG in monocyte/macrophages in post-MI mice[58], and high association (R^2=0.92) between localization of CD68+ macrophages and ^{18}F-FDG signaling in autoimmune myocarditis rat models[59]. Cardiac FDG PET-CT scans require careful pre-scan preparation with a very low carbohydrate diet to downregulate glucose receptors on cardiomyocytes, thus hypothetically isolating inflammatory cells as the only residual glucose-receptor expressing cells. In the only *myocardial* PET/CT study in RA[60], nearly 40% (46/119) of patients without clinical CVD had visually detected myocardial FDG uptake. Using a quantitative software package and scans from healthy controls, a cut-off value for elevated FDG uptake was derived. Using this metric, 18% of RA patients had significantly elevated mean myocardial standardized uptake values (SUV), and myocardial SUV was correlated with RA disease activity ($p=0.005$) in multivariable analyses. The weight of evidence suggests that subclinical myocarditis and/or fibrosis may be present in a significant proportion of RA patients without clinically evident CVD.

Mechanisms by which inflammatory myocarditis is initiated and/or propagated in RA are unknown. Antibodies to proteins that have a post-translational modification called citrullination, termed ACPA (anti-citrullinated protein antibody) are highly specific for RA [61]. Data from autopsied RA hearts indicate higher levels of myocardial citrullination in RA compared to control hearts[62]. It is possible that antibodies are generated in RA not just to synovial, but also to cardiac-specific, citrullinated antigens, triggering an autoimmune response within the heart. In RA patients without clinical CVD, levels of seroreactivity against citrullinated fibrinogen and citrullinated vimentin correlated with higher LVMI ($p<0.05$)[63]. These putative immune complexes may lead to the local myocardial inflammation and remodeling, but these conjectures will require further investigation and confirmation.

Myocardial endothelial (microvascular) dysfunction and LV structure/function in RA.—Another potential mechanism of HF in RA is inflammation-induced endothelial dysfunction, leading to impaired vasodilation of the microvasculature and decreased perfusion of the surrounding territory[64]. This is also thought to be a mechanism underpinning the enhanced risk of HFpEF in mildly inflammatory conditions such as obesity and diabetes [65]. Indeed, in RA, studies utilizing diverse methodologies –e.g., brachial artery reactivity, laser Doppler imaging, peripheral arterial tonometry - have demonstrated *microvascular* (defined by arteries smaller than 500 mm) dysfunction in RA patients and its association with disease activity, circulating cytokines, and future atherosclerosis[64]. However, few studies have directly investigated *myocardial* microvascular function in RA. The *intra-myocardial* arterioles and capillaries of the heart comprise 75% of the resistance in the coronary circulation; thus, dysfunction in these vessels can lead to ischemia even in the absence of significant CAD[65]. Microvascular disease is quantified by myocardial flow reserve (MFR; also called coronary flow reserve) – i.e., the ratio of myocardial blood flow at peak vasodilatory stress to blood flow at rest. In the absence of significant CAD, this ratio is

thought to represent the vasodilatory reserve of the microvascular circulation. MFR cut-offs of < 1.5 or < 2.0 have been suggested to represent microvascular dysfunction[65,66]. In the general population, impaired MFR has been linked with subclinical DD and with HFpEF[66]. Decreased nitric oxide bioavailability resulting from microvascular dysfunction has been suggested as a mechanism leading to concentric LV modeling and myocardial stiffness[66].

There are few investigations of myocardial microvascular perfusion in RA patients without clinical CVD. Using TTE techniques, investigators[67,68] reported significantly lower MFRs in RA patients without HF compared to controls. Using cardiac PET-CT, Recio-Mayoral et al[69] also reported lower (impaired) MFR in RA and SLE patients vs controls ($p<0.001$), and MFR correlated inversely with disease activity (r= −0.65; $p<0.001$). Microvascular dysfunction is a well documented complication of diabetes mellitus (DM); Liao et al[70] reported similar rates of impaired MFR in RA and DM patients (54% and 64%, respectively), and MFR < 2 was significantly associated with all-cause mortality (HR 2.43 [95% CI1.40-4.22]). Amigues et al [71] reported a mean MFR < 2.5 in *29%*, and mean MFR < 2.0 in 12%, of RA patients without clinical CVD. In multivariable analyses, TNF inhibitor (TNFi) use was associated with higher (better) MFR ($p= 0.023$), while lower (worse) MFR was associated with higher IL-6 levels and higher LVMI, suggesting a relationship of depressed MFR with inflammation and myocardial remodeling. Longitudinal studies examining the potential role of microvascular disease in the development of clinical HF in RA are needed.

In summary, RA-specific autoimmune mechanisms that trigger release of inflammatory cytokines may lead to local activation of macrophages and myofibroblasts in the myocardium, subsequent myocardial inflammation, endothelial damage, decreased perfusion, and ultimately, LV remodeling and clinical HF. However, much work is needed to confirm these events and elucidate causative molecular pathways.

Effect of RA DMARDs on HF and on subclinical measures of LV structure and function in RA

The association of inflammatory cytokines with LV remodeling in experimental models generated considerable interest in cytokine blockade as a therapy for HF. However, clinical trials of TNFi's for treatment of moderate to severe HF in the general population were disappointing. In the RENEWAL trial[72] there was neither significant benefit nor increased risk in all-cause-mortality or HF hospitalizations in etanercept vs placebo treated patients (RR 1.10 [95% CI 0.91–1.33; p=0.33]). In contrast, in the ATTACH trial [73], a higher risk of death and/or HF hospitalizations was reported in infliximab vs placebo treated patients (HR 2.84[95% CI 1.01-7.97; $p=0.043$]). An ensuing report of 38 cases of new onset HF in patients receiving etanercept or infliximab for conditions other than HF were reported, raising further concern[74]. As a result, the US Food and Drug Administration (FDA) issued a warning regarding use of TNFi's in individuals with HF.

Consequently, no randomized clinical trials (RCT) of TNF inhibitors to treat HF in RA patients have been conducted. However, several observational studies of the association of TNFi's with HF incidence or prevalence in RA have been published (see Table 4). In the prospective 'RABBIT' RA cohort study, a non-statistically significant difference in incident

HF risk in TNFi vs conventional synthetic DMARD (csDMARD) treatment was reported (adjusted HR 1.66 [95% CI 0.67-4.1])[75]. In a retrospective cohort study of RA patients > 65 years, the hazard ratio (HR) for new HF hospitalizations in TNFi vs MTX users was also numerically elevated but not statistically significant (HR 1.61 [95% CI 0.75-3.49])[76] . Using a combined Medicaid/Medicare database of over 10,000 RA patients, Solomon et al [77] reported no statistically significant difference in risk of incident HF in TNFi vs csDMARDs users (HR 0.84[95% CI 0.62-1.12]). Finally, lower rates of incident HF in TNFi vs csDMARD treated RA patients were observed in two studies[11,78]. Taken together, these studies suggest that TNFi's may reduce, or at least not elevate, risk of HF in RA. While an RCT would provide more definitive evidence, it seems unlikely that such a trial will be forthcoming, given the number of patients and extended length of follow-up needed.

In RA patients *without* HF, the effect of TNFi on measures of LV structure and function has been examined in small sample sizes and with variable outcomes, and which taken together do not offer a clear conclusion (Table 4). In a cross-sectional study, Giles et al[25] reported an association of any biologic DMARD (bDMARD) use (most were receiving TNFi's) with lower LVMI compared to no bDMARD use. In an RCT, Plein et al[27] reported a modest increase in geometric mean LV mass after one year of treatment in 81 RA patients treated with ETN+ MTX. In a cross sectional study, Yokoe et al[79] reported better global circumferential strain (GCS) in patients treated with bDMARD than with csDMARDs. Kotyla et al[80] reported an increase in EF, and decrease in LVM, after 1 year of infliximab in 23 RA patients. Other small and/or very short duration echocardiographic studies are included in Table 4[81–83]. In the absence of an RCT to discern the effects of TNFi's on HF risk in RA, the American College of Rheumatology (ACR) 2021 guidelines for the treatment of RA continue to recommend non-TNFi biologics over TNFi in RA patients with HF, and switch from TNFi to non-TNFi DMARD if HF develops while on a TNFi.

Despite the success of the CANTOs RCT[84] in which an IL-1 antagonist was shown to reduce nonfatal MI, stroke, and CV death in CAD patients in the general population, there is a dearth of studies of IL-1 inhibition in patients with HF. In a clinical trial of combined HFrEF and HFpEF patients in the general population, incidence of HF readmission or death at 24 weeks did not differ between anakinra vs placebo groups[85]. However, in experimental RA models, IL-1 blockade was associated with improvements in LVEF, LV dilatation and fractional shortening[49]. Since IL-1 inhibitors are only modestly efficacious for the treatment of RA, data on the effect of IL-1 on LV function in RA are also scant. In several short-term studies with small sample sizes, Ikonomidis et al [86] reported significant improvements in flow mediated dilation, MFR, and strain measures in RA patients.

Even fewer RA studies examine the impact of IL-6 blockade on HF or LV structure/function or cardiac biomarkers in patients with RA. In a post hoc analysis of RA patients receiving tocilizumab (TCZ) vs placebo, there were no statistically significant differences in decreases in troponin (hsTNT) or NT-proBNP levels between groups [87]. However, Kobayashi et al[88] reported a significant reduction in LVMI ($p<0.001$) after 52 weeks of tocilizumab treatment in RA patients, and a significant correlation between the change in CDAI with change in LVMI ($p = -0.580$; $p=0.007$). However, as noted previously, it is not clear which direction

of change in LVMI (higher vs lower; increasing vs decreasing over time) is considered to be beneficial in RA HF pathophysiology and its natural progression.

In summary, the risk/benefit of TNFi's in RA patients with co-morbid HF remains unclear and mandates further investigation. Likewise, insufficient data preclude conclusions about use of IL-1 or IL-6 inhibitors in clinical HF or to slow or prevent subclinical LV remodeling in RA patients.

As corticosteroids and NSAIDs are both well-recognized factors for triggering or worsening acute HF, current European Society of Cardiology (ESC) guidelines[13] recommend against their use in patients in the general population with HF. Limited data are available in RA patients with HF, however, on the contribution of glucocorticoids and/or nonsteroidal anti-inflammatory drugs (NSAIDs) to the incidence or prevalence of HF, or to abnormal echocardiographic measures of LV structure/function (such as LVMI). In a prospective cohort study of RA patients by *Mantel et al*[5], use of corticosteroids was strongly associated with non-ischemic HF (HR 3.12 [95% CI 1.30–7.44]) but not statistically significantly associated with ischemic HF or overall HF. However, in another prospective study[6] of RA patients, the use of corticosteroids was not a significant risk factor for incident HFpEF (OR 0.99 [95% CI 0.64-1.54]).

As for the association of corticosteroid use and abnormal measures of LV structure and function in RA patients without clinical HF, the data are somewhat conflicting. Each study focuses on a different outcome (LVMI[23], systolic longitudinal strain[35], diastolic function[30,44]) and reported either positive or negative association with corticosteroid use. None of the reviewed studies in RA patients specifically evaluated the association between NSAID use and myocardial measures or HF risk. Given the small number of studies and heterogeneity of findings in this area, clear conclusions are not possible but clinicians are wise to exercise caution in the use of these medications in RA patients with HF.

Future Directions

A keener awareness of the increased risk of HF in RA is needed, particularly given the reports of higher mortality in RA. Typical symptoms and physical exam findings of HF could be misinterpreted as RA-associated interstitial lung disease, and a normal EF on echocardiogram may be dismissed as normal before considering the possibility of HFpEF. The development of guidelines for screening RA patients to identify those at high risk for developing HF would be beneficial, but prospective imaging and biomarker data in RA are currently too scarce to inform guidelines. Davis et al [89] reported that a multi-cytokine immune response score discriminated between normal diastolic function and moderate to severe DD but this cell-based assay may be unwieldy to translate into clinical use. Longitudinal studies that delineate the natural history of pre-clinical echocardiographic findings to clinical HF, and that incorporate novel biomarker investigations, are critically needed in RA.

To supplement RA clinical studies, expanded investigation of *in vitro* HF models specific to RA should be pursued. A promising development in this regard, particularly given the limited availability of RA myocardial tissue, is the generation of engineered human

cardiac tissue from an RA patient's own induced pluripotent stem cells (iPSCs). Rim et al[90] derived iPSCs from RA fibroblast-like synoviocytes, and Lee et al[91] demonstrated successful differentiation of cardiomyocytes from those iPSCs. HF may also be investigated as a potential co-morbidity of the induction of experimental inflammatory arthritis. Zhou et al[92] reported myocardial inflammation and fibrosis, upregulated gene expression of TNF, IL-6, IL-17 and MMP3 in cardiomyocytes and cardiac fibroblasts, and a decline in LV function, in mice with collagen-induced arthritis. Additional work in animal models with concurrent inflammatory arthritis and HF could aid in defining shared molecular pathways between the two processes.

A critical area for further study is investigation of the direct effect of cytokine inhibitors on parameters of LV structure and function in RA patients without clinical HF. If these studies were to indicate absence of a detrimental effect on LV function, then further study of the safety of these agents in RA patients with clinical HF could conceivably progress.

In conclusion, the morbidity and mortality burden of HF in RA patients is higher than in the general population and appears to be predominantly of the HFpEF phenotype. Substantial evidence supports a role for chronic inflammation in driving HF in RA. Whether DMARDs prevent or worsen HF and/or subclinical LV dysfunction in RA remain unclear.

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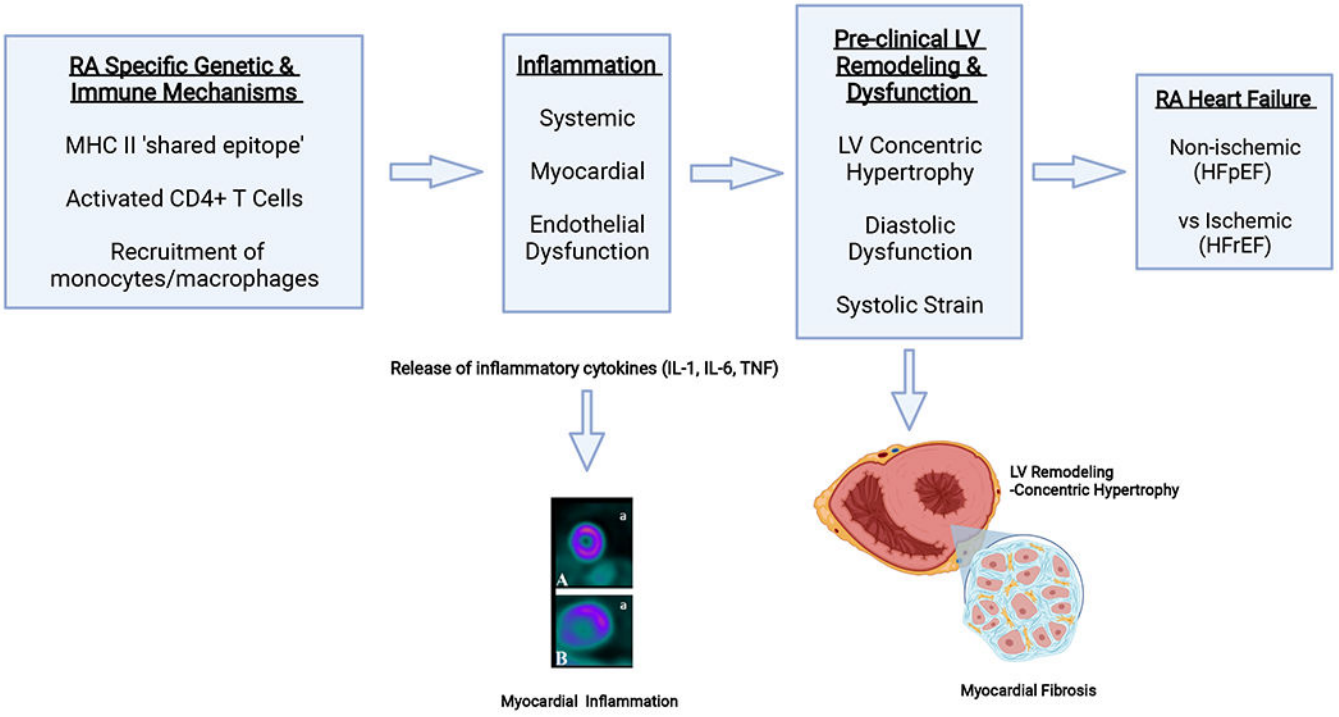

Figure.

Mechanisms Driving LV Dysfunction and HF in RA Patients

Antigen presenting cells expressing major histocompatibility complex II (MHC II) alleles that encode RA specific ‘shared epitopes’ interact with and select CD4+ T cells. Activated antigen-specific CD4+ T cells interact, in turn, with circulating monocytes and/or tissue macrophages to induce release of key inflammatory cytokines (IL-1, IL-6, TNF). These cytokines, possibly coupled with APCA-containing immune complexes, induce myocardial inflammation with subsequent endothelial damage and microvascular dysfunction. In addition, inflammatory cytokines activate local myofibroblasts that promote myocardial fibrosis and LV remodeling (concentric hypertrophy) that results in diastolic dysfunction and/or systolic strain. These changes in turn may lead to clinical HF with preserved EF (HFpEF). Since RA also promotes accelerated atherosclerosis through similar mechanisms, ischemic damage to the myocardium may also contribute to HF resulting in a reduced EF (HFrEF).

Table 1.

Epidemiologic Studies of HF in RA Patients vs Non-RA Patients

Incidence of HF in RA					
Study	**Design**	**N (RA vs. non-RA)**	**HR/OR (95% CI) RA vs. non-RA**	**Incidence (95% CI or p-value) RA vs. non-RA**	**Statistical Adjustments**
Wolfe et al, 2003[12] Wolfe et al,2004[11]	Retrospective longitudinal cohort study	9093 vs 2479 RA vs. OA 13171 vs 2568 RA vs. OA	OR 1.43 (1.28-1.59) RA vs. OA Not reported	Not reported 3.9% (3.4-4.3) vs. 2.3% (1.6-3.3) RA vs. OA	Demographics, CV risk factors
Crowson et al,2005[1]	Retrospective longitudinal cohort study	575 vs 583	Not reported	36.3% vs. 20.4% *p<0.001*	Sex, CV risk factors, alcohol use
Nicola et al, 2005[2], 2006 [4]	Retrospective longitudinal cohort study	575 vs 583; 603 vs 603	HR 1.87 (1.47–2.39)	37.1% vs. 27.7% *p<0.001*	Age, sex, CV risk factors, CAD
Mantel et al, 2017[5]	Prospective cohort study	12,943 vs 113,884	Overall HF: HR 1.22 (1.09-1.37) Ischemic HF: HR 1.27 (1.07-1.51) Non-ischemic HF: HR 1.22 (1.04-1.42)	Rates per 1000 person-years: Overall HF: 5.8 vs 3.1; Ischemic HF: 3.5 vs 1.9; Non-ischemic HF: 2.7 vs 1.4	Age, sex
Ahlers et al, 2020[6]	Prospective cohort study	9889 vs 9889	Cumulative HR (HFpEF and HFrEF): 1.21 (1.03-1.42)	HFpEF: 64% vs 62% p=0.67	Age, sex, race, CAD, CV meds
HF Mortality in RA vs non-RA					
Study	**Design**	**N (RA vs. non-RA)**	**HR/OR (95% CI) RA vs. non-RA**	**Incidence (95% CI or p-value) RA vs. non-RA**	**Statistical Adjustments**
Nicola et al, 2006[4]	Retrospective longitudinal cohort study	603 vs 603		39.0 vs. 29.2 per person-years *p<0.001*	Age, sex, calendar year
Davis et al, 2008[10]	Prospective cohort study	103 vs 852	HR 1.89 (1.26-2.84)	35% vs. 19%	Age, sex, calendar year, CV meds, CAD
Ahlers et al, 2020[6]	Prospective EHR study	323 vs 443	HR 1.68 (1.45-1.95)	22.6% vs 14.6% *p=0.006*	Age, sex, race

*BMI= Body Mass Index; CAD= Coronary Artery Disease; CI= Confidence Interval; CV= Cardiovascular; FH=Family History; HF=Heart Failure; HFpEF=HF with Preserved Ejection Fraction; HFrEF= HF with Reduced Ejection Fraction; HR=Hazard Ratio; HTN= Hypertension; OA= Osteoarthritis; OR= Odds Ratio; RA= Rheumatoid Arthritis

Table 2.

Left Ventricular Structural and Functional Parameters in RA vs. Non-RA Patients Without HF

Left Ventricular Mass Index (LVMI)				
TTE Studies	**Design**	**N (RA vs non-RA)**	**RA vs non-RA(95% CI or p-value)**	**Statistical Adjustments**
Aslam et al, 2013[21]	Meta-analysis; cross-sectional	1614 vs 4222	Mean Difference in LVMI: +6.2 g/m^2 (1.08-11.33)	None
Rudominer et al, 2009[30]	Cross-sectional	89	RA status and LVMI: OR (95% CI) 3.24(1.05, 5.42), β 0.177; p=0.004	Age, BMI, HTN
Myasoedova et al, 2013[23]	Cross-sectional	200 vs 600	LVMI (SD): 84.6± 15.9 g/m^2 vs 91.7± 22.2 g/m^2 (p<0.001)	CV risk factors and comorbidities
Corrao et al, 2015[22]	Meta-analysis of case-control studies; cross-sectional	401 vs 383	Mean Difference in LVMI: +0.47 g/m^2 (0.32-0.62)	None
Midtbo et al, 2017[24]	Cross-sectional	119 vs 46	LVMI g/m$^{2.7}$ (SD):Active RA vs Remission RA vs non-RA: 34.5 (12.1) vs 33.2 (10.2) vs 31.1 (8.1) no significant differences among 3 groups	None
Davis et al, 2017[30]	Prospective longitudinal cohort	160 vs 1391	Mean Difference in LVMI per year:−0.0004% (−8.917, −0.199)	Age, sex, CV risk factors
CMR Studies	Design	N (RA vs non-RA)	RA vs non-RA (95% CI or p-value)	Statistical Adjustments
Giles et al, 2010[25]	Cross-sectional	75 vs 225	Mean Difference in LVMI:−14.7 g/m^2 (p<0.001)	Demographics, CV risk factors
Ahlers et al,2020[6]	Cross-sectional	59 vs 56	LVMI (SD): 44 g/m^2 vs 42 g/m^2 (p=0.19)	None
Bissell et al, 2020[26]	Cross-sectional	76 vs 26	Mean Difference in LVMI: −4.558 g/m^2 (*p<0.001*)	Age, sex, CV risk factors
Plein et al, 2020[27]	Cross sectional: RA vs controls Prospective:RA only	81 vs 30	RA vs non-RA: Mean LVM (g) (95% CI): 78.2 (74.0-82.6) vs 92.9 (84.8-101.7); *p<0.01* RA only: Mean LVM (g) (95% CI) at baseline vs 1 year after treatment: 78.2 (73.7-82.9) vs 81.4 (76.3-86.9); *p=0.01*	Age, sex, SBP, smoking
Systolic Strain				
TTE Studies	**Design**	**N (RA vs non-RA)**	**RA vs non-RA (95% CI or p-value)**	**Statistical Adjustments**
Fine et al, 2014[34]	Cross-sectional	59 vs 59	Systolic Strain (SD):−15.7±3.2% vs −18.1±2.4% (*p<0.001)*	None
Cioffi et al, 2017[35]	Prospective Cohort	209 vs 52	Systolic Strain (SD):−18.4± 3.4% vs −19.9± 2.6% (*p<0.005)*	None
Midtbo et al, 2017[24]	Cross-sectional	78 vs 46	Global Longitudinal Strain (SD): Active vs Remission RA: −18.9 % (3.1) vs −20.6 % (3.5) *p=0.02* No significant differences between active RA vs controls, or remission RA vs controls	None
Lo Gullo et al, 2018[39]	Cross-sectional	41 vs 58	Systolic Strain (SD): −18.13 ± 1.36% vs −23.25 ± 1.80% (*p<0.001)*	None
CMR Studies	**Design**	**N (RA vs non-RA)**	**RA vs non-RA (95% CI or p-value)**	**Statistical Adjustments**
Ntusi et al, 2019[36]	Cross-sectional	69 vs 63	Mid Short Axis Circumferential Strain Rate Without CVRFs: −17.4 ± 1.3 vs. −19.2 ± 1.0 With CVRFs: −16.8 ± 1.1 vs. −18.2 ± 1.2	None
Yokoe et al,2020[79]	Cross-sectional	80 vs 20	Systolic Strain (95% CI): −16.5 (−14.0 to −18.6) vs. −18.2 (−16.2 to −19.6); *p<0.055*	None
Diastolic Function				

Left Ventricular Mass Index (LVMI)				
TTE Studies	**Design**	**N (RA vs non-RA)**	**RA vs non-RA(95% CI or p-value)**	**Statistical Adjustments**
TTE Studies	**Design**	**N (RA vs non-RA)**	**RA vs non-RA (95% CI or p-value)**	**Statistical Adjustments**
Aslam et al, 2013[21]	Meta-analysis; Cross sectional	1614 vs 4222	Mean Differences: ● LAD: +0.09 cm (0.01-0.17) ● IVRT: +9.67 ms (5.78-13.56) ● E/A ratio: −0.17 (−0.25, −0.09) ● DT: +6.38 msec (−2.76, 15.51)	None
Davis et al, 2017[30]	Prospective longitudinal cohort	160 vs 1391	Mean Differences (annualized rate of change): ● LAVI: +0.251 (*p<0.001)* ● E/A ratio: −0.307 (*p<0.001)* ● E/e' ratio: −0.038 (p=0.16) ● DT: −0.009 (p=0.90)	Age, sex, HTN, obesity, diabetes, CAD, smoking

*CAD=Coronary Artery Disease; CVRFs= Cardiovascular Risk Factors; DBP= Diastolic Blood Pressure; DT= Deceleration Time; E/A ratio= Ratio between peak early (E) and late (A) velocity of mitral flow; E/e' ratio= Ratio between peak early (E) velocity of mitral flow and peak early diatolic velocities of lateral/septal mitral annulus (averaged); IVRT= Isovolumetric Relaxation Time; LAD= Left Atrial Dimension; LAVI=Left Atrial Ventricular Index; LVMI=Left Ventricular Mass Index; SBP=Systolic Blood Pressure; SD= Standard Deviation; TTE= Transthoracic Echocardiography

Table 3.

Associations of Inflammatory Biomarkers and RA Characteristics with HF incidence (RA vs non-RA) and with Subclinical LV Structure/Function (RA without HF)

Incidence in RA vs non-RA					
Study	**Design**	**N (RA vs non-RA)**	**Biomarkers HR/OR (95%CI)**	**RA Characteristics HR/OR (95%CI)**	**Statistical Adjustments**
Nicola et al, 2005[2]	Retrospective longitudinal cohort study	575 vs 583	None	RF+ RA vs. non-RA: HR 2.59 (1.95-3.43)	Age, sex, CV risk factors, CAD
Mantel et al, 2017[5]	Prospective cohort study	12,943 vs. 113,884	ESR≥40 vs ESR≤40 in non-ischemic HF: HR 3.03 (1.69-2.73); ESR≥40 vs ESR≤40 in ischemic HF: HR 2.41 (1.15-5.08)	DAS28≥5.1 vs. DAS28≤5.1 in non-ischemic HF: HR 3.35 (1.84-6.09); DAS28≥5.1 vs. DAS28≤5.1 in ischemic HF: HR 2.68 (1.24-5.78)	None
Ahlers et al, 2020[6]	Prospective cohort study	9889 vs. 9889	CRP and HFpEF: OR 1.24 (1.11-1.38) CRP and HFrEF: OR 1.17 (1.03-1.33)	Not reported	Age, sex, race, CAD, and CV Medications, DMARDs
Myocardial Measures (LVMI) in RA Patients without HF					
Study	**Design**	**N (RA Only)**	**Biomarkers HR/OR (95%CI)**	**RA Characteristics HR/OR (95%CI)**	**Statistical Adjustments**
Rudominer et al, 2009[32]	Cross-sectional TTE	89	No significant associations	No significant associations	Age, BMI, HTN
Giles et al, 2010[25]	Cross-sectional CMR	75	No significant associations between LVMI and CRP, IL-6	LVMI associated with: bDMARDs (β −5.75, p<0.05) and CCP (β −0.46; p<0.05)	Age, sex, BSA, SBP, DMARDs, smoking
Myasoedova et al, 2013[33]	Cross-sectional TTE	200	No significant associations between LVMI and CRP, IL-6, TNF	LVMI associated with glucocorticoid use (β −0.082, *p=0.002*)	None
Ntusi et al,2015[57]	Cross sectional CMR	39	Not reported	DAS28 and ECV: ρ 0.61; *p<0.001*	None
Bissell et al, 2020[26]	Cross-sectional CMR	76	Not reported	LVMI not associated with DAS28, ACPA, HAQ-DI, RA duration	Age, Gender, CV risk factors, ACPA
Diastolic Function in RA Patients without HF					
Study	**Design**	**N (RA Only)**	**Biomarkers HR/OR (95%CI)**	**RA Characteristics HR/OR (95%CI)**	**Statistical Adjustments**
Di Franco et al, 2000[46]	Cross-sectional TTE	32	Not reported	RA duration and E/A ratio: r=0.40 (*p=0.01*)	None
Arslan et al, 2006[45]	Cross-sectional TTE	52	Not reported	RA duration and -E/A: r=0.40 (*p=0.004*)	None
Udayakumar et al, 2007[47]	Cross-sectional TTE	45	Not reported	RA duration and -E/A: r=−0.56 (*p=0.001*);	None
Liang et al,2010[44]	Cross-sectional TTE	244	Median IL-6 (IQR) for DD: OR 1.2 (1.01-1.4)	RA duration median (IQR) and DD: OR 3.3 (1.8-5.9)	Age, sex, and CV risk factors
Davis et al, 2017[30]	Prospective longitudinal cohort (5 year changes)	160	CRP and -E/A: r=−0.16 (*p=0.047*); IL-6 and E': r=0.19 (*p=0.02*)	Significant associations of A velocity with glucocorticoid use (*p=0.04*), E/e' ratio with pt global score (*p=0.005*) and RAPID 3 score (*p=0.02*).	None

Incidence in RA vs non-RA					
Study	**Design**	**N (RA vs non-RA)**	**Biomarkers HR/OR (95%CI)**	**RA Characteristics HR/OR (95%CI)**	**Statistical Adjustments**
Systolic Function in RA Patients without HF					
Study	**Design**	**N (RA Only)**	**Biomarkers HR/OR (95%CI)**	**RA Characteristics HR/OR (95%CI)**	**Statistical Adjustment**
Fine et al,2014[34]	Cross-sectional TTE	87	No significant associations between ESR and systolic longitudinal strain	Longitudinal strain and -Corticosteroid: β 1.84; p=0.062 -Methotrexate: β 1.46; p=0.054	Age, gender, SBP, BMI, HR, LVMI
Cioffi et al,2017[35]	Prospective Cohort TTE	209	No significant associations of CRP with GCS/GLS	No association of RA duration, RF/CCP, CDAI, corticosteroid with GCS/GLS	None
Midtbo et al, 2017[33]	Cross-sectional TTE	78	Not reported	DAS28 and GLS: β 0.21; *p=0.02*	Age, sex, BMI, SBP, and LVEF
Lo Gullo et al, 2018[39]	Cross-sectional TTE	41	Not reported	DAS28 and GLS: β 8.075*; p<0.0001* DAS28 and GCS: β 7.214*; p=0.002*	Age, BMI, CRP, ESR, SBP, DBP, others
Ntusi et al, 2019[36]	Cross-sectional CMR	69	CRP circumferential strain rate: β 0.02 (0.01;0.04); *p=0.06*	----	Age, CV risk factors, aortic distensibility

*ACPA=Anti-citrullinated protein/peptide antibodies; bDMARD= biologic Disease Modifying Anti-Rheumatic Drugs ;BSA= Body Surface Area; CCP= Cyclic Citrullinated Protein; CDAI= Clinical Disease Activity Index; CMR= Cardiac Magnetic Resonance; CRP= C-Reactive Protein; DAS28= Disease Activity Score in 28 joints; DBP= Diastolic Blood Pressure; DD= Diastolic Dysfunction; DMARD= Disease Modifying Anti-Rheumatic Drugs; ESR: Erythrocyte Sedimentation Rate; GCS= Global Circumferential Strain; GLS= Global Longitudinal Strain; HAQ-DI= Health Assessment Questionnaire Disability Index; HR=Heart Rate; IL-6= Interleukin-6; IQR= Interquartile Range; LVEF= Left Ventricular Ejection Fraction; RAPID-3= Routine Assessment of Patient Index Data 3; RF=Rheumatoid Factor

Table 4.

Effects of Anti-Cytokine Therapy on Incidence/Prevalence of Clinical HF, and on Subclinical LV Structure and Function, in RA patients

Studies of Incident or Prevalent HF	Design	TNFi vs no Use (N)	Primary HF Outcomes	Adjustments
Wolfe et al, 2004[12]	Retrospective review of longitudinal survey	TNFi (ETN/IFX) vs no TNFi: 5832 vs 7339	Adjusted Rates of HF: TNFi vs no TNFi: 2.8 vs 3.4-3.9 (*p=0.03*) IFX vs ETN vs no TNFi: 2.6 vs 2.9 vs 3.4-3.9	Propensity score matched
Bernatsky et al, 2005[78]	Nested Case Control	TNFi (ETN/IFX) vs csDMARDs: 187 vs 3656	Adjusted RR for HF hospitalization (95% CI): Any DMARDs vs No DMARDs: 0.7 (0.6-0.9)	Age, sex, cohort, ischemic heart disease, stroke, peripheral arterial disease, HTN, DM, HL, RA meds
Listing et al, 2008[75]	Prospective Cohort; RABBIT	TNFi (ADA/IFX/ETN) vs csDMARDS: 2,757 vs 1,491	Prevalent HF adjusted HR (95% CI) for TNFi vs csDMARDs: 1.49 (0.70-3.18) Incident HF adjusted HR (95% CI) for TNFi vs csDMARDs: 1.66 (0.67-4.1) Worsening HF adjusted HR (95% CI) for TNFi vs csDMARDs: 1.18 (0.30-4.73)	Age, male sex, CVD, BMI, DAS28, functional capacity Age, sex, CVD, BMI, functional capacity, disease activity at follow up Age, male sex, GC>10 mg/day
Setoguchi et al, 2008[76]	Retrospective Cohort study; Medicare	TNFi (ADA/IFX/ETN) vs MTX: 1,002 vs 5,593	New HF hospitalization adjusted HR (95% CI) for TNFi vs MTX: -with previous HF: 1.50 (0.41-4.79) -without previous HF: 3.41 (0.73-16.05) -combined (HF or not): 1.61 (0.75-3.49)	Age, sex, race, CV comorbidities including CAD, other DMARDs, ESR, CRP, CKD, diabetes, HL
Solomon et al,2013[77]	Cohort study; Medicaid and Medicare	TNFi (ADA/IFX/ETN) vs csDMARDs: 11,587 vs 8,656	HR (95% CI) new or recurrent HF hospitalizations: TNFi vs csDMARDs: 0.85 (0.63-1.14)	Propensity score matched
Studies of LV Structure and Function in Patients without HF	**Design**	**DMARD Use (N)**	**Primary LV Structure/Function Outcomes**	**Statistical Adjustments**
Kotyla et al, 2012[80]	Prospective Cohort Study: TTE	TNFi (IFX): 23	Before and 1 yr after IFX: median EF: 58.5% vs 63%; p<0.05	None
Santos et al, 2012[81]	Prospective Cohort Study: TTE	TNFi (IFX): 14	Before and 2-hr after IFX: -CO: 7.04 ± 2.3 vs 6.12 ± 2.1 L/min; p<0.001 -SV: 91± 29.0 to 83 ± 28.8 mL/beat; p<0.001	None
Daien et al, 2013[83]	Prospective Cohort Study; TTE	TNFi (ETN) vs csDMARDs: 28 vs 20	Change in LVMI at 3 and 6 months: ETN: −6.3±7.6; −14.2±9.3 g/m2 csDMARD: −2.2±10.9; −2.7±10.2 g/m^2	None
Vizzardi et al, 2016 [82]	Prospective Cohort Study; TTE	TNFi (ADA/IFX/ETN): 13	Baseline vs one year after TNFi: No significant changes in EF or GLS	None
Giles et al, 2010[25]	Cross-sectional: CMR	Non-bDMARD (MTX) vs. bDMARDs (ETN, ADA, IFX, rituximab): 53 vs. 37	Association of any bDMARD use with LVM: β −5.75; p<0.05	Age, sex, BSA, SBP, and smoking
Plein et al, 2020[27]	RCT: CMR	TNFi (ETN) + MTX N=81	Baseline vs one year after treatment: Geometric mean LVM (g) (95% CI): 78.2 (73.7-82.9) vs 81.4 (76.3-86.9); p=0.01	None
Yokoe et al,2020 [79]	Cross-sectional: CMR	csDMARDS or bDMARDS:80	GCS and bDMARDs use: β 0.26 ; p= 0.021	ACPA, SJC, SDAI, MMP-3

*ADA=Adalimumab; CKD= Chronic Kidney Disease; CO= Cardiac Output; csDMARDs= Conventional Synthetic Disease Modifying Anti-Rheumatic Drugs; CVD= Cardiovascular Disease; DM= Diabetes Mellot GC= Glucocorticosteroids; HL= Hyperlipidemia; IFX= Infliximab; MMP-3= Matrix Metalloproteinase-3; MTX= Methotrexate; RCT= Randomized Controlled Trial; SJC=Swollen Joint Count; SDAI= Simplified Disease Activity Index; SV=Stroke Volume; TNFi= Tumor Necrosis Factor Inhibitor