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Preventing Heart Failure in Inflammatory and Immune Disorders

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Abstract

Patients with chronic inflammatory diseases are at increased risk for heart failure due to ischemic heart disease and other causes including heart failure with preserved ejection fraction. Using rheumatoid arthritis and treated HIV infection as two prototypical examples, we review the epidemiology and potential therapies to prevent heart failure in these populations. Particular focus is given to anti-inflammatory therapies including statins and biologic disease modifying drugs. There is also limited evidence for lifestyle changes and blockade of the renin-angiotensin-aldosterone system. We conclude by proposing how a strategy for heart failure prevention, such as the model tested in the Screening To Prevent Heart Failure (STOP-HF) trial, may be adapted to chronic inflammatory disease.

Keywords

Heart Failure; HIV; Rheumatoid Arthritis; Inflammation

Introduction

Heart failure epidemiology and prevention in the general population

An estimated 5.1 million Americans are living with heart failure, and the prevalence is projected to increase by 25% by 2030. At the age of 40, the lifetime risk of developing heart failure is now an astonishing 1 in 5[1]. The rising prevalence may in part be explained by mortality lowering therapies for coronary artery disease and systolic heart failure. For example, in Olmsted County, Minnesota, heart failure mortality decreased from 57% to 48% from 1979-1984 to 1996-2000[2].

Current strategies to prevent heart failure focus on managing risk factors among those at highest risk (i.e. those with Stage A or Stage B disease without clinical symptoms).

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Compliance with Ethics Guidelines

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Intervention strategies include life-style modifications (weight loss, exercise, and smoking cessation) and pharmacologic therapy for risk factors (hypertension, diabetes, and dyslipidemia) to reduce risk of progression to heart failure[3]. Blockade of the renin-angiotensin-aldosterone system (RASS) is of particular importance. Recently, the Screening To Prevent Heart Failure (STOP-HF) trial demonstrated that such a multilevel screening and treatment strategy can effectively reduce left ventricular systolic and diastolic dysfunction and incident heart failure[4].

Inflammation in heart failure

The role of inflammation in the pathogenesis of heart failure has been recognized since Braunwald first noted C-reactive protein (CRP) elevations in the setting of congestive heart failure in 1956[5]. Subsequent investigations have confirmed that pro-inflammatory cytokines and their receptors are elevated in advanced heart failure, including interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-18 (IL-18), and tumor necrosis factor- α (TNF- α)[6, 7].

Furthermore, the incidence of cardiovascular disease, including coronary disease and heart failure, is increased in patients with co-morbid inflammatory disorders, including rheumatoid arthritis (RA)[8], psoriasis[9], lupus[10], and chronic HIV infection[11]. In this review of current literature, we will discuss an approach to heart failure prevention in inflammatory and immune mediated disease with a focus on RA and HIV.

What is the epidemiology of heart failure in inflammatory and immune mediated diseases?

Rheumatoid Arthritis

The increased risk of heart failure in RA may be mediated in part by vascular disease. This includes coronary atherosclerosis and myocardial infarction as well as effects on vascular compliance, endothelial function, and ventriculo-vascular interactions. Subclinical atherosclerotic vascular disease appears to be more common in patients with RA compared to the general population. Carotid intima-media thickness (cIMT), a surrogate marker of CVD (especially stroke) in the general population[12], is higher in patients with RA. In a meta-analysis of smaller studies, RA was associated with 0.09 mm (95%CI: 0.07-0.11 mm) higher cIMT compared to controls[13]. Yet, specific RA factors including duration of RA, Rheumatoid factor status, and disease activity score (DAS28) were not associated with an increased cIMT[13]. In an alternative approach to carotid artery assessment, Van Sijl et al described increases in carotid lumen diameter, circumferential wall stress, and circumferential wall tension in patients with RA, which may indicate a propensity for plaque instability and rupture[14]. Cross-sectional studies also suggest increased arterial stiffness and endothelial dysfunction in patients with RA[15]; however, studies have not shown a consistent association between these measures and disease activity[15].

In addition to vascular disease, RA appears to be associated with subclinical structural heart disease. RA is known to cause rheumatoid nodules that lead to valvular disease (particularly regurgitation), although the severity of valvular lesions is generally less severe than in

patients with lupus. A meta-analysis suggests higher odds of aortic stenosis (OR 5.2; 95% CI 1.1–24.1), aortic regurgitation (OR 1.7; 95% CI 1.0–2.7), mitral regurgitation (OR 3.4; 95% CI 1.7–6.7), tricuspid regurgitation (OR 5.3; 95% CI 2.4–11.6), or combined valvular lesions (OR 4.3; 95% CI 2.3–8.0)[16]. More importantly, inflammatory diseases such as RA may be associated with subclinical myocardial fibrosis and dysfunction. In a recent echocardiography study of patients without significant left ventricular (LV) hypertrophy or clinical heart failure, RA was associated with concentric remodeling and other forms of maladaptive LV geometry (OR 1.44 after adjusting for other cardiovascular risk factors) [17]. Speckle-tracking strain analyses point to subtle alterations in right and left ventricular systolic function[18]. Others have described high rates of diastolic dysfunction[19] that is independently associated with disease duration and IL-6 levels.

The role of MRI to image subclinical myocardial disease in RA has been recently reviewed[20]. Myocarditis, including a unique granulomatous form, has long been recognized in RA based on autopsy series[21], but MRI now allows for detection of subclinical myocarditis in living patients. Interestingly, despite lower LV mass by MRI, left ventricular ejection fraction, cardiac output, and stroke volume all appear to be modestly lower in RA compared to controls[22]. This would suggest mechanisms of LV dysfunction other than myocyte hypertrophy (i.e. LVH) or expansion of the extracellular matrix (i.e. interstitial fibrosis). On the other hand, there appears to be a high prevalence of replacement fibrosis in RA patients with [23] and without[24] clinical HF as detected by late gadolinium enhancement. Future studies utilizing novel T1 mapping techniques may clarify these patterns of myocardial inflammation and fibrosis in RA. These studies demonstrate the potential of non-invasive imaging to elucidate pathophysiologic mechanisms and identify patients with early Stage B heart failure who are at risk of clinical progression in this population.

Although subclinical disease may be present, the more relevant question is whether RA increases the incidence of clinical stage C and D heart failure. In a population based study in Minnesota, Nicola et al. assessed the risk of HF over several decades[8]. At 30 years of follow-up, the cumulative incidence of HF was 34% in those with RA and 25% in those without RA. After adjustment for other cardiovascular risk factors, including ischemic heart disease and demographics, patients with RA had almost twice the risk of incident HF (HR 1.87, 95% CI 1.47-2.39), and the effect was stronger among those with a positive rheumatoid factor (HR 2.59). Patients with RA in a subsequent study from this cohort were also more likely than non-RA patients to have preserved ejection fraction (i.e. HFpEF), and had higher 1-year mortality[25]. Finally, several clinical characteristics including elevated ESR, severe extra-articular manifestations, and corticosteroid use were all associated with HF after adjustment for potential confounders[26]. These findings are compelling but need to be validated in other RA cohorts.

HIV

Since the introduction of effective combination antiretroviral drug therapy (ART) in 1996, the clinical course of chronic HIV infection has been dramatically altered. AIDS is no longer the primary cause of death, but is overshadowed by diseases of aging such as cancer, kidney

disease, and cardiovascular disease. Epidemiologic data suggest that HIV-infection is independently associated with about 1.5-fold higher risk of myocardial infarction[27], stroke[28], and heart failure[11, 29]. Prior generations of antiretroviral medications were implicated in raising CVD risk[30], though newer drugs are much less toxic[31]. Current hypotheses center on the role of residual inflammation and immune activation as an important driver of risk[32].

Subclinical vascular disease is manifest in chronic treated HIV infection as higher levels of cIMT, impaired carotid distensibility, higher coronary artery calcium, and higher volumes of coronary artery plaque. These studies have recently been extensively reviewed[33, 34]. In a representative study from the Multicenter AIDS Cohort Study (MACS), compared to uninfected men, HIV-infected men had higher volumes of noncalcified coronary plaque that was independent of traditional risk factors[35] and was associated with HIV duration and nadir CD4+ T-cell count. Others have recently reported similar findings in HIV-infected women[36]. Arterial inflammation detected by 18-FDG PET/CT[37] and vulnerable plaque morphologies by CT angiography[38] also appear to be disproportionately prevalent in HIV infection and are associated with higher levels of monocyte activation markers.

Prior to effective combination ART, AIDS cardiomyopathy was common and has been well-described[39]; however, the nature of subclinical myocardial disease has changed in the modern treatment era. In an important study using MRI, Holloway et al[40] describe 50% higher intra-myocardial lipid levels and much higher rates of replacement fibrosis detected by late gadolinium enhancement (76% of HIV+ vs. 13% of controls). Myocardial systolic and diastolic strains were also lower in the HIV-infected participants. Similar findings have recently been confirmed by other investigators[41].

The Veterans Administration healthcare system is currently following over 20,000 HIV-infected patients and has provided much of the epidemiologic data regarding the risk of clinical events in this population. Heart failure risk was increased in HIV infected veterans (adjusted HR 1.8), even when those with coronary disease or alcohol abuse were excluded (adjusted HR 1.96)[11]. The risk was significantly higher among patients with ongoing viral replication compared to those with suppressed viremia on ART. This group has also reported similar risks of HF with reduced versus preserved ejection fraction[29].

Observational studies of HIV-infected patients are always limited by the specter of residual confounding because these patients typically have very different risk profiles compared to uninfected control participants. For example, smoking is highly prevalent and other drug use is not always well characterized. Additionally, relatively less is known about HIV-specific risks in women since fewer women are infected and tend not to be well represented in studies. These limitations may be overcome in well-matched cohorts of HIV-infected women and in ongoing studies conducted in sub-Saharan Africa where women are more commonly affected and there is less likelihood of residual confounding.

What is the role of risk factor management for heart failure prevention in patients with RA and HIV?

As in the general population, prevention strategies should target the principle causes of heart failure, particularly ischemic and hypertensive heart disease. Ischemic heart disease can be reduced by lifestyle modifications, aspirin, and statins.

Exercise

Based primarily on the results of the HF-ACTION trial, the 2013 joint ACC/AHA guidelines for management of heart failure recommend exercise to improve functional status and reduce hospital readmissions[42], but it is also likely that exercise prevents heart failure. In a population of men over 45 years old, self-reported physical activity and sedentary time independently predicted incident HF over 10 years in men without HF at baseline[43]. Less is known, however, about the effect of exercise in patients with RA or HIV. A recent clinical trial randomized 40 RA patients to 6 months of supervised aerobic and resistance exercise training versus lifestyle counseling. Aerobic capacity, CVD risk factors, RA disease score, and inflammation all improved significantly in the exercise intervention arm[44]. A subsequent analysis of the same trial reported improvements in microvascular and macrovascular endothelial function[45]. There were dramatic and clinically relevant improvements in risk factors (for example, a 7mmHg reduction in systolic BP and doubling of flow-mediated brachial artery dilation), but these results need to be replicated in other studies and the long-term maintenance effects of these interventions on exercise behavior and CVD risk is unknown. In a small pilot trial of HIV-infected patients, a supervised exercise and resistance training program did not improve myocardial insulin sensitivity or LV diastolic function[46]; although, whether exercise has other effects that lead to decreased clinical HF risk over time is unknown.

Statins

Statins (hydroxymethylglutaryl CoA reductase inhibitors) prevent heart failure by reducing the risk of myocardial infarction and by improving vascular health. Although the MI risk reduction is primarily related to reductions in LDL cholesterol, the “pleiotropic” effects of statins on vascular health and inflammation have been the focus of intense investigation. Statins reduce inflammation and immune activation in RA[47, 48] and in HIV[49, 50], and recent studies have evaluated their effect on vascular disease and HF risk factors in these populations.

In patients with RA, 4 weeks of simvastatin 40mg daily improves endothelial function, particularly among those with the highest levels of systemic inflammation at baseline[51]. Similarly, 12 weeks of atorvastatin 20mg daily appears to improve aortic stiffness[52]. A recently published study suggests that statins improve vascular health in mouse models of inflammatory arthritis by decreasing expression of monocyte chemotactic protein-1-induced protein in endothelial cells[53]. In retrospective clinical studies, statin discontinuation appears to be associated with elevated risk of MI[54] and CVD mortality[55].

In retrospective studies of HIV-infected patients, statin use is associated with dramatic reductions in total mortality[56, 57], although there are no prospective clinical trials. Several ongoing trials (clinicaltrials.gov NCT00965185, NCT00673582, NCT01218802 and others) are testing the effect of statins on endothelial function, carotid stiffness and IMT progression, and arterial inflammation, and results are expected to be reported in 2014.

Hypertension

Treatment of hypertension is one of the most important principles of HF prevention. Yet, there are some anti-hypertensive agents that have theoretical benefit over others to prevent HF. Inhibition of RAAS with ACE inhibitors, angiotensin receptor blockers, and aldosterone antagonists has anti-fibrotic and anti-inflammatory effects beyond reductions in blood pressure. The increased use of these agents may explain the HF risk reduction observed in the STOP-HF trial.

Initial studies using captopril have suggested that ACE inhibition may have benefit in the treatment of RA[58]; however, a subsequent study did not show a clinical benefit with the use of pentopril[59]. Some have therefore speculated that having a thiol group is characteristic of ACE inhibitors with clinical benefit[60]. In a mouse model of inflammatory arthritis, ramipril significantly reduced histo-pathological synovitis, decreased secondary lesion score, and decreased right hand paw edema[61]. In humans, this reduction in generalized inflammation may lead to improved endothelial function as measured by brachial flow-mediated dilation after only 8 weeks of treatment[62]. Longer term effects of ACE inhibition on hard CVD outcomes in RA is unknown.

In the context of chronic HIV infection, the prevalence of hypertension is high and has changed little over time. Furthermore, insufficient control of blood pressure is common[63] and increases the incidence of cardiovascular events in HIV[64]. Telmisartan, an angiotensin II receptor blocker and PPAR- γ receptor agonist, has been extensively studied in HIV because of its potential pleiotropic effects on the metabolic abnormalities in patients chronically treated with ART. In one study, telmisartan reduced blood pressure, improved lipid metabolism, and improved renal function over 144 weeks. It did not substantially interfere with ART and was well tolerated[65]. It may have further renal-protective effects by reducing albuminuria[66], which is a strong predictor of incident heart failure in HIV-infected veterans[67]. Because of the important metabolic and body image consequences of subcutaneous lipoatrophy and visceral lipohypertrophy in HIV[68], the Metabolic Abnormalities, Telmisartan, and HIV infection (MATH) pilot trial was conducted to test the effect of telmisartan on adipose tissue distribution[69]. In this study, 24 weeks of telmisartan reduced total and subcutaneous adipose tissue volumes, but not visceral adipose tissue volumes. Interestingly, there was a reduction in the waist circumference and waist:hip ratio, despite no change in BMI or weight. ACE inhibition may also decrease residual inflammation in patients on ART[70]. Similarly to patients with RA, there are no clinical trial data on the effect of RAAS blockade on hard CVD events in patients with chronic HIV infection.

Can immune modulating agents prevent heart failure?

If chronic inflammation and immune activation are thought to be important drivers of heart failure risk in patients with inflammatory autoimmune diseases or chronic HIV infection, then it is logical that immune therapies may prevent heart failure. In the case of RA, a wealth of clinical trial level data exist regarding the CVD risk profile of these drugs, and there is proven clinical benefit for RA disease modification. In HIV-infection, there is much interest in whether these same drugs may be applied to specific sub-groups of patients (i.e. those who fail to reconstitute their CD4+ T-cell count after ART initiation or those with chronically high levels of circulating inflammatory cytokines), but few clinical studies exist.

Methotrexate

Methotrexate (MTX) is the mainstay of RA treatment because it modifies progression of arthritis, but also appears to have a beneficial effect on mortality[71]. More specifically, in a meta-analysis of observational studies, MTX was associated with 21% lower total CVD and 18% lower risk of MI[72]. MTX may also improve metabolic syndrome parameters, though the evidence is mixed[73]. With regard to heart failure, there are fewer data, but two studies suggest a potentially strong effect. In an older nested case control study, disease modifying therapies (including MTX) were associated with 20% lower risk of incident HF hospitalization[74]. A more recent study found that MTX reduced the risk of HF by half[26] compared to those not receiving MTX.

The Cardiovascular Inflammation Reduction Trial (CIRT) is a randomized, placebo-controlled trial of low-dose MTX to prevent CVD events, which will test the inflammation hypothesis of atherothrombosis in the general population[75]. A smaller 24-week study (NCT01949116) is being conducted in parallel to CIRT in a population of HIV-infected patients at high risk for CVD or with residual inflammation on ART. The primary outcome will be change in brachial endothelial function. By reducing vascular risk, low-dose MTX has the promise of also reducing HF, though data on clinical outcomes are not likely to be available in the near future.

TNF- α antagonists

Tumor necrosis factor- α (TNF- α) antagonists are the most widely used biologic disease modifying drugs to treat inflammatory autoimmune diseases, and their cardiovascular risk profiles have been extensively studied. Because of the compelling role of inflammation in heart failure, clinical trials of anti-TNF therapies to improve HF outcomes in patients without autoimmune disease have been conducted. In the RENEWAL trial, etanercept had no effect on the rate of death or hospitalization, although there was a trend toward worse outcomes in patients with NYHA Class IV symptoms[76]. In ATTACH, infliximab was associated with an increased risk of death and HF hospitalization at higher doses, and no clinical benefit at low doses[77]. There have been some concerns about whether these drugs are associated with risk of heart failure in patients with RA[78], although a recent large observational study of 11,000 users of anti-TNF- α therapies compared to 9,000 users of non-biologic DMARDs found that anti-TNF- α therapies were not associated with risk of hospitalization for HF[79]. This lack of association was consistent in multiple subgroup

analyses and with varied outcome definitions (new versus recurrent HF hospitalization). In a recent mechanistic study, an increase in EF, and a reduction in endothelin-1, interleukin-6 and natriuretic peptides were noted as early as 4 months after initiation of infliximab[80]. There is further evidence that blockade of TNF- α is associated with decreased aortic pulse wave velocity and decreased aortic inflammation by 18-fluorodeoxyglucose positron emission tomography (FDG PET-CT)[81]. The bulk of data now suggest that TNF- α blockade is at least neutral with regard to incident heart failure, but should still be avoided in patients with Class III or IV symptoms. Mechanistic studies suggest that it may eventually prove to be beneficial for a range of CVD outcomes including heart failure in patients with RA.

Interleukin-6 receptor antagonists

Tocilizumab (TCZ) is a monoclonal antibody targeting interleukin-6 receptor that is approved for the treatment of inflammatory arthropathies that may not be responsive to first-line anti-TNF- α therapies. The MEASURE trial evaluated cardiovascular endpoints in patients with RA who received TCZ. Despite slight elevations in LDL concentration, there were positive changes toward a more anti-inflammatory lipoprotein profile overall as early as 12 weeks after initiation; however, there was a statistically significant increase in aortic stiffness at 12 weeks, that was not sustained at 24 weeks.[82] The effect of TCZ on heart failure risk is unknown. A trial of TCZ in HIV-infected patients on ART will soon begin enrollment (NCT02049437). The study aims to test whether IL-6 receptor blockade will improve immune function by decreasing residual inflammation in this population. Inflammatory lipoproteins and endothelial function will be evaluated as secondary outcomes.

Interleukin-1 receptor antagonists

Anakinra, an IL-1 receptor antagonist, is another biologic DMARD that has great potential to decrease heart failure risk in patients with RA. Interleukin-1 (IL-1) is pro-inflammatory cytokine with significant negative effects on the vasculature, myocardial responses to ischemia, and both systolic and diastolic function[83]. Following the observation that circulating levels of IL-1 are elevated in patients with heart failure, investigators have shown improvements in aerobic capacity after IL-1 blockade in HF patients with reduced[84] and preserved EF[85] without chronic inflammatory disorders. In another small study, IL-1 blockade reduced the incidence of clinical heart failure post-MI, but did not improve measures of LV size and function[86].

In patients with RA, a single dose of anakinra improves vascular and left ventricular function and significantly decreases nitro-oxidative stress and endothelin[87]. This group has subsequently demonstrated improvements in myocardial deformation (systolic and diastolic strains)[88] that are correlated with improvements in soluble markers of apoptosis[89]. Interestingly, these changes are more prominent in those with CAD than in those without CAD[90]. There is a recent case report of dramatic clinical improvement after anakinra initiation in a patient with RA and co-morbid HF[91], but large clinical studies of the clinical benefit of anakinra to prevent incident HF are lacking.

Conclusion

Towards a comprehensive strategy of heart failure prevention for chronic inflammatory disease

Patients living with chronic inflammatory autoimmune disease or treated HIV infection are at higher risk for clinical heart failure compared to the general population, and there is an urgent need to develop effective strategies to prevent HF in such high-risk populations. The STOP-HF trial has demonstrated that a concerted multi-pronged strategy may prevent HF in the general population. How might this strategy be applied in patients with chronic inflammatory diseases? Should there be any important modifications to the approach?

First, with regard to selection of at risk patients, it is likely that BNP will be able to effectively identify RA and HIV patients who would benefit from further imaging (i.e. echocardiography, possibly with speckle-tracking strain analyses) to identify stage B HF, though the addition of one or more markers of inflammation may prove to be a useful adjunct. Secondly, in addition to proven strategies such as RAAS inhibition for treatment of hypertension, specific anti-inflammatory immune therapies could be tailored to at-risk patients. Finally, the role of lifestyle modification and interdisciplinary teams to provide prevention care should not be overlooked.

More data on risk stratification and therapy are needed, however, before such prevention strategies will be ready to be tested in clinical trials. In the meantime, rheumatologists and HIV-providers should be encouraged to develop a comprehensive approach to cardiovascular risk-prevention in their daily practice that includes consultation with cardiovascular specialists who are knowledgeable about the unique risks and management issues in these populations.

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