COLLATERAL CARDIOVASCULAR DAMAGE IN INFLAMMATORY JOINT DISEASES

Focus on cardiac dysfunction

Milad Baniaamam

Collateral cardiovascular damage in inflammatory joint diseases

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VRIJE UNIVERSITEIT

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General introduction

Chapter

1

Cardiovascular risk in inflammatory joint diseases, the role of systemic inflammation

Inflammatory joint diseases (IJD), including rheumatoid arthritis (RA), ankylosing spondylitis (AS) and systemic lupus erythematosus (SLE), are chronic (auto)immune disease systemically affecting joints and related tissue and present with extra-articular manifestations induced by systemic and progressive inflammation. RA is the most common type of IJD affecting up to 1 percent of the population and characterized by symmetrical inflammation of the joints, mainly hands and feet [1]. Differently, in AS the inflammatory target point of inflammation are the entheses and the spine [2], while SLE is a complex and heterogeneous autoimmune disease characterized by inflammatory response and immune complex deposits in organs, including joints, skin, kidney's and brain [3]. Importantly, patients with IJD have an increased mortality [4, 5] mainly of cardiovascular origin [6, 7]. The increased mortality is partly explained by the increased prevalence of cardiovascular comorbidities identified in this population. Nowadays, persistent inflammation is known to be a key mechanism in the development of cardiovascular disease [8, 9].

Models describing the role of systemic inflammation in the development of cardiovascular disease indicate an important role for circulating cytokines and oxidative stress. In the development of atherosclerosis, it is hypothesized that circulating cytokines and increased oxidative stress induce endothelial dysfunction and accelerate the development of atherosclerosis. Endothelial dysfunction is a maladaptive state with disruption of vascular homeostasis resulting from a pro-inflammatory state. By expressing adhesion molecules and inflammatory cytokines, endothelial cells amplify an inflammatory cascade facilitating monocyte infiltration in the subendothelial layer. LDL cholesterol accumulates in the subendothelial space and is oxidized, which is essential for the development of atherosclerotic plaques [10]. Furthermore, reactive oxygen species (ROS) are a group of small reactive species that play crucial roles in the regulation of biocellular processes. The balance between ROS and antioxidant species is essential to maintain cellular homoeostasis. Hence, an imbalance in oxidant and antioxidant mechanisms leads to a state of oxidative stress. In several chronic diseases, including RA, there is abundant oxidative stress [11]. Although essential for vascular homeostasis, an excess of ROS might lead to vascular injury. The latter being the result of a complex cascade, including oxidative modification of lipoproteins, endothelial activation, and leucocyte migration and differentiation resulting in acceleration of atherogenesis [10].

Cardiac disease and systemic inflammation

Both, RA and AS, are associated with cardiac dysfunction and, in severe cases, congestive heart failure (CHF) [12-14]. CHF is a cardiac disease where functional or structural disorders of the myocardium impair the ability of the cardiac ventricles to fill (diastolic dysfunction) and/or eject blood (systolic dysfunction). Two different forms of CHF are distinguished, heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF). HFpEF presents with high filling pressures due to diastolic left ventricular dysfunction (LV) leading to impaired relaxation of the left ventricle [15]. HFrEF presents with a failing cardiac pump function due to systolic LV dysfunction. Depending on the severity, clinical presentation of CHF includes dyspnea, fatigue, swollen ankles and exercise intolerance. CHF is one of the most prevalent causes of death in RA patients [13, 14]. Initially, cardiac dysfunction in RA patients was assumed to be secondary to ischaemic heart disease. However, the incidence of congestive heart failure (HFpEF and HFrEF) cannot be explained by atherosclerotic disease alone [16-19]. This also holds for AS patients, where an increased prevalence of LV diastolic dysfunction is found [12].

Accordingly, Paulus and Tschöpe proposed a hypothesis describing the role of systemic inflammation in cardiac dysfunction [20]. According to this hypothesis, systemic inflammation with elevated concentrations of circulating cytokines, such as interleukin 6 (IL-6) and tumor necrosis factor alfa (TNF), can induce oxidative stress and endothelial activation. Consequently, presentation of adhesion molecules (VCAM-1 and E-selectin) by activated endothelial cells leads to monocyte infiltration in the myocardium. These monocytes produce transforming growth factor-β (TGF-β), resulting in the differentiation of fibroblasts into myofibroblasts, with subsequent deposition of collagen in the interstitial space. In addition, oxidative stress results in disrupted crosstalk between endothelial cells and cardiomyocytes, leading to stiffness and hypertrophy of cardiomyocytes and a decreased ability to relax. These processes ultimately lead to preclinical diastolic ventricular dysfunction, which might evolve into (clinical) heart failure with preserved ejection fraction (figure 1).
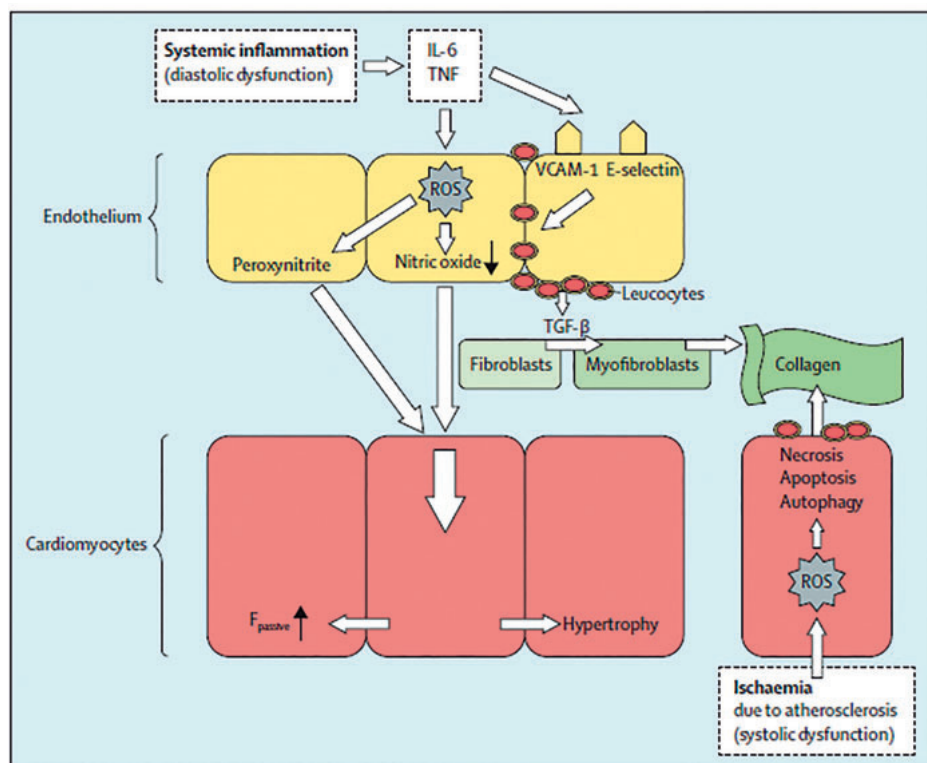
Figure 1: Shared mechanisms in the development of heart failure with preserved or reduced ejection fraction in patients with rheumatoid arthritis and gout Systemic inflammation with elevated concentrations of circulating cytokines, such as IL-6 and TNF, induce oxidative stress and endothelial activation. Consequently, presentation of adhesion molecules (VCAM-1 and E-selectin) by endothelial cells leads to monocyte infiltration in the myocardium. These monocytes produce TGF-β, resulting in the differentiation of fibroblasts into myofibroblasts, with subsequent deposition of collagen in the interstitial space. In addition, intracellular oxidative stress results in disrupted crosstalk between endothelial cells and cardiomyocytes, leading to stiffness and hypertrophy of cardiomyocytes with a subsequent decreased ability to contract and relax. These processes ultimately lead to preclinical diastolic ventricular dysfunction, which might evolve into heart failure with preserved ejection fraction. Ischaemia, mostly secondary to atherosclerosis, leads to autophagy, apoptosis, and necrosis of cardiomyocytes, and deposition of collagen in the interstitial space. This condition can give rise to systolic ventricular dysfunction, which in severe cases can lead to heart failure with reduced ejection fraction [20]. ROS=reactive oxygen species.

Specific cardiac diseases in ankylosing spondylitis

AS is also associated with other cardiac manifestations, i.e. aortic valve regurgitation (AVR) and conduction disorders, which are assumed to be due to systemic inflammation. The current hypothesis on valve involvement in AS is that collagen tissue and more specifically entheses, are the structures where inflammatory processes in AS mainly

take place [21]. Pro-inflammatory cytokines, such as interleukins 23 and 17, have an important role in this inflammatory process and IL-23 stimulates IL-17 production by Th17-cells that further amplifies this inflammation [22-24]. The relevance for cardiac involvement in AS, is that entheses and the part of the aortic valve that inserts into the aortic root are histologically similar [24]. Sherlock et al. demonstrated in mice that both, entheses and this part of the aortic root, contain IL-23 receptor positive T-cells that can induce local inflammation after systemic exposure to Il-23 [24]. In the aortic root, inflammation may cause root dilatation and the inflammation may extend to the annulus, resulting in basal thickening and downward retraction of the cusps, also resulting in AVR [25-27]. The thickening of the annulus itself could also disturb the laminar blood flow resulting in deterioration of valve function.

Important electrical conduction elements, such as the atrial-ventricular (AV) node and the bundle branches are located in very close proximity to the heart valves. In addition to the aortic root and the cusps of the aortic valve, in AS the inflammatory process therefore may extend to the atrial ventricular node (AV-node) and interventricular septum, leading to AV-blocks and bundle branch blocks (BBB's) [27].

Beyond the heart
Beyond the heart, IJD are associated with well-established cardiovascular risk factors such as hypertension, dyslipidemia, less favorable body composition and increased insulin resistance. In part this is related to decreased mobility due to pain and physical restraints and in part to use of non-steroidal anti-inflammatory drugs (NSAIDs). However, it has been shown that systemic inflammation also plays an important role in the development and sustainment of these CV risk factors. For example, systemic inflammation is associated with a more atherogenic lipid profile. A phenomenon where lower levels of total cholesterol are associated with increased CVD risk, also known as the lipid paradox [28-31]. Furthermore, studies demonstrated that RA and AS patients have increased insulin resistance that is correlated with disease activity [32-35]. In addition, systemic inflammation has been linked to less favorable body composition in IJD, whereas increased disease activity leads to increased (visceral) adipose tissue and/or decreased muscle mass [36-38].

Anti-inflammatory therapy and cardiovascular prevention
The key role of systemic and progressive inflammation in development of cardiac disease offers possibilities in CVD prevention and treatment strategies in IJD with

anti-inflammatory therapy. Mounting evidence shows anti-inflammatory therapy in IJD has an ameliorating effects on incident CVD including cardiac diseases [39-41]. Unfortunately, adequate guidelines in this field are still lacking. This is partly due to poorly designed studies and conflicting results, including studies which were not designed to answer this research question. Therefore, a knowledge gap in this field remains where yet unanswered questions should be investigated. Firstly, the question arises about the current prevalence of these cardiac diseases in Dutch RA and AS patients with the current treatment strategies. In the past decennia treatment of IJD has significantly improved by early treatment and the introduction of biologic DMARD's. Biologics, mainly available for patients in wealthy countries, revolutionized treatment and prognosis of IJD patients. The prevalence of CVD including cardiac manifestations in this group might differ in relation to past populations or socio-economic status of the countries distorting the impact of the problem in current clinical practice. Secondly, the effect of anti-inflammatory therapy on the cardiac function should be further elucidated. Thirdly, specific subgroups of IJD patients at high risk for cardiac disease should be identified where additional prevention or treatment are needed. Finally, future studies should assess the cost-effectiveness of implementation of preventive measures in order to establish sustainable guidelines for clinical practice.

Outline and aims of the thesis

This thesis aims to improve knowledge about the role of systemic inflammation in the development of cardiovascular disease and particularly cardiac dysfunction. Furthermore, to elucidate the added value of cardiac screening in this population. In **Part I** of this thesis including chapters 2-5, we focus on the role of inflammation in the development of CVD in IJD patients. **Chapter 2** describes the prevalence, pathophysiology, and guidelines for CVD in IJD, i.e. RA and gout. In **chapter 3** we reviewed the current literature on the effect of anti-inflammatory treatment, i.e. anti-TNF, on the cardiac function and the prevalence and incidence of CHF in RA. We performed echocardiography to assess the effect of anti-TNF on the cardiac function in RA patients with active disease in **chapter 4**. Part I finishes with **chapter 5** describing a case report of a SLE patient with SLE induced heart failure with preserved ejection fraction (HFpEF) where the heart failure was treated with anti-inflammatory therapy. In **part II**, we focus on the role of systemic inflammation and cardiac diseases in AS patients. In this light, in **chapter 6**, we performed a large cross-sectional study in AS patients and osteoarthritis (OA) controls, the CARDAS study, to assess the prevalence of cardiac valve disease, conduction disturbances and cardiac dysfunction in AS. In our

aim to identify a subgroup of AS patients at risk for aortic valve disease, in **chapter 7**, we performed a sub study of the CARDAS study to assess the association between HLA-B27 genotype and aortic root dilatation and aortic valve regurgitation. Finally, **part III** reports on clinical trials focusing on relation between systemic inflammation and cardiovascular disease beyond the heart. **In chapter 8**, we conducted a cross-sectional controlled study in AS patients and healthy controls to assess the difference in retinal vasculature and to assess the value of retinal screening for cardiovascular disease. Furthermore, we assessed the effect of anti-inflammatory therapy on insulin resistance and body composition in RA patients in **chapter 9**.

Table 1. Research questions

Chapter 1	General introduction
	Part I
Chapter 2	What is the role of systemic inflammation on the cardiovascular disease in inflammatory joint disease?
Chapter 3	What is the effect of anti-inflammatory treatment, i.e. biologic DMARD's, on the cardiac function and the incidence and prevalence of congestive heart failure in RA patients described in the literature?
Chapter 4	What is the effect of anti-TNF on the systolic and diastolic cardiac function in RA patients?
Chapter 5	What is the effect of anti-inflammatory treatment in SLE induced HFpEF?
	Part II
Chapter 6	What is the burden for cardiac disease in AS patients and is screening indicated? What is the prevalence of cardiac valve disease, conduction disturbances and cardiac dysfunction in AS?
Chapter 7	Is the HLA-B27 genotype associated with the aortic root dilatation in AS patients?
	Part III
Chapter 8	Does retinal screening in AS patients reveal patients at risk for cardiovascular disease? Do retinal microvascular abnormalities differ between AS patients and healthy volunteers?
Chapter 9	What is the mechanism of anti-inflammatory therapy, i.e. anti-TNF, on reducing risk for cardiovascular disease? Does anti-TNF improve insulin resistance and body composition in RA patients?
Chapter 10	Summary, general discussion and future perspectives

References

1. Alamanos Y, Drosos AA. Epidemiology of adult rheumatoid arthritis. Autoimmun Rev. 2005;4(3):130-6.
2. Zhu W, He X, Cheng K, Zhang L, Chen D, Wang X, et al. Ankylosing spondylitis: etiology, pathogenesis, and treatments. Bone Res. 2019;7:22.
3. Choi J, Kim ST, Craft J. The pathogenesis of systemic lupus erythematosus-an update. Curr Opin Immunol. 2012;24(6):651-7.
4. Dadoun S, Zeboulon-Ktorza N, Combescure C, Elhai M, Rozenberg S, Gossec L, et al. Mortality in rheumatoid arthritis over the last fifty years: systematic review and meta-analysis. Joint Bone Spine. 2013;80(1):29-33.
5. Exarchou S, Lie E, Lindstrom U, Askling J, Forsblad-d'Elia H, Turesson C, et al. Mortality in ankylosing spondylitis: results from a nationwide population-based study. Annals of the rheumatic diseases. 2016;75(8):1466-72.
6. Meune C, Touze E, Trinquart L, Allanore Y. Trends in cardiovascular mortality in patients with rheumatoid arthritis over 50 years: a systematic review and meta-analysis of cohort studies. Rheumatology (Oxford). 2009;48(10):1309-13.
7. Haroon NN, Paterson JM, Li P, Inman RD, Haroon N. Patients With Ankylosing Spondylitis Have Increased Cardiovascular and Cerebrovascular Mortality: A Population-Based Study. Annals of internal medicine. 2015;163(6):409-16.
8. Krishnan E. Inflammation, oxidative stress and lipids: the risk triad for atherosclerosis in gout. Rheumatology (Oxford). 2010;49(7):1229-38.
9. Urman A, Taklalsingh N, Sorrento C, McFarlane IM. Inflammation beyond the Joints: Rheumatoid Arthritis and Cardiovascular Disease. Scifed J Cardiol. 2018;2(3).
10. Kattoor AJ, Pothineni NVK, Palagiri D, Mehta JL. Oxidative Stress in Atherosclerosis. Curr Atheroscler Rep. 2017;19(11):42.
11. Mateen S, Moin S, Khan AQ, Zafar A, Fatima N. Increased Reactive Oxygen Species Formation and Oxidative Stress in Rheumatoid Arthritis. PLoS One. 2016;11(4):e0152925.
12. Heslinga SC, Van Dongen CJ, Konings TC, Peters MJ, Van der Horst-Bruinsma IE, Smulders YM, et al. Diastolic left ventricular dysfunction in ankylosing spondylitis--a systematic review and meta-analysis. Seminars in arthritis and rheumatism. 2014;44(1):14-9.
13. Mok CC, Kwok CL, Ho LY, Chan PT, Yip SF. Life expectancy, standardized mortality ratios, and causes of death in six rheumatic diseases in Hong Kong, China. Arthritis Rheum. 2011;63(5):1182-9.
14. Turesson C, Jarenros A, Jacobsson L. Increased incidence of cardiovascular disease in patients with rheumatoid arthritis: results from a community based study. Annals of the rheumatic diseases. 2004;63(8):952-5.
15. Chatterjee K, Massie B. Systolic and diastolic heart failure: differences and similarities. J Card Fail. 2007;13(7):569-76.

16.   Mantel A, Holmqvist M, Andersson DC, Lund LH, Askling J. Association Between Rheumatoid Arthritis and Risk of Ischemic and Nonischemic Heart Failure. J Am Coll Cardiol. 2017;69(10):1275-85.

17.   Wolfe F, Michaud K. Heart failure in rheumatoid arthritis: rates, predictors, and the effect of anti-tumor necrosis factor therapy. Am J Med. 2004;116(5):305-11.

18.   Schau T, Gottwald M, Arbach O, Seifert M, Schopp M, Neuss M, et al. Increased Prevalence of Diastolic Heart Failure in Patients with Rheumatoid Arthritis Correlates with Active Disease, but Not with Treatment Type. J Rheumatol. 2015;42(11):2029-37.

19.   Davis JM, 3rd, Lin G, Oh JK, Crowson CS, Achenbach SJ, Therneau TM, et al. Five-year changes in cardiac structure and function in patients with rheumatoid arthritis compared with the general population. Int J Cardiol. 2017;240:379-85.

20.   Paulus WJ, Tschope C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. J Am Coll Cardiol. 2013;62(4):263-71.

21.   Ball J. Enthesopathy of rheumatoid and ankylosing spondylitis. Annals of the rheumatic diseases. 1971;30(3):213-23.

22.   Lubberts E. The IL-23-IL-17 axis in inflammatory arthritis. Nature reviews Rheumatology. 2015;11(7):415-29.

23.   Sherlock JP, Buckley CD, Cua DJ. The critical role of interleukin-23 in spondyloarthropathy. Molecular immunology. 2014;57(1):38-43.

24.   Sherlock JP, Joyce-Shaikh B, Turner SP, Chao CC, Sathe M, Grein J, et al. IL-23 induces spondyloarthropathy by acting on ROR-gammat+ CD3+CD4-CD8-entheseal resident T cells. Nat Med. 2012;18(7):1069-76.

25.   Bulkley BH, Roberts WC. Ankylosing spondylitis and aortic regurgitation. Description of the characteristic cardiovascular lesion from study of eight necropsy patients. Circulation. 1973;48(5):1014-27.

26.   Davidson P, Baggenstoss AH, Slocumb CH, Daugherty GW. CARDIAC AND AORTIC LESIONS IN RHEUMATOID SPONDYLITIS. Proceedings of the staff meetings Mayo Clinic. 1963;38:427-35.

27.   Roldan CA, Chavez J, Wiest PW, Qualls CR, Crawford MH. Aortic root disease and valve disease associated with ankylosing spondylitis. J Am Coll Cardiol. 1998;32(5):1397-404.

28.   Myasoedova E, Crowson CS, Kremers HM, Roger VL, Fitz-Gibbon PD, Therneau TM, et al. Lipid paradox in rheumatoid arthritis: the impact of serum lipid measures and systemic inflammation on the risk of cardiovascular disease. Annals of the rheumatic diseases. 2011;70(3):482-7.

29.   Gonzalez-Gay MA, Gonzalez-Juanatey C. Inflammation and lipid profile in rheumatoid arthritis: bridging an apparent paradox. Annals of the rheumatic diseases. 2014;73(7):1281-3.

30. Sundstrom B, Johansson G, Johansson I, Wallberg-Jonsson S. Modifiable cardiovascular risk factors in patients with ankylosing spondylitis. Clin Rheumatol. 2014;33(1):111-7.

31. van Halm VP, van Denderen JC, Peters MJ, Twisk JW, van der Paardt M, van der Horst-Bruinsma IE, et al. Increased disease activity is associated with a deteriorated lipid profile in patients with ankylosing spondylitis. Annals of the rheumatic diseases. 2006;65(11):1473-7.

32. Svenson KL, Lundqvist G, Wide L, Hallgren R. Impaired glucose handling in active rheumatoid arthritis: effects of corticosteroids and antirheumatic treatment. Metabolism. 1987;36(10):944-8.

33. Svenson KL, Pollare T, Lithell H, Hallgren R. Impaired glucose handling in active rheumatoid arthritis: relationship to peripheral insulin resistance. Metabolism. 1988;37(2):125-30.

34. Ferraz-Amaro I, Garcia-Dopico JA, Medina-Vega L, Gonzalez-Gay MA, Diaz-Gonzalez F. Impaired beta cell function is present in nondiabetic rheumatoid arthritis patients. Arthritis Res Ther. 2013;15(1):R17.

35. Kiortsis DN, Mavridis AK, Vasakos S, Nikas SN, Drosos AA. Effects of infliximab treatment on insulin resistance in patients with rheumatoid arthritis and ankylosing spondylitis. Annals of the rheumatic diseases. 2005;64(5):765-6.

36. Wang Z, Nakayama T. Inflammation, a link between obesity and cardiovascular disease. Mediators Inflamm. 2010:Article ID 535918.

37. Briot K, Gossec L, Kolta S, Dougados M, Roux C. Prospective assessment of body weight, body composition, and bone density changes in patients with spondyloarthropathy receiving anti-tumor necrosis factor-alpha treatment. J Rheumatol. 2008;35(5):855-61.

38. Toussirot E, Mourot L, Dehecq B, Wendling D, Grandclement E, Dumoulin G, et al. TNFalpha blockade for inflammatory rheumatic diseases is associated with a significant gain in android fat mass and has varying effects on adipokines: a 2-year prospective study. Eur J Nutr. 2014;53(3):951-61.

39. Baniaamam M, Paulus WJ, Blanken AB, Nurmohamed MT. The effect of biological DMARDs on the risk of congestive heart failure in rheumatoid arthritis: a systematic review. Expert Opin Biol Ther. 2018;18(5):585-94.

40. Nurmohamed M, Bao Y, Signorovitch J, Trahey A, Mulani P, Furst DE. Longer durations of antitumour necrosis factor treatment are associated with reduced risk of cardiovascular events in patients with rheumatoid arthritis. RMD Open. 2015;1(1):e000080.

41. Lee JL, Sinnathurai P, Buchbinder R, Hill C, Lassere M, March L. Biologics and cardiovascular events in inflammatory arthritis: a prospective national cohort study. Arthritis Res Ther. 2018;20(1):171.

Part I

The role of inflammation in the development of cardiovascular disease in inflammatory joint disease patients

Cardiovascular risk in inflammatory arthritis: rheumatoid arthritis and gout

Chapter

2

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Abstract

The increased risk of cardiovascular morbidity and mortality in rheumatoid arthritis and gout has been increasingly acknowledged in past decades, with accumulating evidence that gout, just as with rheumatoid arthritis, is an independent cardiovascular risk factor. Although both diseases have a completely different pathogenesis, the underlying pathophysiological mechanisms in systemic inflammation overlap to some extent. Following the recognition that systemic inflammation has an important causative role in cardiovascular disease, anti-inflammatory therapy in both conditions and urate-lowering therapies in gout are expected to lower the cardiovascular burden of patients. Unfortunately, much of the existing data showing that urate-lowering therapy has consistent beneficial effects on cardiovascular outcomes in patients with gout are of low quality and contradictory. We will discuss the latest evidence in this respect. Cardiovascular disease risk management for patients with rheumatoid arthritis and gout is essential. Clinical guidelines and implementation of cardiovascular risk management in daily clinical practice, as well as unmet needs and areas for further investigation, will be discussed.

Introduction

Cardiovascular disease is the most frequent cause of death worldwide. The 2017 Global Burden of Disease Study showed that 17·8 million people died of cardiovascular disease globally, accounting for 21% of all deaths [1]. Well established, traditional risk factors for cardiovascular disease comprise age, sex, race, hypertension, diabetes, smoking, and hyperlipidaemia, all of which are included in various prediction models. However, over the past 20 years several non-traditional risk factors, such as chronic inflammation, have emerged as amplifiers of cardiovascular disease risk [2].

Rheumatoid arthritis is the most common autoimmune arthritis, with a prevalence of up to 1%, [2] and is characterised by a symmetrical polyarthritis with possible systemic manifestations. Rheumatoid arthritis is an accepted independent risk factor for cardiovascular disease, driven by the underlying chronic inflammatory process. However, traditional cardiovascular risk factors remain important [3].

Gout is the most common crystal-induced, autoinflammatory joint disease with a prevalence of between 0·1% and 10·0% [4]. Gout occurs when monosodium urate crystals are deposited in joints and soft tissues. Hyperuricaemia—defined by a serum urate concentration above the saturation point (ie, ⩾0·41 mmol/L [⩾6·8 mg/dL])—results predominantly from reduced renal excretion of uric acid, which is a consequence of genetics, comorbidities, and therapies. A continuum has been suggested, from asymptomatic hyperuricaemia to asymptomatic subclinical crystal deposition detectable only by ultrasound or dual-energy CT, to the clinical inflammatory state of gout flares, to chronic gouty arthritis with tophi and gouty bone erosions [5]. If not treated adequately, gout is a debilitating disease with systemic manifestations, such as monosodium urate crystal deposition in organs and worsening of cardiorenal function [6,7]. In addition to gout flares, patients with gout frequently have a high burden of cardiovascular comorbidities, which might explain, in part, the high cardiovascular mortality when compared with the general population [8]. During the past 20 years, gout has been shown to be an independent cardiovascular risk factor, with higher cardiovascular mortality than in the general population [9].

In this Review, we will discuss epidemiological data on cardiovascular disease in rheumatoid arthritis and gout, not only for atherosclerotic disease but also for venous thrombotic disease and heart failure, as clinical and subclinical prevalence of the two

diseases is higher than previously thought. The underlying pathophysiology of increased cardiovascular risk relevant to inflammatory arthritis, as well as the observed effect of anti-inflammatory and disease modifying treatments such as urate-lowering therapies in gout, will be reviewed and discussed. Increased cardiovascular risk in patients with inflammatory arthritis necessitates cardiovascular risk assessment and current management guidelines and their practical implications will be discussed. Finally, we consider topics that need further research with the aim to decrease the cardiovascular burden of patients.

Epidemiology

Rheumatoid arthritis

Patients with rheumatoid arthritis have up to a two-times higher risk of developing atherosclerotic cardiovascular disease than the general population, similar to patients with diabetes [10]. The risk of ischaemic heart disease is increased in patients with early rheumatoid arthritis and symptom duration of less than 1 year, and probably even in the subclinical stage [11]. The risk of cerebrovascular incidents is increased by about 50% (relative risk 1·48, 95% CI 0·70-3·12), whereas the risk of myocardial infarction is doubled (relative risk 2·00, 1·23-3·29) [11]. Moreover, patients with rheumatoid arthritis have almost twice the risk of developing congestive heart failure (rate ratio 1·7, 95% CI 1·3-2·1), including both heart failure with preserved ejection fraction and heart failure with reduced ejection fraction [12].

Several factors contribute to increased cardiovascular risk, including comorbidities such as diabetes, dyslipidaemia, and hypertension; [13] albeit the data for hypertension are somewhat conflicting [14]. Lipids seem to have paradoxical associations with cardiovascular risk in rheumatoid arthritis. During active disease, low total cholesterol and LDL cholesterol are associated with increased cardiovascular risk (the so-called lipid paradox) [15]. Effective antirheumatic therapies resulting in reduced disease activity of rheumatoid arthritis reverse the cholesterol reduction, thus leading to increased lipid concentrations, [16] and lipid concentrations in well controlled rheumatoid arthritis are generally stable and similar to those in the general population [11,15,17]. Furthermore, patients with rheumatoid arthritis also have more than a two-times increased risk of venous thrombotic disease compared with the general population (cumulative incidence of 6·7% [SE 1·7] vs 2·8% [1·1], p=0·005) [18].

Studies show that all-cause mortality among patients with rheumatoid arthritis was 54% higher than in the general population, primarily because of cardiovascular disease (32%), [19] with a median shortened life expectancy of 6–7 years [20]. In one study, the estimated standardised cardiovascular-mortality ratio was 1·2 (95% CI 1·05-1·43), [21] which is substantially less than reported in earlier studies. The improvement in cardiovascular mortality in patients with rheumatoid arthritis over the past 20 years could be attributed to the early initiation of more effective antirheumatic treatments (conventional synthetic and biological disease-modifying antirheumatic drugs [DMARDs]) [22]. Decreased disease activity following effective therapy is associated with a lower cardiovascular risk, and vice versa, whereas cardiovascular risk remains unchanged in patients who do not respond to biological DMARDs [23]. However, it should be noted that about 50% of increased cardiovascular disease risk in patients with rheumatoid arthritis is associated with traditional cardiovascular risk factors [24].

Gout

A large retrospective database study in the UK (8386 patients with gout vs 39 766 without gout) showed that the prevalence of hypertension in patients with gout at baseline was twice as high compared with the control group (36% vs 17%). Patients were also more often obese (60% vs 44%) and hyperlipidaemic (6% vs 3%) with more prevalent use of statins (34% vs 26%) [25]. A high prevalence of these traditional risk factors was also seen in the large National Health and Nutrition Examination Survey 2007–08, including 7·7 million US patients with gout. Moreover, the National Health and Nutrition Examination Survey showed that 26% of patients with gout had diabetes compared with almost 8% in the non-gout population (OR 2·36, 95% CI 1·5-3·7) [26].

In a large retrospective Dutch cohort of primary care patients with gout, 796 (30%) of 2655 patients already had established cardiovascular disease at cohort entry compared with 1557 (20%) of 7891 in the non-gout control group. After 3 years of follow-up, 154 (8%) of 1859 patients with gout had developed cardiovascular disease, compared with 318 (5%) of 6334 in the non-gout control group [13]. There was an even higher incidence of cardiovascular disease (47%) in patients managed by rheumatologists, possibly explained by a higher portion of severe gout seen in this setting [8].

Gout is an independent risk factor for cardiovascular disease; however, the strength of the association of hyperuricaemia and gout with other traditional cardiovascular risk factors makes distinguishing the isolated influence of gout on that risk difficult

[27]. Although atherosclerotic disease, hypertension, and chronic kidney disease are associated with elevated serum urate concentrations, the causal relationship and direction of association between urate and these disorders is still under debate [28]. An increase in serum urate concentration leads to an increased risk of hypertension (odds ratio [OR] 1·16 per 0·06 mmol/L increase [1 mg/dL increase], 95% CI 1·07-1·24) and increased LDL cholesterol (men: OR 1·16 per 0·06 mmol/L increase [1 mg/dL increase], 1·01-1·33; women: OR 1·22 per 0·06 mmol/L increase [1 mg/dL increase], 1·06-1·39) [29,30].

In the past decade, several observational studies have suggested an association between hyperuricaemia, gout, and congestive heart failure. A cross-sectional study of 15 722 patients in the USA found the prevalence of congestive heart failure to be 10% in patients with gout versus 2% in patients without gout [31]. Another study in patients with coronary artery disease showed that patients with gout had a higher prevalence of congestive heart failure (500 [36%] of 1406) than those without gout (3847 [25%] of 15 795) [32]. Furthermore, individuals with asymptomatic hyperuricaemia already have an increased risk of congestive heart failure, [33,34] and there appears to be a linear relationship with serum urate concentrations.

Gout increases the risk of mortality from cardiovascular disease (hazard ratio [HR] 1·29, 95% CI 1·14-1·44) [35]. During a mean follow-up of 4 years among 706 patients with gout, [38] (59%) of 64 deaths had a cardiovascular attribution [36]. Looking for trends and possible improvement of cardiovascular mortality in gout, analysis of a medical record database representative of the UK compared cumulative mortality rates of individuals with gout versus non-gout between 1999–2006 and 2007–2014. The investigators found that the high mortality in patients with gout remained unchanged, whereas mortality rates for rheumatoid arthritis have improved over the same time period. This mortality gap might be related to suboptimal gout care (insufficient allocation of medication, insufficient treatment, and low drug adherence), as well as insufficient management of cardiovascular comorbidities. Gout specific characteristics that are associated with high cardiovascular risk are elevated serum urate concentrations (>0·55 mmol/L [>9·1 mg/dL]), longer disease duration (≥2 years), oligoarticular or polyarticular disease, and joint damage and tophi, which all reflect a more severe disease state [8].

Pathophysiology

Although rheumatoid arthritis and gout have different pathogenic stimuli (not known for rheumatoid arthritis; monosodium urate crystal deposition for gout), different immune pathways (eg, antibody-mediated in rheumatoid arthritis; interleukin [IL]-1 driven in gout flares), and in most cases different clinical presentation (more chronic symmetric synovitis in rheumatoid arthritis; mostly monoarthritic gout flares with asymptomatic periods), imaging studies have shown that in gout, subclinical inflammation and synovitis are present, even during asymptomatic periods [37]. Importantly, persistent inflammation is known to be a key mechanism in the development of cardiovascular disease [38,39]. Cardiovascular disease in patients with gout and rheumatoid arthritis can be divided into three main categories: atherosclerosis, thromboembolism, and cardiac dysfunction (figure 1). The pathophysiological mechanisms of these diseases are different. However, the inflammatory processes of gout and rheumatoid arthritis in the development of cardiovascular diseases partly overlap.

Figure 1. Rheumatoid arthritis, gout, and their shared pathophysiological mechanisms behind cardiovascular comorbidities
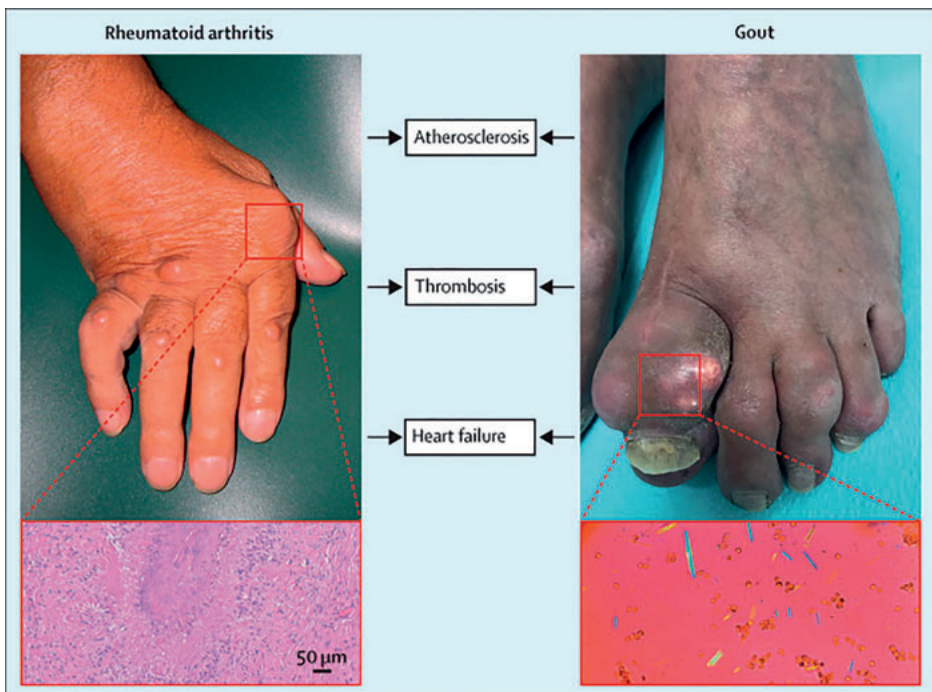
The histological image (left) shows synovitis in rheumatoid arthritis. The polarisation microscopy image (right) illustrates monosodium urate crystals in synovial fluid during a gout flare.

Atherosclerosis

Postulated shared mechanisms of rheumatoid arthritis and gout are systemic inflammation, reactive oxygen species (ROS)-induced oxidative stress, and endothelial dysfunction, all of which lead to atherosclerosis (figure 2).

Figure 2. Summary of shared mechanisms in the development of cardiovascular disease in patients with rheumatoid arthritis and gout
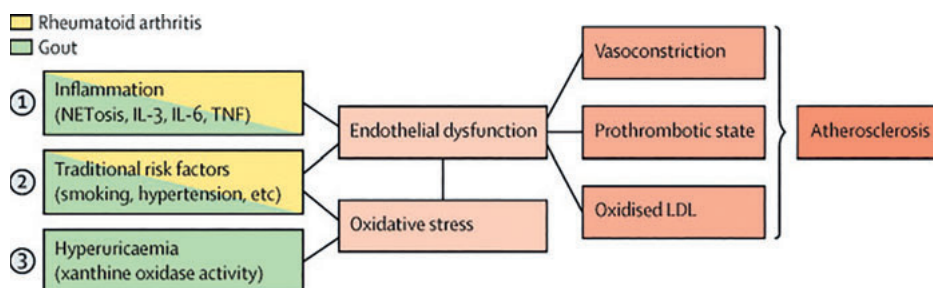
The left column describes gout and rheumatoid arthritis-related mechanisms inducing atherosclerosis. NET=neutrophil extracellular trap.

The pathways of inflammation in rheumatoid arthritis and gout share some components of the innate and adaptive immune system, including activated neutrophils. Exaggerated neutrophil activation has been linked to autoimmunity and autoinflammation in rheumatoid arthritis and gout. One of the supposed links is the formation of neutrophil extracellular traps (NETs). NETosis involves a neutrophil cell death process in which DNA is extruded, together with cytoplasmic and granular contents, to trap and eliminate extracellular pathogens and neutralise inflammatory cytokines. This process, which was first described in gout by Schauer and colleagues, [40] could explain the self-limiting character of gout flares. Extracellular DNA exerts cytotoxic and prothrombotic effects and might be a causal link between inflammation and coagulation. Moreover, complexes of presumably NET-borne DNA stimulate vascular plasmacytoid dendritic cells, with a strong interferon type 1 response, promoting atherogenesis [41]. NETs might also directly cause endothelial dysfunction by activation and induction of damage to endothelial cells, illustrated by the establishment of NETs in atherosclerotic lesions and arterial thrombi in humans [42].

In addition to neutrophils, different proinflammatory cytokines play a central role in the pathogenesis of rheumatoid arthritis and gout. In rheumatoid arthritis, the reason for immune system activation has not been completely elucidated. However, proinflammatory cytokines, such as tumour necrosis factor (TNF), IL-6, and IL-1, are important in the inflammatory process. In gout, the central inflammatory pathogenic process is assumed to be hyperuricaemia, leading to monosodium urate crystal deposition [43]. These crystals provoke a host response, resulting in recurrent gout flares by acting as a danger signal for the innate immune system through activation of the NLRP3 inflammasome with the immediate release of mature IL-1β by resident macrophages, as well the release of other cytokines [44]. The NLRP3 inflammasome has an important role in the initiation of a gout flare. Inflammasome activity causes oxidative stress, mitochondrial dysfunction, endoplasmic reticulum stress, and lysosome rupture, which are all important events in atherogenesis and could lead to atherosclerotic plaque instability and ultimately rupture [42].

ROS are a group of small reactive species that play crucial roles in the regulation of biocellular processes. The balance between ROS and antioxidant species is essential to maintain cellular homoeostasis. Hence, an imbalance in oxidant and antioxidant mechanisms leads to a state of oxidative stress. In several chronic diseases, including rheumatoid arthritis, there is abundant oxidative stress [45]. Although essential for vascular homoeostasis, an excess of ROS might lead to vascular injury. Vascular injury being the result of a complex cascade, including oxidative modification of lipoproteins, endothelial activation, and leucocyte migration and differentiation resulting in acceleration of atherogenesis [46] Oxidative stress might also link gout with cardiovascular disease. Although soluble urate has antioxidant properties, during urate generation the catalytic enzyme xanthine oxidase produces substantial amounts of ROS that affect biocellular mechanisms. There is some experimental evidence that in patients with gout, higher activity of xanthine oxidoreductase (XO) is associated with larger amounts of ROS. Indirectly, it was shown that inhibiting endothelium-bound XO resulted in reduced ROS with favourable effects on vascular function [47,48].

Endothelial dysfunction is a maladaptive state with disruption of vascular homoeostasis resulting from a proinflammatory state. By expressing adhesion molecules and inflammatory cytokines, endothelial cells amplify an inflammatory cascade facilitating monocyte infiltration in the subendothelial layer. LDL cholesterol accumulates in the subendothelial space and is oxidised, which is essential for the development of

atherosclerotic plaques [46]. Endothelial dysfunction is the earliest phenomenon in the development of atherosclerosis and was first described in rheumatoid arthritis in 2002; [49] it has been observed in patients with early rheumatoid arthritis without traditional risk factors and in those with long-standing disease. In rheumatoid arthritis, systemic inflammation with proinflammatory mediators, such as IL-1β and TNF, is assumed to play a role in the development of endothelial dysfunction, as shown in rodent models [50]. Impaired endothelium-dependent arterial responsiveness has been observed in patients with untreated gout, compared with individuals without gout, with the degree of impairment related to both serum urate and high sensitive C-reactive protein concentrations [51].

There are published case series and case reports of urate crystal deposition in the spine and solid organs in histological samples fixed with alcohol (no dissolution of crystals) [52]. A current observational study investigated alcohol-fixed specimens of coronary arteries from explanted hearts with polarisation microscopy and detected strongly birefringent urate crystals in about 10% of coronary arteries [53]. Whether or not crystal deposition in the vessels with subsequent local inflammation contributes to a higher cardiovascular risk in these patients is not known.

Venous thromboembolism
The immune system and coagulation system are linked to increased activity of the fibrinolytic system in patients with inflammatory joint diseases. Tissue factor initiates the extrinsic coagulation cascade and is found on extravascular cells, such as monocytes and neutrophils. C-reactive protein, TNF, IL-6, and complement activation might amplify tissue factor synthesis in monocytes and endothelial cells, and high concentrations of tissue factor have been found in patients with rheumatoid arthritis, particularly in those with a high disease activity [54]. Consequently, increased concentrations of coagulation factors were shown in patients with rheumatoid arthritis [54]. The role for TNF seems plausible, as in the general population this cytokine might induce an imbalance between clotting and fibrinolysis, resulting in a hypercoagulable state. Furthermore, a role for IL-6 was suggested by a randomised trial in patients with rheumatoid arthritis that showed that IL-6 receptor blockade reduced coagulation activation parameters by more than 40% compared with placebo [55]. To date, data on the role of cytokines in the development of thromboembolism in gout are not available and observational data suggests that gout is an independent risk factor for the development of deep vein thrombosis and pulmonary embolism [56]. In addition to extensive neutrophil activation in gout, increased

platelet reactivity has been detected. This finding might serve as one explanation for a prothrombotic state and association with thromboembolism in gout [57].
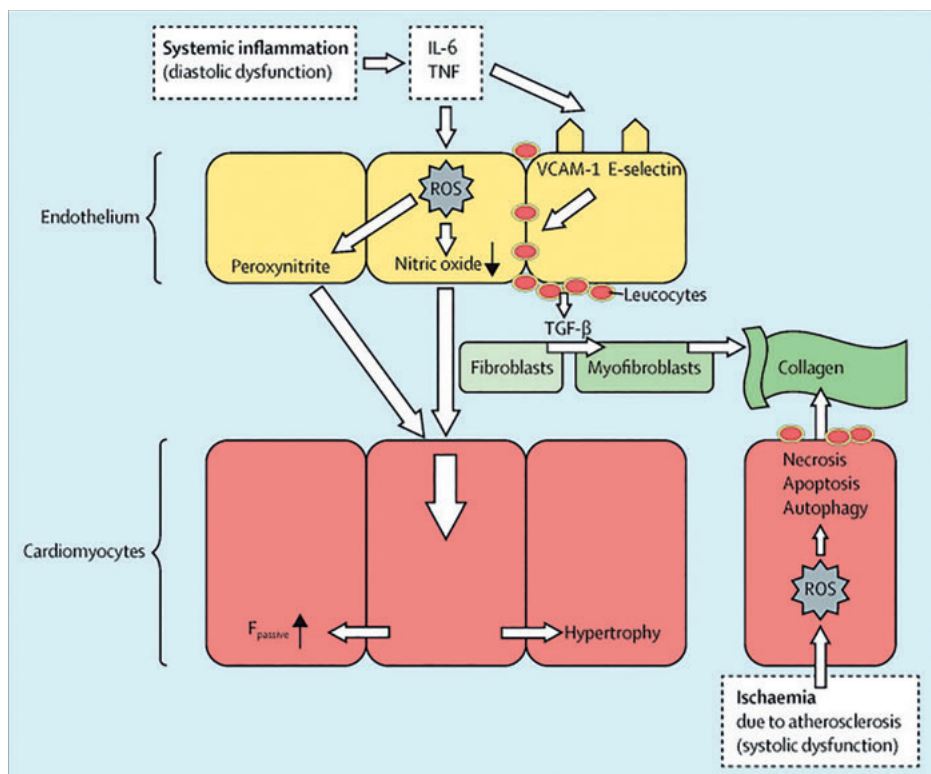
Cardiac dysfunction

Initially, cardiac dysfunction in patients with rheumatoid arthritis was assumed to be secondary to ischaemic heart disease. However, the incidence of congestive heart failure (heart failure with preserved ejection fraction and heart failure with reduced ejection fraction) cannot be explained by atherosclerotic disease alone. A case-control study showed that patients with rheumatoid arthritis had a rapidly increasing risk of developing non-ischaemic congestive heart failure after clinical onset [58]. Congestive heart failure was seen more frequently in patients with rheumatoid arthritis compared with patients with osteoarthritis (adjusted risk 3·9% [95% CI 3·4-4·3] for rheumatoid arthritis vs 2·3% [1·6-3·3] for osteoarthritis) [59]. Patients with rheumatoid arthritis treated with TNF-blocking agents had significantly less congestive heart failure than those who were not receiving anti-TNF treatment [59]. Another study found an increased prevalence of heart failure with preserved ejection fraction in patients with rheumatoid arthritis, which correlated primarily with disease activity and with anti-inflammatory treatments (ie, conventional synthetic DMARDs and biological DMARDs) [60]. In addition, patients with rheumatoid arthritis are susceptible to more rapid subclinical changes in diastolic function than are the general population [61]. Altogether, these studies suggest that systemic inflammatory activity and cardiac dysfunction cannot be attributed to atherosclerosis alone.

Chronic systemic inflammation has two distinct pathways in the development of cardiac dysfunction (figure 3). First, chronic systemic inflammation leads to myocardial remodelling, and, specifically, to diastolic dysfunction. This process starts with inflammation-induced microvascular dysfunction, [63] leading to deposition of collagen with subsequent stiffness and hypertrophy of cardiomyocytes and a decreased ability of the myocardium to contract and relax, which might evolve into heart failure with preserved ejection fraction [64]. Second, systemic inflammation and traditional cardiovascular risk factor-induced coronary microvascular dysfunction and activation lead to atherosclerosis with ischaemic heart disease. This ischaemia leads to autophagy, apoptosis and necrosis of cardiomyocytes, and collagen deposition in the interstitial space giving rise to systolic ventricular dysfunction. In severe cases, heart failure with reduced ejection fraction might develop [62]. Several studies have assessed the effect of anti-inflammatory therapy on cardiac function in rheumatoid arthritis, and a systematic

review revealed that biological DMARD therapy probably has favourable effects on cardiac dysfunction in rheumatoid arthritis [65].

Figure 3. Shared mechanisms in the development of heart failure with preserved or reduced ejection fraction in patients with rheumatoid arthritis and gout

Systemic inflammation with elevated concentrations of circulating cytokines, such as IL-6 and TNF, induce oxidative stress and endothelial activation. Consequently, presentation of adhesion molecules (VCAM-1 and E-selectin) by endothelial cells leads to monocyte infiltration in the myocardium. These monocytes produce TGF-β, resulting in the differentiation of fibroblasts into myofibroblasts, with subsequent deposition of collagen in the interstitial space. In addition, intracellular oxidative stress results in disrupted crosstalk between endothelial cells and cardiomyocytes, leading to stiffness and hypertrophy of cardiomyocytes with a subsequent decreased ability to contract and relax. These processes ultimately lead to preclinical diastolic ventricular dysfunction, which might evolve into heart failure with preserved ejection fraction. Ischaemia, mostly secondary to atherosclerosis, leads to autophagy, apoptosis, and necrosis of cardiomyocytes, and deposition of collagen in the interstitial space. This condition can give rise to systolic ventricular dysfunction, which in severe cases can lead to heart failure with reduced ejection fraction. Adapted from Paulus and Tschöpe, [62] by permission of Elsevier. ROS=reactive oxygen species.

Remarkably, the pathogenesis of cardiac dysfunction in hyperuricaemia and gout has not been adequately investigated to date [66]. Previous studies showed an association between serum urate concentration and inflammation, thus suggesting a comparable pathogenesis with rheumatoid arthritis [67]. Furthermore, increased serum urate concentration and higher activity of ROS-generating XO in gout might lead to endothelial dysfunction with decreased nitric oxide production [68]. Hypertension might also have a causal role because gout and hyperuricaemia are independent predictors of developing hypertension. One interventional study assessing urate-lowering therapy in patients with heart failure did not find significant beneficial effects of allopurinol, probably because there was already advanced structural myocardial damage and multimorbidity in the patient population [69]. Studies with early urate-lowering interventions are needed to answer the question of whether, and to what extent, urate concentration and the associated inflammation in gout constitutes an independent risk factor for cardiac dysfunction [70].

Cardiovascular effects of drug treatment

Rheumatoid arthritis
Most non-steroidal anti-inflammatory drugs (NSAIDs), including the cyclooxygenase inhibitors, are associated with about a two-times increased cardiovascular risk [71]. The exception is probably naproxen, although the published literature is conflicting in this respect [72]. Cardiovascular risk is associated with COX-2 selectivity, and the lower COX-2 selectivity of naproxen than of other NSAIDs (eg, cyclooxygenase inhibitors) is assumed to translate into a lower cardiovascular risk [73]. In clinical practice, weighing the benefits of these drugs against cardiovascular risk is often difficult. The first risk model that could aid in clinical decision making regarding the use of these drugs was published in 2019 [74]. This model was based on the Precision trial, [75] a large randomised controlled trial in which patients with osteoarthritis or rheumatoid arthritis were randomised to naproxen, ibuprofen, or celecoxib [75]. A major toxicity risk calculator was developed from easily accessible cardiovascular risk factors (ie, age, gender, diabetes, cardiovascular disease, hypertension, current smoking, statin use, serum creatinine, rheumatoid arthritis, and haematocrit) to calculate a 1-year risk score yielding three risk categories: low (<1%), intermediate (1–4%), or high risk (>4%). However, external validation is necessary before such a calculator can be implemented in daily clinical practice.

There has been a long-standing debate on whether steroids (eg, low dose of prednisolone, <10 mg daily) have unfavourable cardiovascular effects in an inflammatory situation. This effect is suggested by observational studies, but these data are confounded by indication because of high disease activity and should therefore be interpreted with caution [76]. Hopefully this debate can be settled by the Gloria trial (NCT02585258), a multicentre, 2-year trial assessing the safety and effectiveness of a daily 5 mg dose of prednisolone versus a matching placebo added to standard of care in older patients (aged ≥65 years) with rheumatoid arthritis.

One of the first studies suggesting that cardiovascular mortality risk in rheumatoid arthritis could be reduced by methotrexate was published in 2002 [77]. Of 1240 patients with rheumatoid arthritis with a mean follow-up of 6 years, 191 (15%) patients had died, 84 (44%) of which were cardiovascular deaths. Methotrexate use was associated with a 70% reduction in cardiovascular mortality (HR 0·3, 95% CI 0·2-0·7). Methotrexate also has favourable effects on non-fatal cardiovascular events, with meta-analysis showing a risk reduction of 28% in comparison with treatment without methotrexate [78]. Other conventional synthetic DMARDs, such as sulfasalazine, might also have favourable cardiovascular effects [79]. In addition to beneficial effects on the lipid profile, hydroxychloroquine has been associated with a reduction in cardiovascular events in patients with rheumatoid arthritis [80]. The recent association of high-dose hydroxychloroquine with QT prolongation in patients with COVID-19 has raised questions about the use of hydroxychloroquine in patients with rheumatoid arthritis [81]. As such, it is important to note that disease activity of rheumatoid arthritis itself is associated with QT prolongation [82]. Furthermore, there have been no published reports indicating that the use of hydroxychloquine in patients with rheumatoid arthritis is associated with an increased risk for QT prolongation. Hence, there is no indication to restrict the use of hydroxychloroquine in people with rheumatoid arthritis to require baseline electrocardiograms.

The first large-scale investigation that compared the effect of anti-TNF agents versus conventional synthetic DMARDs on cardiovascular mortality in patients with rheumatoid arthritis found an adjusted HR for death of 0·65 (95% CI 0·46−0·93) [83]. The risk of acute coronary syndrome in rheumatoid arthritis was studied in 7704 patients from a Swedish registry (32 621 patient-years) compared with the general population; [84] the HR for acute coronary syndrome was 2·0 (95% CI 1·8−2·3) for patients who were previously untreated with biologics and 1·6 (1·4−1·9) for patients using TNF inhibitors.

A meta-analysis of 28 studies with 236 525 patients with rheumatoid arthritis investigated the reduction in cardiovascular events with methotrexate and TNF inhibitors in comparison with patients previously untreated with these agents [85]. 5410 Cardiovascular events were observed and the relative risk was 0·72 (95% CI 0·57-0·91) for methotrexate and 0·70 (0·54-0·90) for TNF inhibitors. Hence, favourable cardiovascular effects might be mediated through an overall reduction in inflammation and are not drug specific.

In 2017, Janus kinase (JAK) inhibitors were suggested to be associated with an increased risk of thromboembolic disease [86] and concerns have been reported by the US Food and Drug Administration (FDA) about the safety of tofacitinib. These concerns emerged from a postmarketing trial evaluating the safety of tofacitinib at two doses (5 mg twice daily and 10 mg dose twice daily) versus a control group given a TNF inhibitor [87]. There was an increased incidence of pulmonary embolism and an increased overall mortality in patients taking 10 mg tofacitinib twice daily [88]. Subsequently, a warning was issued indicating that tofacitinib 10 mg twice daily is contraindicated in patients who have an increased thromboembolic risk. In view of these events, it is important that the prescribed dose for the treatment of rheumatoid arthritis is restricted to 5 mg twice daily. The trial programme for baricitinib, the other JAK inhibitor currently licensed for rheumatoid arthritis, identified more thromboembolic events in the 4 mg group in comparison with the placebo group, [89] and as a result the 4 mg dose was not approved in the USA. By contrast, a warning was issued in Europe, indicating that the 4 mg dose should not be used in patients with rheumatoid arthritis with an increased risk of venous thromboembolism. Further studies are needed to investigate and to differentiate between the potential adverse effect of JAK inhibitors and the hypercoagulable character of rheumatoid arthritis.

Gout
First-line treatment of gout flares is usually with an NSAID or cyclooxygenase inhibitor. The duration of treatment, in general, is short, as gout flares in the early stages of disease are often limited to a few days. Whether or not this treatment increases cardiovascular risk is not known. Furthermore, there are no data on the cumulative yearly dose of NSAID or cyclooxygenase inhibitor intake for patients with recurrent gout flares, as these drugs are often available without prescription. In advanced gout in particular, chronic use of these drugs might be relevant with respect to adverse cardiovascular effects.

Colchicine is frequently used for treatment of acute gout flares and is also given as a low-dose regimen to prevent gout flares during initiation of urate-lowering therapy. Colchicine was first used as an anti-inflammatory treatment in cardiovascular disease. A 2018 narrative review showed that colchicine has beneficial effects on atherosclerosis with plaque stabilisation, reduction of cardiovascular damage, and reduction in recurrence of acute coronary syndromes [90]. Colchicine might also have protective effects in stable coronary artery disease [91]. Two retrospective cohort studies in patients with gout showed a lower incidence of combined cardiovascular outcomes in patients treated with colchicine [92,93]. By contrast, a trial showed that short-term low-dose colchicine does not improve endothelial function in patients with coronary artery disease [94]. However, an exploratory analysis indicated that endothelial function was significantly improved in the subgroup of patients with leucocyte activation, further indicating the important role of inflammation in atherosclerosis [94]. Ongoing trials, such as the COLCOT trial (NCT02551094), will hopefully settle the debate about the efficacy of low-dose colchicine for secondary prevention in patients with coronary disease. In patients with gout, more research is needed to establish the effects of colchicine on cardiovascular risk.

Gout flares that do not respond to NSAIDs, cyclooxygenase inhibitors, or colchicine are frequently treated with steroids, either systemically or by intra-articular injection. As data on patients with gout are scarce, one can only speculate as to whether the typically short treatment duration has any unfavourable cardiovascular effects.

In 2013, the anti-IL-1β antibody canakinumab was approved by the FDA and the European Medicines Agency for gout inflammation refractory to conventional anti-inflammatory treatment [95]. A 2019 trial of the IL-1 receptor antagonist, anakinra, showed efficacy in controlling inflammation during gout flare without cardiovascular safety issues [96]. The CANTOS trial, [97] which investigated anti-inflammatory therapy with canakinumab for secondary cardiovascular prevention in patients with myocardial infarction, showed only a modest decrease in recurrent cardiovascular events (about 15%) compared with placebo, and this result was independent of lipid-lowering effects. Whether patients with gout had a cardiovascular benefit from IL-1β-blocking therapy was not answered by this trial.

In patients with diagnosed gout, urate-lowering therapy with a treat-to-target strategy to reduce serum urate below 0·36 mmol/L (6 mg/dL) is an essential therapeutic intervention

recommended by current gout guidelines [98]. The efficacy of a treat-to-target approach on regression of tophi, frequency of gout flares, and MRI-detected synovitis has been shown [99]. To reach the serum urate target, patients could be treated with urate-lowering drugs such as XO inhibitors (eg, allopurinol), uricosurics (and combination with XO inhibitors—eg, benzbromaron), or a recombinant uricase (eg, rasburicase). Urate-lowering therapy should, in theory, reduce the risk of cardiovascular disease in gout. This therapy could decrease the risk by directly lowering urate concentration or indirectly through XO inhibition, with a subsequent reduction in oxidative stress and improvements in endothelial function.

A systematic review and meta-analysis of randomised controlled trials [100] revealed that urate-lowering therapy with allopurinol, a purine XO inhibitor, lowered the incidence of major cardiovascular events (OR 0·65, 95% CI 0·41-1·05), total cardiovascular events (OR 0·57, 0·46-0·72), myocardial infarction or the need of urgent revascularisation (OR 0·38, 0·17-0·83), and new or worsening hypertension (OR 0·32, 0·18-0·58) in patients with various cardiovascular conditions versus the control group, but did not affect overall or cardiovascular mortality. These effects were not observed with non-purine-like XO inhibitors, such as febuxostat [100]. However, febuxostat lowered the composite event rate (cerebral, cardiovascular, and renal events, as well as all deaths) in patients with hyperuricaemia who were at risk of cerebral, cardiovascular, or renal disease compared with a non-febuxostat group (HR 0·75, 95% CI 0·59-0·95) [101].

In a systematic review and meta-analysis in patients with gout urate-lowering therapy with an XO inhibitor was not shown to reduce cardiovascular events compared with placebo [102]. In addition, another systematic review and meta-analysis showed that there was no significant association between all-cause mortality and allopurinol use in patients with gout, albeit the number of studies was small [103]. Finally, a trial of nurse-led gout care in a primary care setting consisting of extensive patient education and involvement, as well as a treat-to-target strategy, was shown to be superior in reaching a serum urate concentration of less than 0·36 mmol/L (6 mg/dL) compared with standard care (95% vs 30%, risk ratio 3·18, 95% CI 2·42-4·18, p<0·0001) [104]. Fewer deaths were observed in the nurse-led care group, but numbers were too small to draw firm conclusions. To date, data regarding the effect of uricosurics or uricase treatment on cardiovascular risk in gout are absent. In general, available evidence is not sufficient to draw definite conclusions and further studies are needed.

In 2019, the FDA issued a public safety alert with a warning of increased risk of death with febuxostat compared with allopurinol [105]. This warning was based on results from the CARES trial. Although febuxostat was shown to be non-inferior to allopurinol for the primary outcome (a composite of death and major cardiovascular events; HR 1·03, upper limit of the one-sided 98·5% CI 1·23, p=0·002 for non-inferiority), the incidence of secondary outcome measures, including death from any cause (HR 1·22, 95% CI 1·01-1·47) and cardiovascular death (HR 1·34, 1·03-1·73), was significantly higher with febuxostat than with allopurinol [106]. Definite conclusions from this trial are difficult to draw: first, no significant difference was observed in the primary outcome of the trial, second, there was a very high rate of discontinuation of therapy, with the majority of deaths occurring after stopping the drug, and finally, a control group without a XO inhibitor was absent [106]. The FDA therefore first mandated febuxostat not to be used in patients with cardiovascular disease but thereafter restricted the approved use to patients who could not be treated effectively or had severe side-effects with allopurinol. Important data will come from the FAST trial, comparing the cardiovascular safety of allopurinol and febuxostat in the management of symptomatic hyperuricaemia (EUDRACT number: 2011–001883–23, ISRCTN72443728).

Management of cardiovascular risk

The recognition of an increased cardiovascular disease risk in arthritis prompted the European League Against Rheumatism (EULAR) to set out evidence-based recommendations for the management of cardiovascular disease risk in inflammatory arthritis, and these guidelines were updated in 2017 [107]. Rheumatoid arthritis is also now accepted as an independent cardiovascular disease risk factor by the European Society of Cardiology guidelines [108]. To reduce the risk of cardiovascular disease in patients with rheumatoid arthritis, optimal disease control is necessary, and cardiovascular disease management should be the responsibility of the rheumatologist. Risk assessment should be done at least once every 5 years, and should be reassessed following major changes in DMARD therapy. Cardiovascular risk management is also important for patients with gout, since gout is associated with a high rate of traditional cardiovascular risk factors and is also considered an independent risk factor for cardiovascular disease and associated mortality. In the 2016 update of EULAR's evidence-based recommendations for the management of gout, two overarching principles were that every patient with gout should receive advice regarding lifestyle

and that they should be screened for cardiovascular comorbidities and cardiovascular risk factors. However, no specific recommendations for cardiovascular risk management were given [109]. This omission was one of the main reasons for the assembly of a EULAR taskforce to develop recommendations for the management of atherosclerotic cardiovascular risk in rheumatic and musculoskeletal diseases, including systemic lupus erythematosus, antiphospholipid syndrome, vasculitis, and gout [110].

Cardiovascular risk prediction models

In Europe, the Systematic Coronary Risk Evaluation calculator is used for cardiovascular disease risk prediction. This model estimates the 10-year risk of cardiovascular mortality and includes age, gender, smoking status, total cholesterol to HDL cholesterol ratio, and systolic blood pressure. However, Systematic Coronary Risk Evaluation was developed solely for the general population and therefore underestimates the cardiovascular risk in patients with rheumatoid arthritis. To correct for this underestimation, EULAR recommends use of a multiplication factor of 1·5 [107]. Importantly, EULAR advises screening for cardiovascular disease risk in all patients with inflammatory arthritis and states that the rheumatologist is responsible for its initiation. Subsequently, several prediction models for cardiovascular disease risk, such as QRISK3, have incorporated rheumatoid arthritis in their risk model [111]. The Expanded Risk Score in rheumatoid arthritis is derived from the CORRONA registry and includes rheumatoid arthritis specific features (laboratory data are not needed) [74]. This risk score appears to perform as well as QRISK3 [112]. The The table shows the characteristics of these algorithms. Thus far, no gout-specific cardiovascular risk scores have been developed, probably because of an absence of consistent data on cardiovascular outcomes.

Table				
Characteristics of different cardiovascular prediction models				
	Age (years)	**Prediction**	**Risk factors and variables**	**Comments**
Systematic Coronary Risk Evaluation	40–70	10-year risk for cardiovascular mortality	Age, gender, smoking habits, total cholesterol to HDL cholesterol ratio, systolic blood pressure	Multiplication by 1·5 to correct for underestimation
QRISK3	24–80	10-year risk for cardiovascular morbidity	Established risk factors and additional factors, such as the stage of chronic kidney disease (assessed in 5 grades), a measure of systolic blood pressure variability, migraine, corticosteroids, systemic lupus erythematosus, atypical antipsychotics, severe mental illness, HIV/AIDS), and erectile dysfunction in men	Helps identifying patients with highest cardiovascular risk
Expanded Risk Score in rheumatoid arthritis	All	10-year risk for cardiovascular morbidity	Rheumatoid arthritis specific factors: disease duration, disease activity, disability, and use of corticosteroids	Laboratory data are not needed; internally validated in the CORRONA registry; [74] not yet externally validated

Antihypertensive agents and statins in rheumatoid arthritis and gout

Statins reduce cholesterol concentrations and cardiovascular disease in patients with rheumatoid arthritis to a similar extent as in the general population. Furthermore, statins are not associated with more adverse events in comparison to the general population. The TRACE RA study compared the effect of 40 mg atorvastatin with placebo in patients with rheumatoid arthritis and found a significant reduction in LDL cholesterol in the atorvastatin group [113]. In this group, LDL concentrations were similar to those observed in the general population. A risk reduction of 34% in major cardiovascular events compared with placebo was observed, although this difference

did not reach statistical significance possibly due to a lower than expected event rate. Furthermore, statins have anti-inflammatory properties that might translate into further reductions in cardiovascular disease risk as well as a modest reduction in rheumatic disease. A meta-analysis has shown the pleiotropic effects of statins, with a decline in inflammation markers (oestrogen receptor, C-reactive protein), pro-inflammatory cytokines (TNF, IL-1, and IL-6), and fewer tender and swollen joints [114].

The EULAR recommendations for gout advise systematic screening and care in terms of cardiovascular diseases and risk factors [98]. This strategy can be complicated because many drugs targeting comorbidities can aggravate hyperuricaemia and gout by lowering renal excretion of uric acid—eg, antihypertensive drugs such as β blockers, non-losartan angiotensin 2 receptor blockers, thiazides, and loop diuretics [115]. This is also true for low-dose aspirin, but as the effect is very modest, use of low-dose aspirin for cardioprotective reasons should not be precluded in high-risk patients with gout [116]. Statins (atorvastatin and simvastatin), and also fenofibrate, have urate-lowering effects by increasing renal-urate excretion [117, 118]. Importantly, initiation of statins lowers the risk of all-cause mortality in gout, and might have greater benefits amongst those without previous circulatory disease [119].

Lifestyle
The effects of dietary measures in rheumatoid arthritis are still uncertain because of an absence of adequately powered studies. Observational studies show that diet, exercise, and stress are associated with outcomes such as inflammation or disease activity. Therefore, EULAR recommends a general healthy lifestyle for all patients with rheumatoid arthritis, defined as a healthy diet (Mediterranean), regular exercise, and smoking cessation. Exercise improves cardiorespiratory fitness and decreases cardiovascular risk in patients with rheumatoid arthritis [120].

There is low-to-moderate quality evidence for beneficial effects of weight loss with respect to lowering serum uric acid, achieving serum uric acid targets, and preventing flares in patients with gout [121]. The EULAR guideline recommends that patients with gout receive advice regarding lifestyle that includes avoidance of alcohol and sugar sweetened drinks, and discourages excessive intake of meat and seafood (purine-low diet). In addition to purines, the intake of fructose is also associated with an increase in uric acid production and should be avoided.

Guidance on smoking cessation is similar to the general population as smoking has multiple adverse effects, such as increasing the risk of cardiovascular disease, respiratory disease, and cancer. Smoking also seems to have a pathogenic role in rheumatoid arthritis, promoting disease activity and reducing response to antirheumatic therapy. In contrast to rheumatoid arthritis, a relationship between smoking and the development of gout has not been found [122].

Cardiovascular risk management in daily clinical practice
Many studies have indicated poor adherence to cardiovascular disease risk, management in rheumatoid arthritis. For example, in a cross-sectional study 282 (71%) of 400 patients with rheumatoid arthritis had hypertension, of which 171 (61%) were treated with antihypertensive medications. Moreover, despite treatment, many of these patients had suboptimal blood pressure [123]. Also, hypercholesterolaemia is underdiagnosed and undertreated in patients with rheumatoid arthritis [124].

Notwithstanding guidelines for the implementation of cardiovascular risk, management in clinical practice is often difficult [125]. Nevertheless, successful implementation of cardiovascular disease risk management was shown in a Dutch programme for cardiovascular disease care [126]. This programme included a collaboration between primary care and secondary care professionals with a shared laboratory system for primary care physicians and rheumatologists, in which primary care physicians received reimbursement for additional costs from health-care insurance companies. Lipid screening (as a proxy for cardiovascular disease risk management) was done in 454 (72%) of 600 patients with rheumatoid arthritis and increased to almost 90% after primary care physicians were sent reminder letters. Implementation of cardiovascular risk management for patients with gout has not been systematically studied and to what extent it has been applied in either primary or secondary care is unknown.

Research agenda
Unfortunately, despite several guidelines for cardiovascular disease risk management, implementation in daily clinical practice is still poor. A study in the UK confirmed this in a group of 673 patients with gout in primary care. Monitoring of lipids (34 [5%]), blood pressure (178 [26%]), and glucose (43 [6%]) within 1 month after their first gout consultation was infrequently recorded [127]. This finding indicates the urgent unmet need for optimisation of cardiovascular risk management in these patients. At the same time, we should not forget that patients often also have other comorbid

conditions. Optimal preventive treatment requires attention to these comorbidities, which are commonly seen in inflammatory arthritis and include osteoporosis, fatigue, and depression. The rationale is that the underlying mechanisms of these common comorbidities, particularly in rheumatoid arthritis, overlap. In our view, such a multimorbidity, holistic approach is the optimal way to achieve substantial improvement in the quality of life of these patients. Lastly, further randomised controlled trials with cardiovascular endpoints are needed, especially in gout, to ascertain optimal serum urate concentrations to improve the cardiovascular-risk profile. Another relevant question is whether early urate-lowering therapy—in case of asymptomatic hyperuricaemia and evidence of crystal deposition by ultrasound or dual-energy CT—has favourable cardiovascular effects, as shown for early treatment intervention in patients with rheumatoid arthritis.

Conclusions and future research

Rheumatoid arthritis and gout—two inflammatory joint diseases with different underlying causes—are associated with about a 50–70% increased risk of cardiovascular disease compared with the general population. These patients not only have inflammation of joints but also experience systemic effects, including cardiovascular and haematological manifestations. Different underlying pathophysiological mechanisms, such as systemic inflammation, elevated oxidative stress, endothelial dysfunction, and changes in lipid profiles, might contribute to a substantially higher cardiovascular risk in these patients. The increased cardiovascular risk includes not only a higher rate of ischaemic cardiovascular disease but also subclinical heart failure, which seems far more prevalent than previously thought. Early therapeutic intervention with current antirheumatic treatment in rheumatoid arthritis has shown favourable effects on cardiovascular disease risk. Unfortunately, in gout, evidence that urate-lowering therapy has consistent beneficial effects on cardiovascular outcomes is still scarce. Following the recognition that inflammation has an important causative role for cardiovascular risk in gout, anti-inflammatory therapy and urate-lowering therapies are expected to reduce the cardiovascular burden of these patients. Therefore, optimal anti-inflammatory control of patients with rheumatoid arthritis and effective urate-lowering therapy in patients with gout are the main treatment goals to date. In addition to adequate control of disease activity, attention of the treating physician should be given to the treatment of concomitant cardiovascular diseases and management of risk factors—eg, adequate

control of hypertension and dislipidaemia. For individual cardiovascular risk estimation in patients with rheumatoid arthritis and gout, the use of established cardiovascular risk scores (eg, Systematic Coronary Risk Evaluation) could be implemented in daily assessments. The inclusion of a multiplication factor for gout in cardiovascular risk scores, as already accepted for rheumatoid arthritis, should be considered.

Search strategy and selection criteria

We followed the main steps in writing a narrative review, and MTN formulated cardiovascular research questions addressing epidemiological and pathophysiological aspects of rheumatoid arthritis and gout, cardiovascular effects of drug treatment, and management of cardiovascular risk. References for this Review were identified through searches of PubMed with the terms "rheumatoid arthritis", "gout", "hyperuricemia", "gouty", "arthritis, "gouty", "atherosclerosis", "cardiovascular disease", "cardiovascular event", "myocardial ischemia", "cerebrovascular disease", "stroke", "angina pectoris", "coronary disease", "coronary artery disease", "coronary arterial disease", "peripheral artery disease", "peripheral arterial disease", "congestive heart failure", "cardiac dysfunction", and "cardiovascular risk management" from Jan 1, 1998, to April 1, 2019. Articles were also identified through searches of the authors' own files. Only papers published in English were reviewed. The final reference list was generated on the basis of originality and relevance to the broad scope of this Review.

References

1. GBD 2017 Causes of Death Collaborators Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018;392:1736–1788.

2. van der Woude D, van der Helm-van Mil AHM. Update on the epidemiology, risk factors, and disease outcomes of rheumatoid arthritis. Best Pract Res Clin Rheumatol. 2018;32:174–187.

3. Liao KP. Cardiovascular disease in patients with rheumatoid arthritis. Trends Cardiovasc Med. 2017;27:136–140.

4. Kuo CF, Grainge MJ, Zhang W, Doherty M. Global epidemiology of gout: prevalence, incidence and risk factors. Nat Rev Rheumatol. 2015;11:649–662.

5. Dalbeth N, Stamp L. Hyperuricaemia and gout: time for a new staging system? Ann Rheum Dis. 2014;73:1598–1600.

6. Tausche AK, Manger B, Müller-Ladner U, Schmidt B. Gout as a systemic disease. Manifestations, complications and comorbidities of hyperuricaemia. Z Rheumatol. 2012;71:224-230.

7. Bursill D, Taylor WJ, Terkeltaub R. Gout, Hyperuricaemia and Crystal-Associated Disease Network (G-CAN) consensus statement regarding labels and definitions of disease states of gout. Ann Rheum Dis. 2019;78:1592–1600.

8. Disveld IJM, Fransen J, Rongen GA. Crystal-proven gout and characteristic gout severity factors are associated with cardiovascular disease. J Rheumatol. 2018;45:858–863.

9. Lottmann K, Chen X, Schädlich PK. Association between gout and all-cause as well as cardiovascular mortality: a systematic review. Curr Rheumatol Rep. 2012;14:195–203.

10. van Halm VP, Peters MJ, Voskuyl AE. Rheumatoid arthritis versus diabetes as a risk factor for cardiovascular disease: a cross-sectional study, the CARRE Investigation. Ann Rheum Dis. 2009;68:1395–1400.

11. Solomon DH, Karlson EW, Rimm EB. Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis. Circulation. 2003;107:1303–1307.

12. Nicola PJ, Maradit-Kremers H, Roger VL. The risk of congestive heart failure in rheumatoid arthritis: a population-based study over 46 years. Arthritis Rheum. 2005;52:412–420.

13. Janssens HJ, Arts PG, Schalk BW, Biermans MC. Gout and rheumatoid arthritis, both to keep in mind in cardiovascular risk management: a primary care retrospective cohort study. Joint Bone Spine. 2017;84:59–64.

14. Panoulas VF, Metsios GS, Pace AV. Hypertension in rheumatoid arthritis. Rheumatology (Oxford) 2008;47:1286–1298.

15. Robertson J, Peters MJ, McInnes IB, Sattar N. Changes in lipid levels with inflammation and therapy in RA: a maturing paradigm. Nat Rev Rheumatol. 2013;9:513–523.

16. 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;70:482–487.

17. Boers M, Nurmohamed MT, Doelman CJ. Influence of glucocorticoids and disease activity on total and high density lipoprotein cholesterol in patients with rheumatoid arthritis. Ann Rheum Dis. 2003;62:842–845.

18. Bacani AK, Gabriel SE, Crowson CS, Heit JA, Matteson EL. Noncardiac vascular disease in rheumatoid arthritis: increase in venous thromboembolic events? Arthritis Rheum. 2012;64:53–61.

19. van den Hoek J, Boshuizen HC, Roorda LD. Mortality in patients with rheumatoid arthritis: a 15-year prospective cohort study. Rheumatol Int. 2017;37:487–493.

20. Lassere MN, Rappo J, Portek IJ, Sturgess A, Edmonds JP. How many life years are lost in patients with rheumatoid arthritis? Secular cause-specific and all-cause mortality in rheumatoid arthritis, and their predictors in a long-term Australian cohort study. Intern Med J. 2013;43:66–72.

21. van den Hoek J, Roorda LD, Boshuizen HC. Trend in and predictors for cardiovascular mortality in patients with rheumatoid arthritis over a period of 15 years: a prospective cohort study. Clin Exp Rheumatol. 2016;34:813–819.

22. Myasoedova E, Gabriel SE, Matteson EL, Davis JM, 3rd, Therneau TM, Crowson CS. Decreased cardiovascular mortality in patients with incident rheumatoid arthritis (RA) in recent years: dawn of a new era in cardiovascular disease in RA? J Rheumatol. 2017;44:732–739.

23. Dixon WG, Watson KD, Lunt M, Hyrich KL, Silman AJ, Symmons DP. Reduction in the incidence of myocardial infarction in patients with rheumatoid arthritis who respond to anti-tumor necrosis factor alpha therapy: results from the British Society for Rheumatology Biologics Register. Arthritis Rheum. 2007;56:2905–2912.

24. Crowson CS, Rollefstad S, Ikdahl E. Impact of risk factors associated with cardiovascular outcomes in patients with rheumatoid arthritis. Ann Rheum Dis. 2018;77:48–54.

25. Clarson LE, Hider SL, Belcher J, Heneghan C, Roddy E, Mallen CD. Increased risk of vascular disease associated with gout: a retrospective, matched cohort study in the UK clinical practice research datalink. Ann Rheum Dis. 2015;74:642–647.

26. Zhu Y, Pandya BJ, Choi HK. Comorbidities of gout and hyperuricemia in the US general population: NHANES 2007–2008. Am J Med. 2012;125:679–687.

27. Kleber ME, Delgado G, Grammer TB. Uric acid and cardiovascular events: a mendelian randomization study. J Am Soc Nephrol. 2015;26:2831–2838.

28. Jordan DM, Choi HK, Verbanck M. No causal effects of serum urate levels on the risk of chronic kidney disease: a mendelian randomization study. PLoS Med. 2019;16

29. Kuwabara M, Hisatome I, Niwa K. Uric acid is a strong risk marker for developing hypertension from prehypertension: a 5-year Japanese cohort study. Hypertension. 2018;71:78–86.

30. Kuwabara M, Borghi C, Cicero AFG. Elevated serum uric acid increases risks for developing high LDL cholesterol and hypertriglyceridemia: a five-year cohort study in Japan. Int J Cardiol. 2018;261:183–188.

31. Stack AG, Hanley A, Casserly LF. Independent and conjoint associations of gout and hyperuricaemia with total and cardiovascular mortality. QJM. 2013;106:647–658.

32. Pagidipati NJ, Clare RM, Keenan RT, Chiswell K, Roe MT, Hess CN. Association of gout with long-term cardiovascular outcomes among patients with obstructive coronary artery disease. J Am Heart Assoc. 2018;7

33. Huang H, Huang B, Li Y. Uric acid and risk of heart failure: a systematic review and meta-analysis. Eur J Heart Fail. 2014;16:15–24.

34. Krishnan E. Gout and the risk for incident heart failure and systolic dysfunction. BMJ Open. 2012;2

35. Clarson LE, Chandratre P, Hider SL. Increased cardiovascular mortality associated with gout: a systematic review and meta-analysis. Eur J Prev Cardiol. 2015;22:335–343.

36. Perez-Ruiz F, Martínez-Indart L, Carmona L, Herrero-Beites AM, Pijoan JI, Krishnan E. Tophaceous gout and high level of hyperuricaemia are both associated with increased risk of mortality in patients with gout. Ann Rheum Dis. 2014;73:177–182.

37. Chowalloor P, Raymond WD, Cheah P, Keen H. The burden of subclinical intra-articular inflammation in gout. Int J Rheum Dis. 2020;23:661–668.

38. Krishnan E. Inflammation, oxidative stress and lipids: the risk triad for atherosclerosis in gout. Rheumatology (Oxford) 2010;49:1229–1238.

39. Urman A, Taklalsingh N, Sorrento C, McFarlane IM. Inflammation beyond the joints: rheumatoid arthritis and cardiovascular disease. Scifed J Cardiol. 2018;2

40. Schauer C, Janko C, Munoz LE. Aggregated neutrophil extracellular traps limit inflammation by degrading cytokines and chemokines. Nat Med. 2014;20:511–517.

41. Döring Y, Soehnlein O, Weber C. Neutrophil extracellular traps in atherosclerosis and atherothrombosis. Circ Res. 2017;120:736–743.

42. Megens RT, Vijayan S, Lievens D. Presence of luminal neutrophil extracellular traps in atherosclerosis. Thromb Haemost. 2012;107:597–598.

43. Chatfield SM, Grebe K, Whitehead LW. Monosodium urate crystals generate nuclease-resistant neutrophil extracellular traps via a distinct molecular pathway. J Immunol. 2018;200:1802–1816.

44. Kienhorst LB, van Lochem E, Kievit W. Gout is a chronic inflammatory disease in which high levels of interleukin-8 (CXCL8), myeloid-related protein 8/myeloid-related protein 14 complex, and an altered proteome are associated with diabetes mellitus and cardiovascular disease. Arthritis Rheumatol. 2015;67:3303–3313.

45. Mateen S, Moin S, Khan AQ, Zafar A, Fatima N. Increased reactive oxygen species formation and oxidative stress in rheumatoid arthritis. PLoS One. 2016;11

46. Kattoor AJ, Pothineni NVK, Palagiri D, Mehta JL. Oxidative stress in atherosclerosis. Curr Atheroscler Rep. 2017;19:42.

47. Dai Y, Cao Y, Zhang Z, Vallurupalli S, Mehta JL. Xanthine oxidase induces foam cell formation through LOX-1 and NLRP3 activation. Cardiovasc Drugs Ther. 2017;31:19–27.

48. Zamudio-Cuevas Y, Martínez-Flores K, Fernández-Torres J. Monosodium urate crystals induce oxidative stress in human synoviocytes. Arthritis Res Ther. 2016;18:117.

49. Bergholm R, Leirisalo-Repo M, Vehkavaara S, Mäkimattila S, Taskinen MR, Yki-Järvinen H. Impaired responsiveness to NO in newly diagnosed patients with rheumatoid arthritis. Arterioscler Thromb Vasc Biol. 2002;22:1637–1641.

50. Totoson P, Maguin-Gaté K, Nappey M, Wendling D, Demougeot C. Endothelial dysfunction in rheumatoid arthritis: mechanistic insights and correlation with circulating markers of systemic inflammation. PLoS One. 2016;11

51. Krasnokutsky S, Romero AG, Bang D. Impaired arterial responsiveness in untreated gout patients compared with healthy non-gout controls: association with serum urate and C-reactive protein. Clin Rheumatol. 2018;37:1903–1911.

52. Towiwat P, Chhana A, Dalbeth N. The anatomical pathology of gout: a systematic literature review. BMC Musculoskelet Disord. 2019;20:140.

53. Park JJ, Roudier MP, Soman D, Mokadam NA, Simkin PA. Prevalence of birefringent crystals in cardiac and prostatic tissues, an observational study. BMJ Open. 2014;4

54. van den Oever IA, Sattar N, Nurmohamed MT. Thromboembolic and cardiovascular risk in rheumatoid arthritis: role of the haemostatic system. Ann Rheum Dis. 2014;73:954–957.

55. McInnes IB, Thompson L, Giles JT. Effect of interleukin-6 receptor blockade on surrogates of vascular risk in rheumatoid arthritis: MEASURE, a randomised, placebo-controlled study. Ann Rheum Dis. 2015;74:694–702.

56. Li L, McCormick N, Sayre EC. Trends of venous thromboembolism risk before and after diagnosis of gout: a general population-based study. Rheumatology (Oxford) 2020;59:1099–1107.

57. Conway R, Murphy CL, Madigan A. Increased platelet reactivity as measured by plasma glycoprotein VI in gout. Platelets. 2018;29:821–826.

58. Mantel Ä, Holmqvist M, Andersson DC, Lund LH, Askling J. Association between rheumatoid arthritis and risk of ischemic and nonischemic heart failure. J Am Coll Cardiol. 2017;69:1275–1285.

59. Wolfe F, Michaud K. Heart failure in rheumatoid arthritis: rates, predictors, and the effect of anti-tumor necrosis factor therapy. Am J Med. 2004;116:305–311.

60. Schau T, Gottwald M, Arbach O. Increased prevalence of diastolic heart failure in patients with rheumatoid arthritis correlates with active disease, but not with treatment type. J Rheumatol. 2015;42:2029–2037.

61. Davis JM, 3rd, Lin G, Oh JK. Five-year changes in cardiac structure and function in patients with rheumatoid arthritis compared with the general population. Int J Cardiol. 2017;240:379–385.

62. Paulus WJ, Tschöpe C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. J Am Coll Cardiol. 2013;62:263–271.

63. Mygind ND, Michelsen MM, Pena A. Coronary microvascular function and cardiovascular risk factors in women with angina pectoris and no obstructive coronary artery disease: the iPOWER study. J Am Heart Assoc. 2016;5

64. Westermann D, Lindner D, Kasner M. Cardiac inflammation contributes to changes in the extracellular matrix in patients with heart failure and normal ejection fraction. Circ Heart Fail. 2011;4:44–52.

65. Baniaamam M, Paulus WJ, Blanken AB, Nurmohamed MT. The effect of biological DMARDs on the risk of congestive heart failure in rheumatoid arthritis: a systematic review. Expert Opin Biol Ther. 2018;18:585–594.

66. Bardin T, Richette P. Impact of comorbidities on gout and hyperuricaemia: an update on prevalence and treatment options. BMC Med. 2017;15:123.

67. Leyva F, Anker SD, Godsland IF. Uric acid in chronic heart failure: a marker of chronic inflammation. Eur Heart J. 1998;19:1814–1822.

68. Kang DH, Park SK, Lee IK, Johnson RJ. Uric acid-induced C-reactive protein expression: implication on cell proliferation and nitric oxide production of human vascular cells. J Am Soc Nephrol. 2005;16:3553–3562.

69. Givertz MM, Anstrom KJ, Redfield MM. Effects of xanthine oxidase inhibition in hyperuricemic heart failure patients: the Xanthine Oxidase Inhibition for Hyperuricemic Heart Failure Patients (EXACT-HF) study. Circulation. 2015;131:1763–1771.

70. Pontremoli R. The role of urate-lowering treatment on cardiovascular and renal disease: evidence from CARES, FAST, ALL-HEART, and FEATHER studies. Curr Med Res Opin. 2017;33(suppl 3):27–32.

71. Trelle S, Reichenbach S, Wandel S. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. BMJ. 2011;342

72. Bally M, Dendukuri N, Rich B. Risk of acute myocardial infarction with NSAIDs in real world use: Bayesian meta-analysis of individual patient data. BMJ. 2017;357

73. Angiolillo DJ, Weisman SM. Clinical pharmacology and cardiovascular safety of naproxen. Am J Cardiovasc Drugs. 2017;17:97–107.

74. Solomon DH, Shao M, Wolski K, Nissen S, Husni ME, Paynter N. Derivation and validation of a major toxicity risk score among nonsteroidal antiinflammatory drug users based on data grom a randomized controlled trial. Arthritis Rheumatol. 2019;71:1225–1231.

75. Nissen SE, Yeomans ND, Solomon DH. Cardiovascular safety of celecoxib, naproxen, or ibuprofen for arthritis. N Engl J Med. 2016;375:2519–2529.

76.   van Sijl AM, Boers M, Voskuyl AE, Nurmohamed MT. Confounding by indication probably distorts the relationship between steroid use and cardiovascular disease in rheumatoid arthritis: results from a prospective cohort study. PLoS One. 2014;9

77.   Choi HK, Hernán MA, Seeger JD, Robins JM, Wolfe F. Methotrexate and mortality in patients with rheumatoid arthritis: a prospective study. Lancet. 2002;359:1173-1177.

78.   De Vecchis R, Baldi C, Palmisani L. Protective effects of methotrexate against ischemic cardiovascular disorders in patients treated for rheumatoid arthritis or psoriasis: novel therapeutic insights coming from a meta-analysis of the literature data. Anatol J Cardiol. 2016;16:2–9.

79.   van Halm VP, Nurmohamed MT, Twisk JW, Dijkmans BA, Voskuyl AE. Disease-modifying antirheumatic drugs are associated with a reduced risk for cardiovascular disease in patients with rheumatoid arthritis: a case control study. Arthritis Res Ther. 2006;8:R151.

80.   Rempenault C, Combe B, Barnetche T. Metabolic and cardiovascular benefits of hydroxychloroquine in patients with rheumatoid arthritis: a systematic review and meta-analysis. Ann Rheum Dis. 2018;77:98–103.

81.   Jankelson L, Karam G, Becker ML, Chinitz LA, Tsai MC. QT prolongation, torsades de pointes, and sudden death with short courses of chloroquine or hydroxychloroquine as used in COVID-19: a systematic review. Heart Rhythm. 2020 doi: 10.1016/j.hrthm.2020.05.008. published online May 10.

82.   Lazzerini PE, Capecchi PL, Bertolozzi I. Marked QTc prolongation and torsades de pointes in patients with chronic inflammatory arthritis. Front Cardiovasc Med. 2016;3:3.

83.   Jacobsson LT, Turesson C, Nilsson JA. Treatment with TNF blockers and mortality risk in patients with rheumatoid arthritis. Ann Rheum Dis. 2007;66:670–675.

84.   Ljung L, Askling J, Rantapää-Dahlqvist S, Jacobsson L, ARTIS Study Group The risk of acute coronary syndrome in rheumatoid arthritis in relation to tumour necrosis factor inhibitors and the risk in the general population: a national cohort study. Arthritis Res Ther. 2014;16:R127.

85.   Roubille C, Richer V, Starnino T. The effects of tumour necrosis factor inhibitors, methotrexate, non-steroidal anti-inflammatory drugs and corticosteroids on cardiovascular events in rheumatoid arthritis, psoriasis and psoriatic arthritis: a systematic review and meta-analysis. Ann Rheum Dis. 2015;74:480–489.

86.   EP Vantage Olumiant clot signal echoes Xeljanz experience. July 26, 2017. https://seekingalpha.com/article/4090841-olumiant-clot-signal-echoes-xeljanz-experience

87.   US FDA FDA responds to safety signal reported in required postmarketing trial for Xeljanz. Feb 25, 2019. https://www.fda.gov/news-events/fda-brief/fda-brief-fda-responds-safety-signal-reported-required-postmarketing-trial-xeljanz

88.   European Medicines Agency Restrictions in use of Xeljanz while EMA reviews risk of blood clots in lungs. May 17, 2019. https://www.ema.europa.eu/en/news/restrictions-use-xeljanz-while-ema-reviews-risk-blood-clots-lungs

89. Taylor PC, Weinblatt ME, Burmester GR. Cardiovascular safety during treatment with baricitinib in rheumatoid arthritis. Arthritis Rheumatol. 2019;71:1042–1055.

90. Spartalis M, Spartalis E, Tzatzaki E. The beneficial therapy with colchicine for atherosclerosis via anti-inflammation and decrease in hypertriglyceridemia. Cardiovasc Hematol Agents Med Chem. 2018;16:74–80.

91. Fiolet ATL, Nidorf SM, Mosterd A, Cornel JH. Colchicine in stable coronary artery disease. Clin Ther. 2019;41:30–40.

92. Crittenden DB, Lehmann RA, Schneck L. Colchicine use is associated with decreased prevalence of myocardial infarction in patients with gout. J Rheumatol. 2012;39:1458–1464.

93. Solomon DH, Liu CC, Kuo IH, Zak A, Kim SC. Effects of colchicine on risk of cardiovascular events and mortality among patients with gout: a cohort study using electronic medical records linked with Medicare claims. Ann Rheum Dis. 2016;75:1674–1679.

94. Kajikawa M, Higashi Y, Tomiyama H. Effect of short-term colchicine treatment on endothelial function in patients with coronary artery disease. Int J Cardiol. 2019;281:35–39.

95. Bardin T. Canakinumab for the patient with difficult-to-treat gouty arthritis: review of the clinical evidence. Joint Bone Spine. 2015;82(suppl 1):eS9–eS16.

96. Janssen CA, Oude Voshaar MAH, Vonkeman HE. Anakinra for the treatment of acute gout flares: a randomized, double-blind, placebo-controlled, active-comparator, non-inferiority trial. Rheumatology (Oxford) 2019;58:1433–1452.

97. Ridker PM, Everett BM, Thuren T. Antiinflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med. 2017;377:1119–1131.

98. Richette P, Doherty M, Pascual E. 2018 updated European League Against Rheumatism evidence-based recommendations for the diagnosis of gout. Ann Rheum Dis. 2020;79:31–38.

99. Bursill D, Dalbeth N. What is the evidence for treat-to-target serum urate in gout? Curr Rheumatol Rep. 2018;20:11.

100. Bredemeier M, Lopes LM, Eisenreich MA. Xanthine oxidase inhibitors for prevention of cardiovascular events: a systematic review and meta-analysis of randomized controlled trials. BMC Cardiovasc Disord. 2018;18:24.

101. Kojima S, Matsui K, Hiramitsu S. Febuxostat for Cerebral and cardiorenovascular events prevention study. Eur Heart J. 2019;40:1778–1786.

102. Zhang T, Pope JE. Cardiovascular effects of urate-lowering therapies in patients with chronic gout: a systematic review and meta-analysis. Rheumatology (Oxford) 2017;56:1144–1153.

103. Hay CA, Prior JA, Belcher J, Mallen CD, Roddy E. Mortality in patients with gout treated with allopurinol: a systematic review and meta-analysis. Arthritis Care Res (Hoboken) 2020 doi: 10.1002/acr.24205. published online April 14.

104. Doherty M, Jenkins W, Richardson H. Efficacy and cost-effectiveness of nurse-led care involving education and engagement of patients and a treat-to-target urate-lowering strategy versus usual care for gout: a randomised controlled trial. Lancet. 2018;392:1403–1412.

105. US FDA FDA adds boxed warning for increased risk of death with gout medicine uloric (febuxostat) Feb 21, 2019. https://www.fda.gov/drugs/drug-safety-and-availability/fda-adds-boxed-warning-increased-risk-death-gout-medicine-uloric-febuxostat

106. White WB, Saag KG, Becker MA. cardiovascular safety of febuxostat or allopurinol in patients with gout. N Engl J Med. 2018;378:1200–1210.

107. Agca R, Heslinga SC, Rollefstad S. EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 update. Ann Rheum Dis. 2017;76:17–28.

108. Piepoli MF, Hoes AW, Agewall S. 2016 European guidelines on cardiovascular disease prevention in clinical practice: the sixth Joint Task Force of the European Society of Cardiology and other societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR) Eur Heart J. 2016;37:2315–2381.

109. Richette P, Doherty M, Pascual E. 2016 updated EULAR evidence-based recommendations for the management of gout. Ann Rheum Dis. 2017;76:29–42.

110. European League Against Rheumatism EULAR recommendations for cardiovascular risk management in rheumatic and musculoskeletal diseases (including SLE and the antiphospholipid syndrome) 2019. https://www.eular.org/clinical_affairs_initiatives.cfm

111. Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. BMJ. 2017;357

112. Salaffi F, Carotti M, Di Carlo M. The Expanded Risk Score in Rheumatoid Arthritis (ERS-RA): performance of a disease-specific calculator in comparison with the traditional prediction scores in the assessment of the 10-year risk of cardiovascular disease in patients with rheumatoid arthrit. Swiss Med Wkly. 2018;148

113. Kitas GD, Nightingale P, Armitage J. A Multicenter, randomized, placebo-controlled trial of atorvastatin for the primary prevention of cardiovascular events in patients with rheumatoid arthritis. Arthritis Rheumatol. 2019;71:1437–1449.

114. Lv S, Liu Y, Zou Z. The impact of statins therapy on disease activity and inflammatory factor in patients with rheumatoid arthritis: a meta-analysis. Clin Exp Rheumatol. 2015;33:69–76.

115. Choi HK, Soriano LC, Zhang Y, Rodríguez LA. Antihypertensive drugs and risk of incident gout among patients with hypertension: population based case-control study. BMJ. 2012;344

116. Zhang Y, Neogi T, Chen C, Chaisson C, Hunter DJ, Choi H. Low-dose aspirin use and recurrent gout attacks. Ann Rheum Dis. 2014;73:385–390.

117. Waldman B, Ansquer JC, Sullivan DR. Effect of fenofibrate on uric acid and gout in type 2 diabetes: a post-hoc analysis of the randomised, controlled FIELD study. Lancet Diabetes Endocrinol. 2018;6:310–318.

118. Derosa G, Maffioli P, Reiner Ž, Simental-Mendía LE, Sahebkar A. Impact of statin therapy on plasma uric acid concentrations: a systematic review and meta-analysis. Drugs. 2016;76:947–956.

119. Keller SF, Rai SK, Lu N. Statin use and mortality in gout: a general population-based cohort study. Semin Arthritis Rheum. 2018;48:449–455.

120. Stavropoulos-Kalinoglou A, Metsios GS, Veldhuijzen van Zanten JJ, Nightingale P, Kitas GD, Koutedakis Y. Individualised aerobic and resistance exercise training improves cardiorespiratory fitness and reduces cardiovascular risk in patients with rheumatoid arthritis. Ann Rheum Dis. 2013;72:1819–1825.

121. Nielsen SM, Bartels EM, Henriksen M. Weight loss for overweight and obese individuals with gout: a systematic review of longitudinal studies. Ann Rheum Dis. 2017;76:1870–1882.

122. Jee Y, Jeon C, Sull JW, Go E, Cho SK. Association between smoking and gout: a meta-analysis. Clin Rheumatol. 2018;37:1895–1902.

123. Panoulas VF, Douglas KM, Milionis HJ. Prevalence and associations of hypertension and its control in patients with rheumatoid arthritis. Rheumatology (Oxford) 2007;46:1477–1482.

124. van Breukelen-van der Stoep DF, van Zeben D, Klop B. Marked underdiagnosis and undertreatment of hypertension and hypercholesterolaemia in rheumatoid arthritis. Rheumatology (Oxford) 2016;55:1210–1216.

125. Heslinga M, Van Den Oever I, Jonker DL. Suboptimal cardiovascular risk management in rheumatoid arthritis patients despite an explicit cardiovascular risk screening programme. Scand J Rheumatol. 2019;48:345–352.

126. Weijers JM, Rongen-van Dartel SAA, Hoevenaars DMGMF, Rubens M, Hulscher MEJL, van Riel PLCM. Implementation of the EULAR cardiovascular risk management guideline in patients with rheumatoid arthritis: results of a successful collaboration between primary and secondary care. Ann Rheum Dis. 2018;77:480–483.

127. Roddy E, Mallen CD, Hider SL, Jordan KP. Prescription and comorbidity screening following consultation for acute gout in primary care. Rheumatology (Oxford) 2010;49:105–111.

The effect of biological DMARDs on the risk of Congestive Heart Failure in Rheumatoid Arthritis, a systematic review

Chapter

3

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Abstract

Introduction

A common cardiovascular manifestation in rheumatoid arthritis (RA) is congestive heart failure (CHF) in which inflammation is considered to play a pivotal role. Although anti-inflammatory therapy such as biological disease-modifying anti-rheumatic drugs (bDMARDs) have the potential of improving the cardiac function and reducing the risk of CHF, the published studies showed contrasting results. This review aims to systematically summarize and analyze literature regarding the effect of bDMARDs on the cardiac function and on the risk of CHF in RA.

Areas covered

Observational cohort, randomized controlled trials and case-controlled studies were included. The systematic literature search was conducted in PubMed, Wiley/Embase, Cochrane, Web of Science and clinicaltrials.gov (up to 2017). Two authors assessed abstracts for inclusion and methodological quality was assessed by one reviewer.

Expert opinion

RA patients have a clinically relevant increased risk of developing CHF needing further attention. However, we found a lack of high quality studies. Future studies should focus on distinguishing the effect of myocardial inflammation reduction versus antibody-specific myocardial cellular effects of bDMARDs to improve the understanding of the effects of bDMARDs in RA patients and the relation with the development of CHF.

1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease affecting approximately 1% of the adult population[1]. Cardiovascular disease (CVD) is the main cause of premature mortality and the most observed comorbidity in RA [2, 3]. Therefore, RA is recognized as an independent risk factor for the development of CVD in addition to the "classic" risk factors indicated by the Framingham study [2]. One of the most common cardiovascular manifestation is congestive heart failure (CHF), with a relative risk of twofold compared to the normal population which is not solely explained by traditional cardiovascular risk factors and/or clinical ischemic heart disease [4, 5]. Though the exact pathophysiology is not yet known, systemic inflammation is considered to play a pivotal role in the development of CHF as well as atherosclerotic disease [6, 7]. Anti-inflammatory therapy such as biological disease-modifying anti-rheumatic drugs (bDMARDs) or may have the potential of reducing the risk of developing CHF secondary to suppression of systemic inflammation. However, prior studies showed contrasting results in respect to the effect of bDMARDs on cardiac function. Therefore, this review aims to systematically summarize and analyze literature on the effect of bDMARDs on the cardiac function and on the risk of developing CHF in RA patients.

2. Objective

To determine the effect of bDMARDs on the risk of developing congestive heart failure in patients with rheumatoid arthritis.

3. Methods

3.1. Criteria for considering studies for this review

3.1.1. Types of studies
We included RCTs, retrospective cohorts, prospective cohorts and case-control studies.

Inclusion criteria
- Studies including adults over the age of 18 years.
- Patients diagnosed with rheumatoid arthritis.
- Treatment with bDMARDs.

Exclusion criteria
- Case reports
- Case-series
- Guidelines and updates
- Phase III clinical trials
- Animal studies
- (systematic) reviews
- Non-English articles

3.1.2. Type of participants
Adults diagnosed with rheumatoid arthritis

3.1.2. Type of interventions

Interventions
Administration of a bDMARD registered as treatment for RA.

- Etanercept (anti-TNF)
- Infliximab (anti-TNF)
- Adalimumab (anti-TNF)
- Certolizumab pegol (anti-TNF)
- Golimumab (anti-TNF)
- Tocilizumab (anti-interleukin-6)
- Abatacept (T-cell co-stimulation blocker)

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· Rituximab (CD20 induced B-cell apoptosis)
· Anakinra (anti-interleukin-1)

Comparison
· Prednisolone
· Conventional synthetic disease-modifying anti-rheumatic drugs (csDMARD)
· Placebo
· Healthy volunteers

3.1.3. Type of outcome measures
a) Incidence/prevalence of congestive heart failure.
b) Cardiac function assessed by echocardiography, MRI or cardiac serum biomarkers.

3.2. Search methods for identification of studies
The systematic review is based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses method (PRISMA) [8, 9]. With support of a search specialist* we searched the following databases:

· Wiley/Embase library database up to 20 March 2017;
· the PubMed database up to 6 April 2017;
· the Cochrane database up to 2 May 2017;
· the Web of Science database up to 2 May 2017;
· Clinicaltrials.gov up to 2 May 2017 (no results).

3.3. Data collection and analysis

3.3.1. Selection studies
Two authors (MB, AB) independently assessed and selected studies eligible for this systematic review. Disagreement was resolved by consensus. One author (MB) reviewed the methodology criteria and methods.

3.3.2. Data extraction and management
One author (MB) extracted data items from the selected studies with the use of a standardized excel data form [10]. The items included: author, title, year, journal, country, date of data abstraction, study design, objective of study, single/multi center, region, method of selection, enrollment start date, enrollment end date, methods

used to prevent and control for confounding, selection bias, and information bias for observational studies, funding, author's financial relationship and other potential conflicts of interest, inclusion criteria, exclusion criteria, subjects included, length of follow up, mean/median age, % female subjects, mean/median age RA onset, mean/median RA duration, bDMARD and dose , description of co-medication, disease activity baseline, disease activity follow up, outcome, measurement method, outcome baseline, outcome follow up, measure of effect or association used, between group summary, statistical method, limitations.

The same author assessed the quality of the evidence by the following quality assessment tools:

- The Newcastle-Ottawa Scale [11] for retrospective cohorts and case control studies.
- A Modified Newcastle-Ottawa scale for prospective cohorts. To make the quality assessment applicable for prospective cohorts we removed question 3 and 4 of part Selection from the original Newcastle-Ottawa scale and added a question regarding whether the study had a control group or not.
- QUADAS-2 [12] for cross-sectional studies.

4. Results

The search resulted in 1177 potential articles from Medline/PubMed (n=155), Wiley/Cochrane library (n=13), Web of Science (n=211), EMBASE (n=798) and clinicaltrials.gov (no results). Subsequently, 1124 articles were excluded based on double-blind screening of title and abstract including 238 duplicates. The remaining 52 full text articles were assessed and 21 articles were eligible for this systematic review. See Figure 1 for the flowchart of the search and selection process. All the included studies comprised RA patients for whom bDMARD therapy was necessary. Due to the small number of published articles we included a broad spectrum of type of studies including: RCT's, retrospective cohorts, prospective cohorts and case-control studies. Included articles were divided in three main categories: cardiac function imaging studies, CHF prevalence/incidence studies and cardiac function biomarker studies. Cardiac function imaging studies consisted of studies assessing the change of cardiac function by magnetic resonance imaging (MRI) or echocardiography. Echocardiographic assessment techniques included speckle tracking echocardiography, Doppler tissue

echocardiography and/or conventional echocardiography. Prevalence and/or incidence of CHF studies included retrospective and prospective studies, cross-sectional studies and a nested case-control study. NT-proBNP was the main biomarker used to assess the cardiac function. Cardiac hemodynamic assessment was performed with the use of the Portapres system, a non-invasive hemodynamic beat to beat monitoring system. All included articles are summarized in table 1.

Figure 1. Flow chart of the search and selection process.
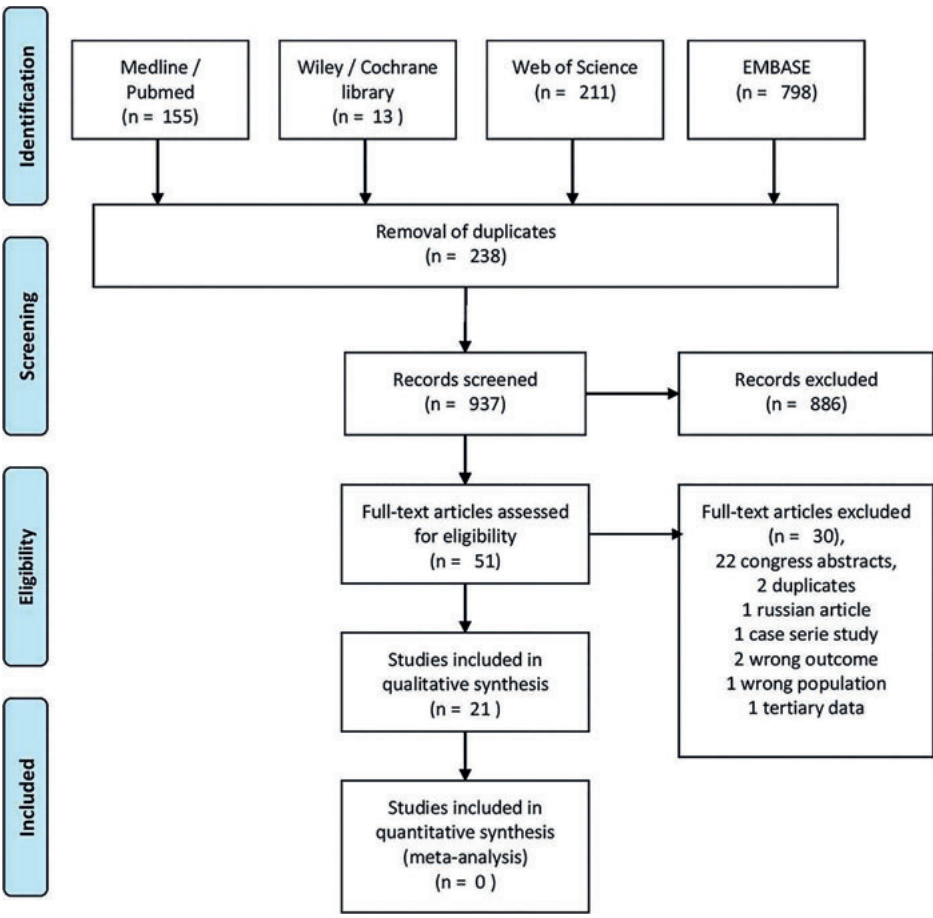
4.1. Cardiac function imaging studies

The following 3 studies investigated the cardiac function with the use of cardiac MRI (cMRI)[13]. Kobayashi H. et al. found a significant higher left ventricle mass index and lower EF in RA patients at baseline. After one year of tocilizumab treatment (anti-interleukin-6) they observed a significant increase of the ejection fraction (EF), decrease of the left ventricle mass index (LVMI) and normalization of several left ventricle (LV) morphological features compared with the control group [13]. In addition, these findings were positively correlated with amelioration of the disease activity. However, in a cross-sectional study Giles et al. observed a significant lower LV mass in RA patients compared with their control group [14].

Furthermore, Kobayashi Y. et al. demonstrated in a pilot study a significant improvement of regional left ventricular (LV) function by cMRI strain analysis after 52 weeks tocilizumab treatment [15]. This systematic review includes 6 studies in which cardiac function was assessed by echocardiography. Vizzardi et al. assessed the cardiac function by speckle tracking echocardiography in a longitudinal 2, 3 and 4 chamber view in which RA patients underwent echocardiography before starting anti-tumor necrosis factor (TNF) (etanercept, adalimumab or infliximab) and after 1 year therapy. Their results exhibited no modification of the LV function after 1 year anti-TNF therapy [16].

In a prospective controlled observational cohort Ikonomidis 2009 et al. showed improvement of myocardial deformation parameters in RA patients after 30 days treatment with anakinra (anti-interleukin-1) assessed by speckle echocardiography [17]. Anakinra treatment was more effective in improving LV deformation parameters than corticosteroid treatment in the control group. In another study Ikonomidis et al. investigated the effect of anakinra on cardiac function in 60 RA patients without coronary artery disease (CAD) compared to 20 RA patients with CAD. To serve as control, the same groups were administrated placebo after a 48-hours wash out period and repeated the assessment. The results demonstrated significant improvement of the cardiac function 3 hours after administration investigated by tissue Doppler and speckle tracking parameters of myocardial deformation and LV twisting. In addition, the echocardiographic parameters showed more improvement of the cardiac function in RA patients with known CAD compared to RA patients without CAD [18]. Two studies investigated the effect of anti-TNF on the cardiac function. Kotyla et al. showed an 8% improvement (p<0.05) of the EF in 23 RA patients after 1 year infliximab administration [19].

In contrast, Cetin et al. prospectively investigated the effect of infliximab in RA patients on the LV function controlled by prednisolone therapy after 3 months administration. An improvement of only one diastolic function parameter (E/E') was found in the infliximab-treated compared to the prednisolone-treated patients [20]. Ikonomidis et al.[21] conducted an observational trial investigating both acute and chronic effects of anakinra therapy. In the acute study they observed the effect of anakinra on the cardiac function of 23 RA patients administrated with anakinra or placebo at baseline and after 3 hours. To serve as control, this was repeated in a double-blinded controlled cross-over manner after a wash-out period of 48 hours. They observed an improvement of the systolic as well the diastolic function assessed by tissue Doppler echocardiography. In the chronic study they compared echocardiographic results of 23 RA patients before and after 30 days anakinra treatment controlled by 19 prednisolone-treated RA patients. Similarly, the chronic study showed a significant improvement of the diastolic and systolic cardiac function after anakinra administration. However, no effect was observed in the prednisolone-treated control group [21]. Furthermore, Santos et al. used a non-invasive hemodynamic beat-to-beat monitoring system to observe on the indexed cardiac output (CO) and stroke volume (SV) during two hours before and after infusion with infliximab in 14 RA patients without history of CHF. The same group served as control, as the same procedure was repeated 2 weeks later after infusion with saline. They showed a significant reduction of SV and CO output after infusion with infliximab, subsequently -13% and -9%. In contrast to the control group which did not show any difference after infusion with saline [22].

4.2. CHF prevalence/incidence studies

In addition to the direct effects of bDMARDs on cardiac function, many studies focused on the incidence rate of CHF in RA patients treated with bDMARDs. Giles et al. conducted a cross-sectional study with cMRI in RA patients with no self-reported history of CVD. Patients treated with anti-TNF showed an inverse association with mean LV stroke and LV end-diastolic volumes [14]. Schau et al. conducted a cross-sectional study assessing heart failure by a diagnostic work up according to the European society of cardiology recommendations where they found similar prevalences of CHF in RA patients treated with bDMARDs and conventional synthetic (cs)DMARD's. Of the 157 included RA patients, 90 (57%) were treated with bDMARDs of which 21 (23%) had CHF compared to 67 (43%) csDMARD treated RA patients of which 17 (25%) were diagnosed with CHF [23]. In a nested case-control study, Bernatsky et al. studied the rate of the first occurrence of CHF hospitalization in RA patients with no history of CHF derived

from two large North-American insurance claims databases. Their analysis showed a relative risk of 0.5 (CI 95% CI 0.2-0.9) of hospitalization for patients treated with TNF blockers in comparison to RA patients not treated with TNF blockers and DMARD's [24]. In another large insurance claims database cohort, Solomon et al. compared the incidence of CHF hospital admission of csDMARD users with TNF-blocker users in RA patients. In this RA population, TNF blockers were not associated with a risk of CHF hospital admissions compared with csDMARDs, displayed in a hazard ratio (HR) of 0.85 (95% CI 0.63 to 1.14) [25]. Curtis et al. also investigated administrative claims of a large U.S. health care organization for the cumulative incidence of CHF in RA (and Crohn's disease) patients. They observed a not statistically significant increased crude relative risk of heart failure among all TNF-α exposed RA patients (relative risk 4.3) [26]. In a large observational cohort of RA patients in the UK, Morgan et al. examined the long-term safety of etanercept in comparison with csDMARD's. They compared 4453 etanercept users with 3774 csDMARD users. Although the mean disease duration and disease activity was significantly higher in the etanercept group compared to the csDMARD group, the etanercept group showed approximately half the incidence rate for the development of congestive heart failure (unadjusted rate of 1.7 vs 3.3 per 1000 person-years) [27]. Al-Aly et al. examined the effect of anti-TNF on cardiovascular outcomes and long-term survival in a large registry cohort from U.S. veterans with RA. Their analysis showed no proportional risk of anti-TNF for developing congestive heart failure compared to other DMARDs (HR 1.05 95% CI 0.909–1.217) [28]. A large German register cohort found that anti-TNF treatment did not increase the risk of worsening of prevalent heart failure and therefore suggested that anti-TNF is more likely to be beneficial than harmful with regards to the risk of heart failure [29].

In pooled health care utilization databases Setoguchi et al. estimated the risk of CHF hospitalization in anti-TNF users among elderly patients with RA with and without previous CHF. In their cohort, anti-TNF users had a greater risk of CHF hospitalization in comparison to MTX users (HR1.7 CI 95% 1.07-2.69) [30]. A single center retrospective study in Veterans showed similar risk for developing CHF in the anti-TNF treated RA group, RA control group and the non-RA control group (respectively 7%, 8%, 7%; p=0.940) [31]. Wolfe et al. determined the incidence and prevalence of heart failure in patients with RA in a two year cohort treated with anti-TNF compared to no anti-TNF therapy and found a significant lower adjusted incidence and prevalence in patients treated with anti-TNF (0.2 vs 0.2-0.3 and 2.8 vs 3.4-3.9, respectively) [32].

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4.3. Cardiac function biomarker studies

Two studies used BNP/NT-proBNP as assessment tool to describe the effect of bDMARDs on the cardiac function. In one of these studies, Peters et al. showed a significant decrease in NT-proBNP of 18% after 16 weeks of administration of adalimumab in RA patients without pre-existent heart conditions [33]. Likewise, in a sub analysis of a previous described study, Kotyla et al. found a 48% decrease of NT-proBNP levels after 12 months of administration with infliximab. Thus, indicating an improvement of cardiac function after TNF blocking therapy [19].

5. Summary of findings

The major findings of this systematic review are as follows, (1) it is unlikely that anti-TNF bDMARDs increase the risk of developing CHF, (2) bDMARDs probably have favorable effects on the cardiac function in RA, however, larger trials are needed for verification, (3) anti-TNF bDMARDs lowered plasma NT-proBNP levels, thus assuming an improvement of the cardiac function.

Table 1. Data summary sheet

Study	Year	Design	Number exposed	Control	Mean/ median length of follow up	Exposure (biologics)
Cardiac function imaging studies						
Vizzardi et al. [16]	2015	Prospective cohort	13	-	1 year	Adalimumab, Infliximab, Etanercept
Kobayashi et al. [15]	2016	Prospective cohort	13	-	1 year	Tociluzimab
Kobayashi et al. [13]	2014	Prospective cohort	20	-	1 year	Tociluzimab
Kotyla et al. [19]	2012	Prospective cohort	23	-	1 year	Infliximab
Çetin et al. [20]	2014	Prospective controlled cohort	20	30	3 months	Infliximab
Ikonomidis et al. [18]	2014	Double blinded cross-over trial	RA + CAD = 60 RA – CAD = 20	30 (only baseline)	3 h	Anakinra
Santos et al. [22]	2012	Prospective controlled cohort	14	Intervention group served as own control	2 h	Infliximab
Giles et al. [14]	2010	Cross-sectional	36	-	n/a	Anti-TNF
Ikonomidis et al. [17]	2009	Prospective cohort	23	-	30 days	Anakinra

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Mean/ median disease duration	Assessment tool	Outcome measure	Result	*p* value	Quality assessment
11.4 (±4.9) years	Speckle echo-cardiography	Change in peak systolic regional strain values	No significant change	-	Low
30 [14-129] months	cMRI	Change in mean peak radial strain (cMRI)	APD +20%*	*p*=0.028	Low
30 months	cMRI	Change in LVMI, EF and EDV (cMRI)	APD LVMI: -24%* EF: +8%* EDV: -15%*	LVMI: *p*<0.001 EF: *p*=0.003 EDV: *p*=0.0025	Low
7.1 (±1) years	Conventional echocardiog-raphy	Change in conventional echocardiograpy	APD LVEF: +8%*	LVEF: *p*<0.05	Low
98.4 (±77.4) months	Conventional and tissue dop-pler echocar-diograpy	Change in conventional and tissue doppler echocardiography	APD E/E': -15%*	E/E': *p*<0.05	Medium
RA+CAD= 12 [5–23.5] years RA-CAD= 11 [1–27.1] years	Conventional, tissue doppler and speckle echocardiog-raphy	Change in 2D, tissue doppler and speckle echo-cardiography	APD CAD vs. N-CAD EF: 12%* vs. 0.5%* E/E': 29%* vs. 15%*	CAD vs. N-CAD EF: *p*<0.05 E/E': *p*<0.05	Low
10.9 (±4.4) years	Noninvasive hemodynamic monitoring system	Change in cardiac output	CO: -13%* vs +2%	CO: *p*<0.05 vs *p*= 0.93	Medium
7 [4-17] years	cMRI	Ventricular dimensions	RC LVEDV: -10.3* (95% CI 20.3, -0.2)	LVEDV: *p*<0.05	Medium
11.6 [6.5-35] years	Speckle echo-cardiography	Change in Speckle echocar-diography	APD RSt: -24% Cst: -15% LSt: 21%	RSt: *p*=0.026 Cst: *p*=0.005 LSt: *p*=0.001	Low

Table 1. Continued.

Study	Year	Design	Number exposed	Control	Mean/ median length of follow up	Exposure (biologics)
Ikonomid-is et al. [21]	2008	Prospective controlled cohort	23	23	30 days	Anakinra
Ikonomid-is et al. [21]‡	2008	Double blinded controlled cross-over trial	23	-	3 h	Anakinra
CHF prevalence/incidence studies						
Schau et al. [23]	2015	Controlled cross-sectional	64	77	n/a	Anti-TNF
Bernatsky et al. [24]	2005	Nested case-control	12	175	1 year	Anti-TNF
Morgan et al. [27]	2014	Prospective registry cohort	4453	-	4.8 years (± 2.4)	Etanercept
Solomon et al. · [25]	2013	Retrospective insurance claims cohort	11587	-	4458 person-years	Adalimumab, Infliximab, Etanercept
Al-Aly et al. [28]	2011	Retrospective veterans cohort	3796	-	2.3 years	Adalimumab, Infliximab, Etanercept
Setoguchi et al. [30]	2008	Retrospective health care cohort	1002	-	1.7 years (±1.6)	Adalimumab, Infliximab, Etanercept
Listing et al. [29]	2008	Prospective cohort	2757	-	36 months	Adalimumab, Infliximab, Etanercept
Curtis et al. [26]	2007	Retrospective healthcare claims cohort	1138	-	n/a	Etanercept, Infliximab
Cole et al. [31]	2007	Retrospective veterans cohort	103	-	n/a	Adalimumab, Infliximab, Etanercept
Wolfe et al. [32]	2004	Prospective cohort	5832	-	n/a	Infliximab, Etanercept

Mean/ median disease duration	Assessment tool	Outcome measure	Result	*p* value	Quality assessment
11 [1-27] years	Tissue doppler echocardiography	Change in tissue doppler echocardiography	APD E/E': -21%* vs. +4%	E/E': *p*<0.001 vs. *p*=-0.7	Low
11 [1-27] years	Tissue doppler echocardiography	Change in tissue doppler echocardiography	APD E/E': -13%* vs. -4%	E/E': *p*=0.018 vs. *p*=0.9	Low
n/a		Prevalence CHF	APD -3.5%	-	Low
n/a		First occurrence of CHF hospitalization	RR 0.50* (95% CI 0.2-0.9)	-	High
13.5 (±9.4) years		Incidence of CHF	IRR 1.94	-	Low
n/a		Incidence of CHF hospitalizations	HR 0.84 (95% CI 0.62-1.12)	-	Medium
n/a		Incidence of CHF	HR 1.05 (95% CI 0.909-1.217)	*p*=0.50	Medium
n/a		Incidence of CHF hospitalizations	RR 1.61* (95% CI 1.08-2.39)	*p*<0.05	High
9 [5–16] years		Incidence of CHF hospitalizations	HR 0.65 [95% CI 0.29–1.44]	*p*=0.29	High
n/a		Cumulative incidence of presumed CHF	RR 4.3	-	Medium
n/a		Incidence of CHF hospitalizations	APD -1.4%	p<0.05	Medium
14.9 (± 11.1) years		Incidence of CHF	IRR 1 - 0,7	-	High

Table 1. Continued.

Study	Year	Design	Number exposed	Control	Mean/ median length of follow up	Exposure (biologics)
Cardiac function biomarker studies						
Kotyla et al. [19‡]	2012	Prospective cohort	23	-	1 year	Infliximab
Peters et al. [33]	2010	Prospective cohort	171	-	16 weeks	Adalimumab

RA: Rheumatoid arthritis; IRR: incidence rate ratio; APD: absolute percentage difference; CAD: coronary artery disease; CHF: congestive heart failure; cMRI: cardiac magnetic resonance imaging; LSt: longitudinal strain; CSt: circumferential strain; RSt: radial strain; RR: relative risk; HR: hazard ratio; CI: confidence interval.

*$p < 0.05$

‡ These authors described two types of analysis in their articles and therefore they are presented twice in this data summary table.

6. Discussion

RA patients have a twofold increased risk of developing CHF compared to the general population [4]. Early recognition of CHF in RA patients is important as these patients have increased risk for mortality and comorbidity [34]. Therefore, it is necessary to understand the pathophysiologic mechanisms of RA induced CHF. Thus far there is strong evidence this correlation is partly due to the increased risk of developing ischemic heart disease secondary to accelerated atherosclerosis caused by systemic inflammation [35, 36]. However, this is not solely explained by the increased risk of traditional cardiovascular risk factors and/or clinical ischemic heart disease [5]. Accumulating evidence suggests a direct effect of inflammation on the myocardium. Previous autopsy studies showed significantly higher prevalences of subclinical focal or diffuse inflammatory infiltration of the pericardium and myocardium compared to the normal population [37, 38]. These observations support the assumption that ventricular dysfunction may at least partly be due to myocardial inflammation. In addition, several studies found increased serum levels of cytokines in patients with chronic and/or acute CHF [39]. However, one large international placebo-controlled trial investigating the effect of etanercept in patients with CHF New York Heart Association (NYHA) class II to IV showed no effect on hospitalization or mortality [40]. Furthermore, a smaller placebo-controlled trial with a similar study design investigating the effect of infliximab administrated with 5 mg/kg

Mean/ median disease duration	Assessment tool	Outcome measure	Result	*p* value	Quality assessment
7.1 (± 1) years	Biochemical analyses	Change in NT-proBNP	APD -44%*	p<0.01	Low
8 [3-17] years	Biochemical analyses	Change in NT-proBNP	APD -17%*	p=0.004	Medium

or 10 mg/kg showed a significant increased risk for mortality and hospitalization due to CHF [41]. Obviously, further research in this area is needed.

In this systematic review, we found conflicting results in studies assessing the effects of bDMARDs on the cardiac function and the risk for developing CHF. Most of the cardiac imaging studies demonstrated favorable effects of bDMARDs on the cardiac function after treatment with anti-interleukin-1, anti-interleukin-6 or anti-TNF.

6.1. Cardiac imaging studies

A large number of studies presented in this systematic review described the effect of biologics on the cardiac outcome with cardiac imaging. The cMRI is considered as the golden standard for LV volumetric and EF (systolic function) assessment. Although cMRI is more accurate and reproducible in comparison to echocardiography, it is a very expensive and time-consuming examination. Therefore, for routine clinical practice, echocardiography is the most used examination tool in assessing cardiac function as it is a relatively fast and less costly. However, cMRI is superior in assessing the systolic function and echocardiography has the lowest interobserver variability in assessing the diastolic function. Furthermore, there is relative inexperience in assessing the diastolic function with cMRI compared to echocardiography [42, 43].

6.1.1. Anti-interleukin-1

All studies investigating the effect of anti-interleukin-1 (anakinra) exhibited improvement of the cardiac function. Surprisingly, two studies conducted by Ikonomidis et al. even demonstrated an improvement a few hours after administration with anti-interleukin-1. This could be explained by fast reduction of the interleukin-1 driven oxidative stress and myocardial damage by complete neutralization of interleukin-1

[18, 21]. In addition, one of these studies showed a greater improvement of the cardiac function in RA patients with history of CAD as these patients had higher levels of oxidative stress compared to patients without history of CAD. Notably, murine studies demonstrated interleukin-1 induced contractile dysfunction in isolated cardiomyocytes and a reversible cardiomyopathy [44]. Although, anakinra nowadays is used in infrequently in RA patients, it is registered as an anti-rheumatic biologic agent medicine and still applied in daily clinical practice. Therefore, anakinra studies were included in this systematic review.

6.1.2. Anti-interleukin-6
Interleuking-6 acts as a pro-inflammatory cytokine in the inflammatory cascade. As interleukin-6 levels are elevated in RA and CHF patients, it is of interest to study the effects of neutralizing interleukin-6 on cardiac function. This is supported by studies showing maladaptive hypertrophy and decreasing contractile function in the myocardia in acute and chronic serum elevation [45]. Neutralizing interleukin-6 could therefore inhibit the detrimental cardiac effects. Recently, it was demonstrated that anti-interleukin-6 treatment in RA patients improved the cardiac function [13, 15].

6.1.3. Anti-TNF
Studies investigating the effect of anti-TNF on the cardiac function in RA patients were inconclusive. Only, Santos et al. showed impairment of the LVEF and stroke volume (SV) two hours after infusion with infliximab assessed by a non-invasive beat-to-beat monitoring system. It might be that TNF has a cardio protective role in hypoxic cardiac stress [46], that might be dose related. This is supported by the ATTACH trial which evaluated the effect of infliximab in CHF patients with stable NYHA III or IV treated with Infliximab 5 mg/kg or 10 mg/kg. The 5 mg/kg treatment group showed no worsening of symptoms, hospitalization or death compared with the placebo group. The 10 mg/kg treatment group however showed significant increase in subjective clinical worsening and risk for death and hospitalization. Serum analysis in both treatment groups showed plasma levels of infliximab 2-100 times the therapeutic drug level, thus, describing the 5 mg/kg group as a high dose and 10 mg/kg as a very high dose Infliximab infusion. In contrast, infliximab treatment in RA is administrated with 3 mg/kg, making the previous results not applicable to RA patients [41]. In addition, two large international controlled trials named the RENNAISSANCE and the RECOVER trial in which dilated cardiomyopathy (non-RA) patients with EF < 50% were given etanercept (1, 2 or 3 weekly 25 mg s.c.) during 24 weeks, showed no significant effect towards outcome of death/

worsening heart failure compared to the control group shown by a combined hazard ratio of 1.10 (95% CI 0.91 - 1.33) [41]. Furthermore, patients in the RECOVER trial receiving etanercept in a medium dose (25 mg two weekly) showed no significant effect towards outcome of death/worsening heart failure with a hazard ratio of 0.87 (95% CI .61 – 1.24).

The cardiac imaging studies described in this systematic review have relatively small populations, often using different assessment tools and susceptible for confounding. Furthermore, many of these studies scored low in the quality assessments, mainly due to unclear description of the subjects and lack of a (adequate) control group. Albeit, that most data indicated improvement of cardiac function after administration of bDMARDs, the results should be interpreted cautiously.

It is known that cardiac myocytes and endothelial cells contribute to establishment of a pro-inflammatory environment and mobilize inflammatory mediators into the myocardium. Through this pathway different cytokines and chemokines (including TNF-a, interleukin-1 and interleukin-6) are produced during environmental distress (e.g. hypoxia, pathological mechanical stretch, and inflammation) which can lead to cardiac hypertrophy and dysfunction [47]. Hence, as bDMARDs are strong anti-inflammatory drugs, they may also show ameliorating effects on the cardiac function due to their anti-inflammatory effects. In fact, all cardiac imaging studies comparing disease activity after follow up showed significant improvement in disease activity (CRP, DAS-28, HAQ etc.). However, none of these studies addressed the underlying pathways. In this respect it is interesting that a comparable decrease in hospitalization was demonstrated in RA patients treated with anti-TNF or methotrexate monotherapy, both strong anti-inflammatory drugs [24].

6.4. CHF prevalence/incidence studies

The long-term retrospective and prospective cohort studies investigated prevalences and incidence rates of CHF in only RA patients treated with anti-TNF agents. Based on the results of the cardiac imaging studies showing a trend towards a favorable effect on the cardiac function, we hypothesize that patients treated with bDMARDs might have a lower risk of developing heart failure. Interestingly, in contrast to the results of the cardiac imaging studies, incidence and prevalence studies mostly showed no significant difference in the clinical risk of developing CHF in RA patients treated with bDMARDs compared to non-bDMARDs. The incidence and prevalence studies were, in general, higher quality studies compared to the cardiac imaging studies. More importantly, most

studies did not show harmful effects by bDMARDs as was found in the ATTACH trial (that, however, comprised non-RA patients with severe heart failure). Solely Setoguchi et al, in a relatively small study, demonstrated an increased incidence of CHF in elderly RA patients, with long-standing disease, treated with anti-TNF. The discrepancy may be explained by the higher average population age and the higher prevalence of prevalent CVD (~30%) compared to the other studies [30].

6.5. Cardiac function biomarker studies

For the assessment of the cardiac function, BNP and NT-proBNP are the most widely used and recommended biomarkers in current guidelines. ProBNP is a neurohormone released by the cardiac muscle during hemodynamic stress — that is, when the ventricles are dilated, hypertrophic, or subject to increased wall tension. After cleavage by circulating endoprotease into BNP and the bio-inactive NT-proBNP, BNP counteracts the cardiac hemodynamic distress by increasing arterial vasodilation, diuresis, and natriuresis, and reducing activity of the renin–angiotensin–aldosterone system and the sympathetic nervous system[48]. Comparable with most of the cardiac imaging studies, biomarker studies also show favorable effects of anti-TNF on the cardiac function. These studies found a decrease of serum NT-proBNP after treatment with anti-TNF [19, 33]. As NT-proBNP is a strong predictor for cardiac (dys)function and measurable in patients with even asymptomatic heart failure, a decrease of serum NT-proBNP indicates improvement of the cardiac function and a decreased risk for developing heart failure [33, 48]. Another explanation for decrease of serum NT-proBNP could be reduction of myocardial stress due to a decrease of circulating volume. However, no study has demonstrated this effect induced by biologic treatment. In contrast to the long-term decrease of serum NT-proBNP there is a potential acute increase of serum NT-proBNP in patients treated with infliximab [49]. This was demonstrated by Santos et al. who showed an acute decrease of SV and CO after infusion with infliximab [22]. The acute decrease of cardiac function could be explained by a cytotoxic effect of infliximab, or as result of temporary increased circulating volume. Nevertheless, as mentioned above, it is not clear whether the decrease of NT-proBNP is primarily due to the effect of anti-TNF or (partially) secondary due to decrease of systemic inflammation, as in both studies RA patients showed a significant decrease of inflammation parameters.

7. Strengths and Limitations

This systematic review gives a broad overview of available data of the effect of bDMARDs on the cardiac function and the risk for developing CHF in patients with RA. We used strict and standardized tools conducting this review as follows: an extensive literature search in collaboration with a search specialist, two investigators independently assessed the relevance of studies by title and abstract.

The main limitation in our systematic review was the large methodological heterogeneity between the studies making valid comparisons of the results difficult. This was mainly caused by different assessment tools, different study outcomes, different corrected confounders and different bDMARD agents. It was therefore not possible to do a meta-analysis or a statistical test for publication bias (e.g. egger test). Furthermore, cardiac imaging studies were mostly done in too small populations and were mainly of low scientific quality. This was partly caused by lack of control groups and high susceptibility for confounders. Furthermore, a potential risk for bias is through confounding by indication due to the fact anti-TNF is more often used in RA patients with higher disease activity than other DMARD treated RA patients. As disease activity is associated with increased risk for CVD this could have flawed the results. Another very important point is the risk of selection bias, since anti-TNF treated RA patients are possibly less likely to develop CHF as physicians are less willing to start anti-TNF in patients with known CHF or in high risk for CHF patients. This could explain why the evidence is less strong than expected. Another important confounder which was not often adjusted for, was co-treatment with MTX and or prednisolone. MTX and prednisolone are associated with respectively, a decreased and an increased risk for developing CHF. Therefore, it was not possible to conclude about the effects of bDMARDs only regarding CHF. This also applies for other DMARDs as well, however, their effects on CVD have not been adequately investigated yet. However, in clinical practice the use of bDMARDs are often in combination with MTX. It could therefore be discussed whether MTX should be considered as confounder or the effect of bDMARDs should be assessed in combination with MTX. Furthermore, in prospective cohorts, severe CHF is considered as an exclusion criteria and therefore the effect of bDMARDs on RA patients with severe CHF remains unknown. Moreover, the relevance might be limited due the relatively short follow up period. However, referring to the cardiac imaging studies, bDMARDS have the potential to affect the cardiac function measured with cardiac imaging assessment tools in a short time period (months-years). This could impact the risk of developing CHF in the longer

period. Finally, CHF is a complex diagnosis which was not well defined in all studies. Variability in definition and diagnosis might have influenced the correlation.

8. Conclusion

Based on the available literature we concluded that bDMARDs probably do not increase the risk for developing CHF and even might have an ameliorating effect on cardiac function. However, the literature might be flawed by selection bias, channeling bias and confounding. Therefore, firm recommendations cannot be provided. This review indicates that rigorously conducted and adequately powered studies are needed, especially RCTs, to elucidate the effect of bDMARDs on the risk for developing CHF in RA patients.

9. Expert opinion

RA patients have a clinically relevant increased risk of developing CHF which demands further attention. There is uncertainty about the safety of bDMARD treatment in RA patients with CHF or high risk for CHF, which was the reason to conduct this systematic review. Previous studies revealed a potential cellular effect of bDMARDs on myocytes through different mode of actions. However, in this research area we found a lack of consensus in study design, including description of CHF and cardiac dysfunction, an assessment tool for the cardiac function and a representative population. An unambiguous conclusion with respect to the clinical impact could therefore not be drawn. Only, if future studies overcome these shortcomings valid recommendations can be derived about decisions in bDMARD treatment in RA patients with CHF and RA patients at a high risk for developing CHF. Furthermore, there is accumulating evidence demonstrating that systemic disease activity in general plays a pivotal role in de development of cardiac dysfunction. This understanding is important as bDMARDs possibly express their effect by two main pathways: through reduction of overall myocardial inflammation and possibly by specific antibody mediated cellular effect in the myocardium. Until these two pathways are not clearly understood they should be distinguished were possible in future studies. For example, future clinical studies assessing the effect of anti-TNF should primarily correlate the disease activity with cardiac function. Unraveling the role of inflammation on the cardiac function will

raise understanding of the role of bDMARDs on cardiac dysfunction. Therefore, more studies investigating primarily the correlation between systemic disease activity and cardiac dysfunction irrespective of anti-rheumatic treatment are needed. Actually, we expect shift from studies assessing the role of bDMARDs on cardiac function to studies investigating the systemic inflammatory state on the (preclinical) stage of cardiac dysfunction. If future studies succeed in mapping out these pathophysiological and pharmacodynamical pathways RA patients with CHF or at high risk for developing CHF can be treated more adequately. Thus, reducing the risk of developing or worsening of CHF and possibly even improving cardiac dysfunction. As overall bDMARDs do not seem to worsen CHF or increase the risk for developing CHF we believe bDMARDs may become a future option in RA patients with CHF or a high risk for developing CHF without any uncertainty. This would be supported if future studies show reversibility of cardiac dysfunction by anti-inflammatory treatment such as bDMARDs. Moreover, if some bDMARDs have additional ameliorating cellular effect on myocyte function, these bDMARDs could be used as first treatment option in RA patients with CHF or increased risk for developing CHF.

References

1. Alamanos Y, Drosos AA. Epidemiology of adult rheumatoid arthritis. Autoimmun Rev 2005 Mar;4(3):130-6.
2. Agca R, Heslinga SC, van Halm VP, et al. Atherosclerotic cardiovascular disease in patients with chronic inflammatory joint disorders. Heart 2016 May 15;102(10):790-5.
3. Meune C, Touze E, Trinquart L, et al. Trends in cardiovascular mortality in patients with rheumatoid arthritis over 50 years: a systematic review and meta-analysis of cohort studies. Rheumatology (Oxford) 2009 Oct;48(10):1309-13.
4. 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 Feb;52(2):412-20.
5. Han C, Robinson DW, Jr., Hackett MV, et al. Cardiovascular disease and risk factors in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. J Rheumatol 2006 Nov;33(11):2167-72.
6. Mantel A, Holmqvist M, Andersson DC, et al. Association Between Rheumatoid Arthritis and Risk of Ischemic and Nonischemic Heart Failure. J Am Coll Cardiol 2017 Mar 14;69(10):1275-85.
7. Cesari M, Penninx BW, Newman AB, et al. Inflammatory markers and onset of cardiovascular events: results from the Health ABC study. Circulation 2003 Nov 11;108(19):2317-22.
8. Gasparyan AY, Ayvazyan L, Blackmore H, et al. Writing a narrative biomedical review: considerations for authors, peer reviewers, and editors. Rheumatol Int 2011 Nov;31(11):1409-17.
9. Li T, Vedula SS, Hadar N, et al. Innovations in data collection, management, and archiving for systematic reviews. Ann Intern Med 2015 Feb 17;162(4):287-94.
10. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
11. http://www.bristol.ac.uk/population-health-sciences/projects/quadas/quadas-2/.
12. Kobayashi H, Kobayashi Y, Giles JT, et al. Tocilizumab treatment increases left ventricular ejection fraction and decreases left ventricular mass index in patients with rheumatoid arthritis without cardiac symptoms: assessed using 3.0 tesla cardiac magnetic resonance imaging. J Rheumatol 2014 Oct;41(10):1916-21.
13. Giles JT, Malayeri AA, Fern, et al. Left Ventricular Structure and Function in Patients With Rheumatoid Arthritis, As Assessed by Cardiac Magnetic Resonance Imaging. Arthritis and Rheumatism 2010 Jan;62(4):940-51.
14. Kobayashi Y, Takei M, Giles JT, et al. Association of tocilizumab treatment with changes in measures of regional left ventricular function in rheumatoid arthritis, as assessed by cardiac magnetic resonance imaging. Int J Rheum Dis 2016;19(11):1169-74.

15. Vizzardi E, Cavazzana I, Franceschini F, et al. Left ventricular function in rheumatoid arthritis during ant-TNF-alpha treatment: A speckle tracking prospective echocardiographic study. Monaldi Arch Chest Dis Card Ser 2015 jun;84(1-2):716.

16. Ikonomidis I, Tzortzis S, Lekakis J, et al. Lowering interleukin-1 activity with anakinra improves myocardial deformation in rheumatoid arthritis. Heart (British Cardiac Society) 2009 Jan;95(18):1502-7.

17. Ikonomidis I, Tzortzis S, Pavlidis G, et al. Increased benefit of interleukin-1 inhibition on vascular function, myocardial deformation, and twisting in patients with coronary artery disease and coexisting rheumatoid arthritis. Circ Cardiovasc Imaging 2014 Jul;7(4):619-28.

18. Kotyla PJ, Owczarek A, Rakoczy J, et al. Infliximab treatment increases left ventricular ejection fraction in patients with rheumatoid arthritis: assessment of heart function by echocardiography, endothelin 1, interleukin 6, and NT-pro brain natriuretic peptide. J Rheumatol 2012 Jan;39(4):701-6.

19. Çetin S, Mustafa GV, Göksal K, et al. Infliximab, an anti-TNF-alpha agent, improves left atrial abnormalities in patients with rheumatoid arthritis: preliminary results. Cardiovasc j Afr 2014 Jul;25(4):168-75.

20. Ikonomidis I, Lekakis JP, Nikolaou M, et al. Inhibition of interleukin-1 by anakinra improves vascular and left ventricular function in patients with rheumatoid arthritis. Circulation 2008 Jan;117(20):2662-69.

21. Santos RC, Figueiredo VN, Martins LC, et al. Infliximab reduces cardiac output in rheumatoid arthritis patients without heart failure. Rev Assoc Med Bras 2012 Jan;58(6):698-702.

22. Schau T, Gottwald M, Arbach O, et al. Increased Prevalence of Diastolic Heart Failure in Patients with Rheumatoid Arthritis Correlates with Active Disease, but Not with Treatment Type. J Rheumatol 2015 Nov;42(11):2029-37.

23. Bernatsky S, Hudson M, Suissa S. Anti-rheumatic drug use and risk of hospitalization for congestive heart failure in rheumatoid arthritis. Rheumatology (Oxford) 2005 Jan;44(5):677-80.

24. Solomon DH, Rassen JA, Kuriya B, et al. Heart failure risk among patients with rheumatoid arthritis starting a TNF antagonist. Ann Rheum Dis 2013 Nov;72(11):1813-8.

25. Curtis JR, Kramer JM, Martin C, et al. Heart failure among younger rheumatoid arthritis and Crohn's patients exposed to TNF-alpha antagonists. Rheumatology (Oxford) 2007 Nov;46(11):1688-93.

26. Morgan CL, Emery P, Porter D, et al. Treatment of rheumatoid arthritis with etanercept with reference to disease-modifying anti-rheumatic drugs: Long-term safety and survival using prospective, observational data. Rheumatology 2014 Jan;53(1):186-94.

27. Al-Aly Z, Pan H, Zeringue A, et al. Tumor necrosis factor-- blockade, cardiovascular outcomes, and survival in rheumatoid arthritis. Translational Research 2011 Aug;157(1):10-8.

28. Listing J, Strangfeld A, Kekow J, et al. Does tumor necrosis factor alpha inhibition promote or prevent heart failure in patients with rheumatoid arthritis? Arthritis Rheum 2008 Mar;58(3):667-77.

29. Setoguchi S, Schneeweiss S, Avorn J, et al. Tumor necrosis factor-alpha antagonist use and heart failure in elderly patients with rheumatoid arthritis. American heart journal 2008;156(2):336-41.

30. Cole J, Busti A, Kazi S. The incidence of new onset congestive heart failure and heart failure exacerbation in Veteran's Affairs patients receiving tumor necrosis factor alpha antagonists. Rheumatol Int 2007 Apr;27(4):369-73.

31. Wolfe F, Michaud K. Heart failure in rheumatoid arthritis: rates, predictors, and the effect of anti-tumor necrosis factor therapy. 2004 Mar;116(5):305-11.

32. Peters MJL, Welsh P, McInnes IB, et al. Tumour necrosis factor - blockade reduces circulating N-terminal pro-brain natriuretic peptide levels in patients with active rheumatoid arthritis: Results from a prospective cohort study. Ann Rheum Dis 2010 Nov;69(7):1281-85.

33. Bui AL, Horwich TB, Fonarow GC. Epidemiology and risk profile of heart failure. Nat Rev Cardiol 2011 Jan;8(1):30-41.

34. Kahlenberg JM, Kaplan MJ. Mechanisms of premature atherosclerosis in rheumatoid arthritis and lupus. Annu Rev Med 2013;64:249-63.

35. Del Rincon I, O'Leary DH, Freeman GL, et al. Acceleration of atherosclerosis during the course of rheumatoid arthritis. Atherosclerosis 2007 Dec;195(2):354-60.

36. Lebowitz WB. The heart in rheumatoid arthritis (rheumatoid disease). A clinical and pathological study of sixty-two cases. Ann Intern Med 1963 Jan;58:102-23.

37. Bonfiglio T, Atwater EC. Heart disease in patients with seropositive rheumatoid arthritis; a controlled autopsy study and review. Arch Intern Med 1969 Dec;124(6):714-9.

38. Gullestad L, Ueland T, Vinge LE, et al. Inflammatory cytokines in heart failure: mediators and markers. Cardiology 2012;122(1):23-35.

39. Mann DL, McMurray JJ, Packer M, et al. Targeted anticytokine therapy in patients with chronic heart failure: results of the Randomized Etanercept Worldwide Evaluation (RENEWAL). Circulation 2004 Apr 06;109(13):1594-602.

40. Anker SD, Coats AJ. How to RECOVER from RENAISSANCE? The significance of the results of RECOVER, RENAISSANCE, RENEWAL and ATTACH. Int J Cardiol 2002 Dec;86(2-3):123-30.

41. Kinno M, Nagpal P, Horgan S, et al. Comparison of Echocardiography, Cardiac Magnetic Resonance, and Computed Tomographic Imaging for the Evaluation of Left Ventricular Myocardial Function: Part 1 (Global Assessment). Curr Cardiol Rep 2017 Jan;19(1):9.

42. Leong DP, De Pasquale CG, Selvanayagam JB. Heart failure with normal ejection fraction: the complementary roles of echocardiography and CMR imaging. JACC Cardiovasc Imaging 2010 Apr;3(4):409-20.

43. Van Tassell BW, Raleigh JM, Abbate A. Targeting interleukin-1 in heart failure and inflammatory heart disease. Curr Heart Fail Rep 2015 Feb;12(1):33-41.

44. Dayer JM, Choy E. Therapeutic targets in rheumatoid arthritis: the interleukin-6 receptor. Rheumatology (Oxford) 2010 Jan;49(1):15-24.

45. Nakano M, Knowlton AA, Dibbs Z, et al. Tumor necrosis factor-alpha confers resistance to hypoxic injury in the adult mammalian cardiac myocyte. Circulation 1998 Apr 14;97(14):1392-400.

46. Ghigo A, Franco I, Morello F, et al. Myocyte signalling in leucocyte recruitment to the heart. Cardiovasc Res 2014 May;102(2):270-80.

47. Braunwald E. Biomarkers in heart failure. N Engl J Med 2008 May 15;358(20):2148-59.

48. Tomas L, Lazurova I, Pundova L, et al. Acute and long-term effect of infliximab on humoral and echocardiographic parameters in patients with chronic inflammatory diseases. Clin Rheumatol 2013 Sep;32(1):61-66.

3

The effect of anti-TNF therapy on cardiac function in rheumatoid arthritis: an observational study

Chapter

4

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Abstract

Objectives – Congestive heart failure (CHF) is the second most prevalent cause of death in rheumatoid arthritis (RA). The systemic inflammatory state in RA patients is deemed responsible for this finding. Anti-inflammatory treatment with anti-tumor necrosis factor (anti-TNF) therapy decreases CV risk and subsequently might improve the cardiac function by lowering the overall inflammatory state. This study investigated the effect of anti-TNF on the cardiac function in RA patients.

Methods – Fifty one RA patients were included, of which thirty three completed follow-up. Included patients were >18 years, had moderate–high disease activity and no history of cardiac disease. Patients were assessed at baseline and after six months of anti-TNF treatment. Patients underwent conventional Speckle tracking and tissue Doppler echocardiography in combination with clinical and laboratory assessments at baseline and follow-up.

Results – The left ventricular ejection fraction (LVEF) and global longitudinal strain (GLS) showed no changes during follow-up, LVEF 63% (±9) to 62% (±8) p = 0.097 and GLS −20 (±4) to −20 (±3) p = 0.79, respectively. Furthermore, E/e' nor E/A changed significantly between baseline and follow-up, respectively 8 (7−9) and 8 (7−9) p = 0.17 and 1.1 (±0.4) and 1.1 (±0.4) p = 0.94. Follow-up NT-proBNP decreased with 23%, from 89 ng/L (47−142) to 69 ng/L (42−155), p = 0.10. Regression analysis revealed no association between change in inflammatory variables and cardiac function.

Conclusion – Echocardiography showed no effect of anti-TNF treatment on the cardiac function in RA patients with low prevalence of cardiac dysfunction. Moreover, NT-proBNP decreased, possibly indicating (subtle) improvement of the cardiac function.

Introduction

Patients with rheumatoid arthritis (RA) have a 1.5-fold increased risk of cardiovascular (CV) mortality [1,2]. The systemic inflammatory state in RA patients is deemed responsible for this increased risk by causing endothelial dysfunction and accelerating atherosclerosis [3,4]. Second after myocardial infarction, congestive heart failure (CHF) is one of the most prevalent causes of death in RA patients [5,6]. The damage caused by a myocardial infarction and formation of subsequent scar tissue might be a cause of the elevated incidence of heart failure. However, a direct effect of the systemic inflammation itself has also been suggested as a cause for the development of left ventricular (LV) dysfunction. The latter is possibly explained by a process in which circulating pro-inflammatory mediators, such as tumor necrosis factor (TNF), induce coronary endothelial activation leading to stiffness of the myocardium and interstitial fibrosis deposition, resulting in impairment of the relaxation of the myocardium (diastolic dysfunction) [7]. Particularly, RA studies have shown an increased prevalence of left ventricular diastolic dysfunction [8–10]. This explanation is underlined by studies demonstrating that the increased incidence of CHF is only partly due to increased prevalence of CV risk factors, such as hypertension, dyslipidemia and increased insulin resistance. However, even after correction for these traditional risk factors, the increased risk for CHF remains [11,12].

Several studies have shown that anti-inflammatory treatment with anti-TNF therapy decreases the CV risk in RA [13–15]. It is plausible that anti-TNF therapy improves the cardiac function by lowering the overall inflammatory state by decreasing coronary endothelial activation and slowing down the process of coronary atherosclerosis [16], thus potentially decreasing the risk of developing CHF in RA patients.

However, previous studies assessing the effect of anti-TNF on the cardiac function have shown conflicting results [17,18]. Firstly, anti-TNF therapy is contra-indicated in (RA) patients with CHF (New York Heart Association class III and IV) [18], following trials from the early '00s suggesting that anti-TNF possibly worsens CHF and increases mortality in non-RA patients with systolic CHF. It must be recognized, however, that the interpretation of these results is still controversial to date [18]. Moreover, several trials did not show a detrimental effect of anti-TNF therapy on the incidence of newly onset CHF in RA patients [19,20]. Two imaging studies assessing the effect of infliximab on the cardiac function with echocardiography showed improved measures of systolic

and diastolic function, subsequently an increased left ventricular ejection fraction (LVEF) and a decrease of E/e' (parameter for diastolic function) after at least 3 months treatment, suggesting improvement of the systolic as well as diastolic function [21,22]. Finally, one study investigating the effect of anti-TNF on the cardiac function with Speckle tracking echocardiography did not show improvement of function [23]. Overall, it should be realized that these studies had relatively small sample sizes and altogether, it is presently unknown whether and to what extent TNF blocking therapy has a favorable effect on the cardiac function in patients with RA.

This study aimed to elucidate the effect of anti-inflammatory therapy, i.e., anti-TNF, on the systolic and diastolic cardiac function in RA patients assessed with comprehensive echocardiography (including conventional, tissue-Doppler and Speckle tracking) and cardiac biomarkers.

Methods

Study population—a prospective study in fifty one RA patients was performed. Subjects were recruited randomly from a large rheumatology outpatient clinic (Reade) in Amsterdam, the Netherlands and Amsterdam UMC, Vrije Universiteit Amsterdam, department of Rheumatology, the Netherlands from December 2014 and June 2018. All participants gave written informed consent and the protocol (NL49652.048.14) was approved by the medical ethics committee of the Slotervaart hospital and Reade, Amsterdam, the Netherlands. Echocardiography and clinical and laboratory assessments were done at baseline and after 6 months of anti-TNF therapy. Inclusion criteria consisted of patients fulfilling the 1987 ACR criteria for RA [24], being at least 18 years old, having moderate–high disease activity (DAS28 ≥ 3,2) or increased inflammatory biomarkers (i.e., erythrocyte sedimentation rate (ESR) > 15, C-reactive protein (CRP) > 10) and being scheduled for anti-TNF treatment. Patients started subcutaneous treatment with adalimumab (40 mg biweekly), etanercept (50 mg weekly), certolizumab pegol (400 mg biweekly during first two doses followed by 200 mg biweekly) or golimumab (50 mg monthly). Patients with a medical history of cardiac disease such as myocardial infarction and heart failure, and patients who used anti-TNF therapy 3 months prior to start of the study were excluded. Patients were assessed at baseline and after 6 months of anti-TNF treatment.

Clinical assessment—disease activity was assessed by the disease activity score DAS28 [25]. Physical examination included height, weight, blood pressure measurement and joint examination. Blood sample measurements (non-fasting) included standard hematological assessment, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), triglyceride levels, total cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein (LDL), NT-proBNP and Troponin-T. All blood samples were assessed in a single laboratory. Health Assessment Questionnaire (HAQ) and patients global assessment of disease activity (VAS). Furthermore, smoking status, history and family history for cardiovascular disease (CVD) were assessed anamnestically.

Echocardiography—transthoracic echocardiography (TTE)—was performed by certified echo technicians at the European Society of Cardiology (ESC)-certified department of echocardiography of the Amsterdam University medical center, location VUmc, using a Philips ultrasound system (Epiq 7 and IE 33, Philips, Amsterdam, NL). All echocardiographic recordings were stored digitally and were afterwards analyzed by an experienced cardiologist specialized in echocardiography (T.C.K.). TTE was performed according to the following protocol based on the guidelines provided by European Association of Echocardiography [26]. Assessment of the cardiac function consisted of apical four-, three- and two-chamber views, and 2D color and spectral flow Doppler recordings. Left ventricular mass (LVM) was computed based on the Devereux and Reichek formula [27]. Pulse wave tissue Doppler imaging was assessed in the apical views to obtain mitral annular velocities. The sample volume was located at, or within 1 cm of the septal (e' sept) and lateral (e' lat) mitral valve insertion sites. Doppler spectral velocity recordings of the mitral inflow were assessed with the sample volume aimed at the tips of mitral valves. From the trans mitral Doppler velocity recordings, the E wave deceleration time (DT), peak E and A velocities and the E/A ratio were acquired. Left atrial volume was obtained using the modified biplane Simpson's rule. LVEF and diastolic and systolic volumes were computed by Simpson's from the apical four- and two-chamber view. The left ventricular global longitudinal strain (GLS) was measured using QLab (version 10.3, Philips, Amsterdam, NL) (Figure 1). As the quality of echocardiography is subject to external factors such as excessive fat tissue, not all cardiac parameters were assessed per patient. The total number of cardiac parameter assessments are therefore described per variable in Table 1.

Figure 1. Flowchart of inclusion.
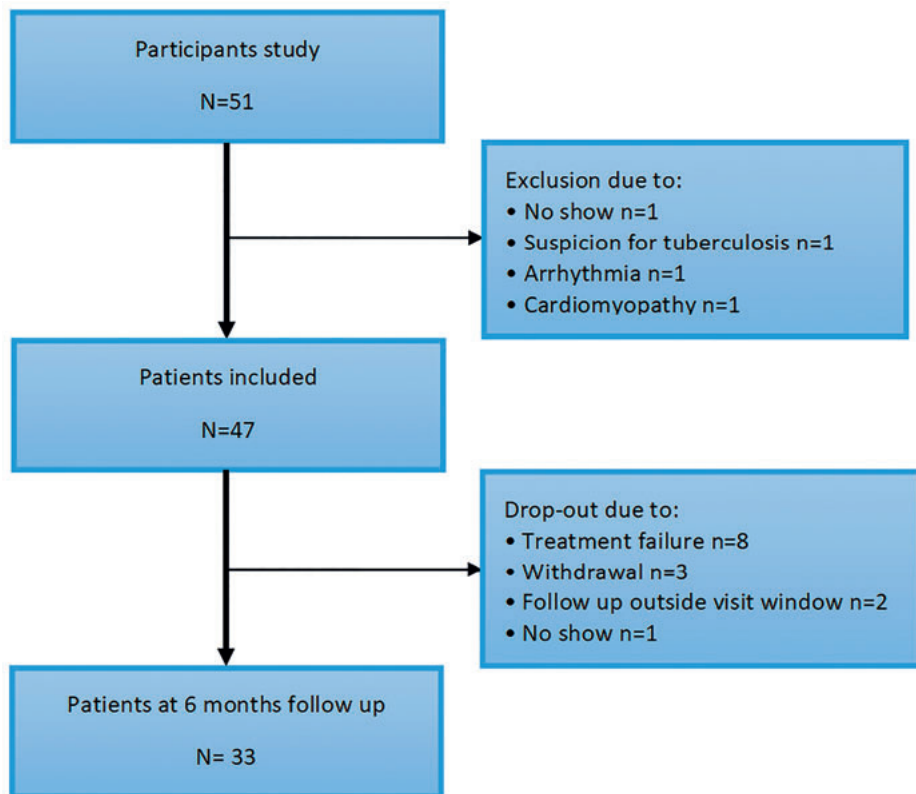
Table 1. Baseline characteristics.

Patient Characteristics	*n* = 47
Age, years	57 (±11)
Gender, female (*n*, %)	32 (68%)
RA disease duration, years	5 (2–19)
BMI, kg/m^2	26.0 (±4.5)
History of vascular disease (*n*, %)	1 (2%)
Hypertension (*n*, %)	4 (9%)
Systolic blood pressure, mmHg	130 (±15)
Diastolic blood pressure, mmHg	80 (±10)
Hypercholesterolemia (*n*, %)	3 (6%)
Diabetes mellitus type 2 (*n*, %)	1 (2%)
Smoking (*n*, %)	13 (29%)
Rheumatoid factor positive (*n*, %)	33 (66%)
Anti-cyclic citrullinated protein positive (*n*, %)	32 (68%)
LDL, mmol/L	2.93 (±0.90)
HDL, mmol/L	1.57 (±0.50)

Table 1. Continued.

Patient Characteristics	n = 47
Medication	
Current oral corticosteroid use (*n*, %)	13 (28%)
Intra-muscular/intra-articular corticosteroid in the past 3 months (*n*, %)	9 (19%)
csDMARD use	43 (92%)
Methotrexate (with or without other csDMARD(s))	33 (70%)
Other csDMARD(s)	10 (21%)
Biological therapy (*n*, %)	
Etanercept	16 (34%)
Adalimumab	23 (49%)
Certolizumab	7 (15%)
Golimumab	1 (2%)
Disease activity parameters	
DAS28	4.44 (±1.23)
CRP, mmol/L	6.3 (3.1–20.0)
ESR, mm/h	22.5 (9.0–42.5)
Health assessment questionnaire (HAQ)	1.25 (0.75–1.50)
Cardiac parameters	
E/e' ratio (*n* = 46)	7.9 (6.6–9.0)
E/A ratio(*n* = 46)	1.1 (±0.36)
Deceleration time, ms (*n* = 43)	0.22 (±0.06)
LA volume index, mL/m^2 (*n* = 33)	28.40 (±7.53)
LV ejection fraction, % (*n* = 29)	63.1 (±8.8)
GLS (*n* = 44)	−19.8 (±3.5)
Impaired GLS (>−17%) (*n*, %) (*n* = 44)	6 (14%)
LV mass index, g/m^2 (*n* = 42)	68.46 (±17.97)
Diastolic LV dysfunction (*n*, %) (*n* = 46)	
No diastolic dysfunction	38 (83%)
grade I	2 (4%)
grade II	1 (2%)
grade III	0 (0%)
indeterminate	5 (11%)
Systolic LV dysfunction (*n*, %) (*n* = 29)	2 (7%)
Aortic valve stenosis (*n*, %) (*n* = 46)	0 (0%)
Aortic valve regurgitation (*n*, %) (*n*=46)	6 (13%)
mild	6 (13%)
moderate	0 (0%)
severe	0 (0%)
Mitral valve stenosis (*n*, %) (*n* = 46)	0 (0%)
Mitral valve regurgitation (*n*, %) (*n* = 45)	18 (38%)
mild	18 (38%)
moderate	0 (%)
severe	0 (0%)

4

Table 1. Continued.

Patient Characteristics	*n* = 47
H2FPEF score	
0–1 points	32 (70%)
2–4 points	15 (30%)
5–6 points	0 (0%)
Cardiac biomarkers	
Troponin-T, µg/mL	6 (3–8)
NT-proBNP, ng/L	88.6 (47.0–142.0)

Values are displayed as mean ± standard deviation (SD), median (IQR) or frequencies with corresponding percentages (%). RA = rheumatoid arthritis, BMI = body mass index, LDL = low density lipoprotein, HDL = high density lipoprotein, csDMARD = conventional synthetic Disease Modifying Anti Rheumatic Drug(s), DAS28 = disease activity score-28, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, LA = left atrial, LV = left ventricular, GLS = global longitudinal strain, NT-ProBNP = N-terminal pro hormone-brain natriuretic peptide.

In addition, the modified H2FPEF score was used to calculate the a priori chance of the diastolic dysfunction in this cohort [28]. The peak TRV >2.8 m/s was suggestive for pulmonary hypertension.

Electrocardiography (ECG)—ECGs performed were standard 12-lead ECGs, recorded at 25 mm/s paper speed. ECGs were analyzed by a single investigator (T.C.K.) whom was blinded to the clinical status of all the patients.

Definitions—systolic LV dysfunction was defined as an LVEF <50%. Abnormal GLS was defined as >−17%. Diastolic function assessment was based on the ASE/EACVI 2016 guidelines [29] categorized in 4 grades: normal diastolic function and grade I-III (or indeterminate).

Statistical analysis—characteristics of the population are expressed as ± standard deviation (SD), median (interquartile range) (IQR) or percentages. For comparisons of paired continuous variables between baseline and follow-up with normal distribution, paired student-s t-test was used. In case of non-normal distribution, the Wilcoxon signed-ranks test or log transformation was used. For comparisons of dichotomous variables between baseline and follow-up, the Pearson's chi-square test was performed. Regression analysis was used to assess the possible effect of change in systemic inflammation on the cardiac function with the follow-up cardiac function parameter as a dependent variable adjusted for the baseline cardiac function parameter, the baseline inflammatory parameter and delta inflammatory parameter (absolute change of the inflammatory variable at follow-up). As inflammatory parameters, the DAS28, CRP and ESR were used. LVEF, GLS, E/e', E/A and NT-proBNP were used as values for cardiac function.

All analyses were done with SPSS version 23 (SPSS, Chicago, IL, USA) and two-sided p-values less than 0.05 were considered statistically significant.

The sample size was based on the primary outcome, i.e., diastolic LV function as assessed with Doppler echocardiography and was calculated using the McNemar's test for sample size estimation. With an expected improvement of 25% in diastolic LV function during anti-TNF therapy [23,30] and a significance level of 5% and 90% power, the total calculated sample size was forty four subjects. To account for a loss to follow-up of 10%, fifty one patients were included.

Results

Patient Characteristics

The baseline characteristics are described in Table 1. A total of fifty one subjects participated in the study. Four patients were excluded at baseline for various reasons (no show, suspicion of tuberculosis or cardiac disease de novo, arrhythmia and cardiomyopathy, depicted in Figure 2). The mean age of the patients was 57 (±11) years, of which 68% were female. Median RA disease duration was 5 (2-19) years and disease activity was moderate-high, with a mean DAS28 score of 4.44 (±1.23). Overall, the patient-s mobility was moderately impaired with a median HAQ score of 1.25 (0.75-1.50). One patient had a confirmed vascular event (ischemic CVA) in the history.
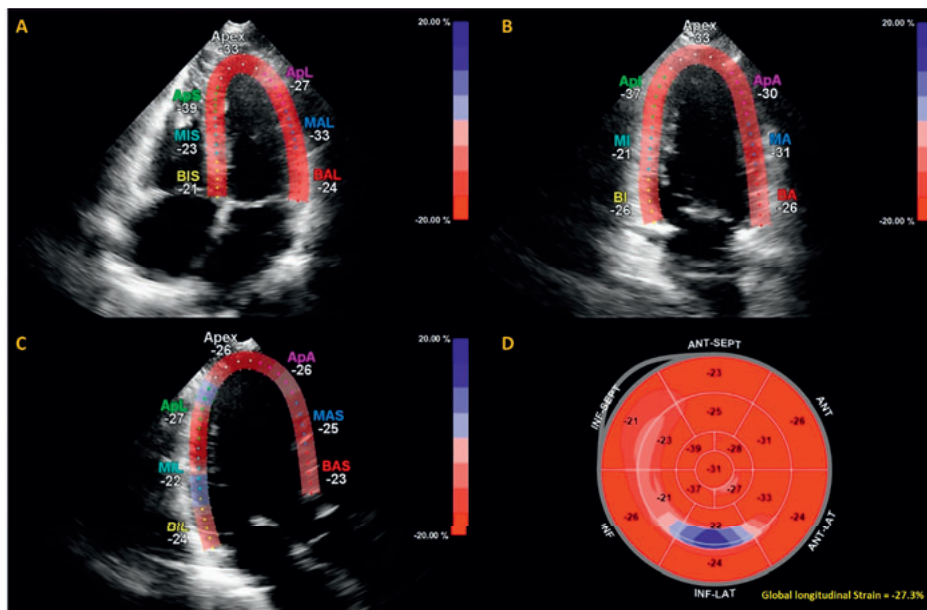
Figure 2. Example of calculation of global longitudinal strain (GLS) by speckle tracking for the apical four-, three- and two-chamber views (A, B and C). The strain during one cardiac cycle is shown for each of the color-coded (red and blue) left ventricular segments. The longitudinal strain bull's eye plot (D) determined from 2D speckle tracking imaging offers a visual overview of the regional and global left ventricular myocardial function in a diagram. In this example of one of the subjects in this study, the GLS is −27.3%, which is in the normal range.

Cardiac Function at Baseline

At baseline, three (7%) patients had diastolic LV dysfunction, of which two (4%) had diastolic dysfunction grade I, and one (2%) had diastolic LV dysfunction grade II. Importantly, two cases of diastolic dysfunction (grade I) was due to the presence of systolic dysfunction. None of the patients with diastolic dysfunction had hypertension nor diabetes mellitus (DM). In comparison, three of the thirty eight (8%) patients with normal diastolic function had hypertension and one (3%) had DM. Systolic LV dysfunction based on the ejection fraction was seen in two patients (4%). The GLS showed impaired systolic LV function in six patients (14%).

A total of thirty seven ECGs were assessed of which three ECGs showed abnormalities. These were a left bundle branch block, a pathologic Q-wave (without a known history of myocardial infarction) and a first degree atrioventricular block.

Disease Activity and Cardiac Function at six Months Follow-Up

A total of thirty three patients completed follow-up. Fourteen patients dropped out of which eight due to treatment failure (lack of efficacy), three participants withdrew out of the study and of two patients fell out of the follow-up date. DAS28 decreased significantly after six months anti-TNF therapy, from 4.44 (±1.23) to 2.72 (±1.23), p < 0.001. Furthermore, on average the patients mobility as scored with the HAQ improved from 1.3 (0.8-1.5) to 0.5 (0.0-1.3), p = 0.001. LVEF and GLS showed no change after 6 months of anti-TNF therapy, respectively 63.0% (±8.7) to 62.0% (±7.9), p = 0.097 and −19.8 (±3.5) to -19.9 (±2.6), p = 0.79. See Table 2.

Table 2. Effect of anti-TNF on the cardiac parameters and disease activity parameters.

	Baseline (n = 47)	Follow-Up (n = 33)	p-Value
Cardiac parameters			
E/e'	7.9 (6.6–9.0)	7.7 (7.1–9.1)	0.17
E/A	1.1 (±0.4)	1.1 (±0.4)	0.94
Deceleration time, sec	0,22 (±0.06)	0.22 (±0.04)	0.44
LA volume index, mL/m^2	28.4 (±7.5)	30.3 (±5.4)	0.21
LV ejection fraction, %	63.0 (±8.7)	62.0 (±7.9)	0.097
GLS	−19.8 (±3.5)	−19.9 (±2.6)	0.79
LV mass index, gram/m^2	68.5 (±18.0)	73.0 (±22.4)	0.66
Troponin-T, µg/mL	6 (3–8)	7 (4–9)	0.43
NT-proBNP, ng/L	89 (47–142)	69 (42–155)	0.10
Disease activity parameters			
DAS28	4.44 (±1.23)	2.72 ± 1.23	<0.001 *
CRP, mg/L	6.3 (3.1–20.0)	2.6 (0.8–7.6)	0.009 *
ESR, mm/h	23 (9.0–43)	8 (5–15)	<0.001 *
HAQ	1.3 (0.8–1.5)	0.5 (0.0–1.3)	0.001 *

Values are displayed as mean ± standard deviation (SD), median (IQR) or frequencies with corresponding percentages (%). LA = left atrial, LV = left ventricular, GLS = global longitudinal strain, NT-proBNP = N-terminal pro hormone-brain natriuretic peptide, DAS28 = disease activity score-28, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, HAQ = health assessment questionnaire. * Significance level of $p \leqslant 0.05$.

From thirty of the thirty three patients with successful follow-up, it was possible to grade the diastolic function. Of these patients, twenty eight had normal diastolic function, one had diastolic dysfunction grade I and one diastolic dysfunction grade II. No patients had diastolic dysfunction grade III. Compared to the baseline, only in one case was the diastolic function changed from normal to grade I. Additionally, neither the E/e' nor the E/A showed a significant change after six months of anti-TNF therapy, respectively 7.9 (6.6-9.0) to 7.7 (7.1-9.1), p = 0.17 and 1.1 (±0.4) to 1.1 (±0.4), p = 0.94.

NT-proBNP values decreased, although this did not reach statistical significance, with a reduction of 23% at follow-up compared to baseline, respectively 89 ng/L (47-142) to 69 ng/L (42-155, p = 0.10). Troponin-T did not show any change at follow-up, 6 (3-8) µg/mL to 7 (4-9) µg/mL, p = 0.43.

The highest quartile for the LV ventricular filling pressure (E/e') was compared with the other three quartiles, respectively E/e'>9 vs E/e'<9. Seven patients had an E/e'>9 at baseline who completed follow-up. In these patients, no echocardiographic parameters improved nor worsened after anti-TNF therapy (Table 3).

Table 3. Effect of anti-TNF in patients in the highest E/e' quartile (E/e'>9).

E/e'>9 (*n*)	Baseline	Follow-Up	*p*-Value
E/A (6)	1.0 (±0.4)	1.0 (±0.3)	0.97
E/e' (7)	11.8 (±3.0)	10.9 (±4.2)	0.34
deceleration time, sec (4)	0.23 (±0.06)	0.26 (±0.05)	0.34
ejection fraction (4)	62.0 (±7.4)	62.2 (±9.5)	0.97
LV mass index, gram/m^2 (5)	83.0 (±26.1)	100.6 (54.1)	0.28
LA volume index, mL/m^2 (4)	36.6 (±3.8)	36.6 (±3.8)	0.87
GLS (6)	−18.0 (±3.5)	−18.2 (±2.7)	0.90

Values are displayed as mean ± standard deviation (SD) or median (IQR). LA = left atrial, LV = left ventricular, GLS = global longitudinal strain, * Significance level of *p* ≤ 0.05.

Regression analyses showed no association between changes in inflammatory parameters, i.e., DAS28 and ESR, and changes in cardiac parameters, i.e., E/e', E/A, GLS and NT-proBNP, between baseline and follow-up.

Discussion

To our knowledge, this is the first and largest study investigating the effect of first line anti-TNF therapy on the cardiac function in a Western RA cohort assessed with comprehensive echocardiography (including conventional, Speckle tracking and tissue Doppler) in combination with cardiac biomarkers. In contrast to what was expected, the echocardiographic results did not show improvement but importantly also showed no worsening of the cardiac function. Moreover, this study found a 23% decrease of NT-proBNP after six months of anti-TNF therapy, although this did not reach statistical significance.

Overall, diastolic function categorized in grades changed in only one case. The E/e'-ratio, a robust marker for predicting LV filling pressures and indirectly diastolic (dys) function [31], also did not show a significant change at follow–up compared to baseline, not even when comparing the highest quartile with the other quartiles. Examination of the systolic ventricular function was done using the LVEF and the more sensitive GLS to pick up more subtle changes. However, again, no improvement nor deterioration was observed. These unexpected results can be explained by the following causes. First, this could have been due to the low prevalence of cardiac dysfunction at baseline as only three (7%) patients had diastolic dysfunction. Therefore, the study may have been underpowered to show the improvement of the cardiac function. According to the literature, RA patients are more likely to have echocardiographic parameters of diastolic dysfunction in comparison to the general population [8,32,33]. Unexpectedly, our population had a lower-than-expected prevalence of diastolic dysfunction. This is explained because in our study diastolic function was assessed according to the updated 2016 ASE/EACVI grading criteria [29]. This grading algorithm applies several echocardiographic parameters and is more critical than previous grading algorithms of the 2009 ASE/EACVI criteria [34] and the Redfield criteria [35]. The primary goal of the 2016 ASE/EACVI update was to simplify the approach and hence increase the utility of the guidelines in daily clinical practice. However, recent studies also demonstrate a higher specificity and a lower sensitivity of the 2016 ESE/EACVI criteria resulting in a lower overall prevalence of diastolic dysfunction compared to the 2009 ASE/EACVI criteria. In addition, the 2016 ASE/EACVI criteria shows superiority over the 2009 criteria in predicting mortality, myocardial infarction and heart failure [36] and importantly in predicting increased left ventricular pressure measured with invasive assessment [37], thus making it currently the best available non-invasive diastolic dysfunction assessment tool. In comparison, previous studies mostly used the Redfield criteria, which is primary focused on the E/A ratio and the E-wave deceleration time (DT). When applying the 2009 ASE/EACVI and Redfield criteria in our cohort, the prevalence of diastolic dysfunction at baseline is considerably higher with respectively fifteen (33%) and eleven patients (23%). However, again, no relevant changes were observed at follow-up.

Second, this population had a relatively short disease duration and a relatively low disease activity compared to other studies, demonstrating an increased prevalence of cardiac dysfunction in RA patients compared to healthy subjects [8,38]. In addition, our population was relatively cardiac healthy as patients were relatively young and had low

prevalence of cardiovascular comorbidities, and were thus less prone to the development of cardiac dysfunction. This is also suggested by the low H2FPEF score calculated for this cohort. The H2FPEF score is a method to assess the risk of the presence of heart failure with preserved ejection fraction (HFpEF) in patients with dyspnea and comprises a major risk factor for developing diastolic dysfunction. A large majority of the subjects (94%) had a H2FPEF score ranging from 0–2 and thus, a low a priori chance for diastolic dysfunction. This is also confirmed by the low serum NT-proBNP at baseline, indicating a normal cardiac wall tension. Another possibility could be due to the limitation of echocardiography in the assessment of diastolic function and the lacking ability to detect subtle diastolic changes. Possibly more sensitive assessment methods, such as exercise echocardiography [39], exercise right heart catheterization [40] or cardiac magnetic resonance imaging (MRI) [41], could help detect mild diastolic dysfunction and subtle diastolic changes. However, GLS analysis, a sensitive assessment method for the systolic dysfunction, did not show any alteration of the cardiac function. Furthermore, a large number of the patients used corticosteroids prior to the start of anti-TNF therapy, thereby affecting the anti-inflammatory effect of anti-TNF. Importantly, we found that that anti-TNF therapy had no detrimental effect on the cardiac function in patients with normal and relatively mild cardiac dysfunction.

Interestingly, studies assessing the effect of biologic agents with modes of action other than TNF-blockade show more evident ameliorating effects on the cardiac function. Several studies conducted by Ikonimidos et al. investigating the effect of anti-interleukin (IL)-1 therapy (anakinra) showed a significant improvement in cardiac function assessed with echocardiography [38,42,43]. Studies assessing the effect of anti-IL-6 (tocilizumab) on cardiac function assessed with cardiac MRI also showed an ameliorating effect on the diastolic function [44,45]. A possible explanation for this could be that IL-1 is produced earlier in the cytokine cascade and is the triggering factor of several cytokines including IL-6 and TNF-a [46]. Thus, theoretically, its inhibition may be more effective in controlling inflammation and thus improving LV function than inhibition of the later-released TNF-a. Whether anti-IL-1 and/or anti-IL-6 therapy have indeed more pronounced effects on cardiac function then anti-TNF is not known, as direct comparative studies have not been conducted. NT-proBNP is a predictor of CV mortality and morbidity in patients with or without a history of CVD and RA patients [47–49] and in our study, a 23% NT-pro BNP decrease after 6 months anti-TNF treatment was observed. This is in line with the findings of Kotyla et al., and Peters et al., where infliximab treatment or adalimumab treatment during 4 months led to comparable

decreases of serum NT-proBNP in RA patients [22,50]. There are a few explanations for this phenomenon. Firstly, reduction of inflammation could have led to reduced ventricular stress. This is confirmed by the literature describing that inflammation contributes to arterial stiffening and consecutively increases ventricular load [51,52]. Secondly, low grade inflammation of cardiac tissue can lead to a stress response of the myocardium, leading to increased NT-proBNP production. This could explain the overall relationship between NT-proBNP and systemic inflammation [53,54]. However, a direct effect of anti-TNF on the production or secretion of NT-proBNP cannot be ruled out.

A major strength of this study is the comprehensive and prospective approach in the assessment of cardiac function with the use of conventional Doppler and Speckle tracking echocardiography in combination with cardiac biomarkers. Therefore, this study was able to determine the different outcomes assessing the cardiac function. The main limitation of this study was, as the prevalence of cardiac dysfunction was unexpectedly low, the rather limited sample size.

Conclusions

In conclusion, echocardiography showed no improvement nor deterioration of anti-TNF treatment on the cardiac function in RA patients with a low prevalence of cardiac dysfunction. However, NT-proBNP decreased 23% after anti-TNF treatment, which might suggest subtle improvement of the cardiac function.

References

1. Avina-Zubieta, J.A.; Choi, H.K.; Sadatsafavi, M.; Etminan, M.; Esdaile, J.M.; Lacaille, D. Risk of cardiovascular mortality in patients with rheumatoid arthritis: A meta-analysis of observational studies. Arthritis Rheum. 2008, 59, 1690–1697.

2. Maradit-Kremers, H.; Nicola, P.J.; Crowson, C.S.; Ballman, K.V.; Gabriel, S.E. Cardiovascular death in rheumatoid arthritis: A population-based study. Arthritis Rheum. 2005, 52, 722–732.

3. Libby, P. Role of inflammation in atherosclerosis associated with rheumatoid arthritis. Am. J. Med. 2008, 121 (Suppl. 1), S21–S31.

4. Crowson, C.S.; Liao, K.P.; Davis, J.M., III; Solomon, D.H.; Matteson, E.L.; Knutson, K.L.; Hlatky, M.A.; Gabriel, S.E. Rheumatoid arthritis and cardiovascular disease. Am. Heart J. 2013, 166, 622–628.

5. Mok, C.C.; Kwok, C.L.; Ho, L.Y.; Chan, P.T.; Yip, S.F. Life expectancy, standardized mortality ratios, and causes of death in six rheumatic diseases in Hong Kong, China. Arthritis Rheum. 2011, 63, 1182–1189.

6. Turesson, C.; Jarenros, A.; Jacobsson, L. Increased incidence of cardiovascular disease in patients with rheumatoid arthritis: Results from a community based study. Ann. Rheum Dis. 2004, 63, 952–955.

7. Paulus, W.J.; Tschope, C. A novel paradigm for heart failure with preserved ejection fraction: Comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. J. Am. Coll Cardiol. 2013, 62, 263–271.

8. Aslam, F.; Bandeali, S.J.; Khan, N.A.; Alam, M. Diastolic dysfunction in rheumatoid arthritis: A meta-analysis and systematic review. Arthritis Care Res. 2013, 65, 534–543.

9. Renjith, A.S.; Marwaha, V.; Aggarwal, N.; Koshy, V.; Singal, V.K.; Kumar, K. Prevalence of left ventricular dysfunction in rheumatoid arthritis. J. Fam. Med. Prim. Care 2017, 6, 622–626.

10. Giles, J.T.; Fernandes, V.; Lima, J.A.; Bathon, J.M. Myocardial dysfunction in rheumatoid arthritis: Epidemiology and pathogenesis. Arthritis Res. Ther. 2005, 7, 195–207.

11. Mantel, A.; Holmqvist, M.; Andersson, D.C.; Lund, L.H.; Askling, J. Association Between Rheumatoid Arthritis and Risk of Ischemic and Nonischemic Heart Failure. J. Am. Coll. Cardiol. 2017, 69, 1275–1285.

12. Nicola, P.J.; Maradit-Kremers, H.; Roger, V.L.; Jacobsen, S.J.; Crowson, C.S.; Ballman, K.V.; Gabriel, S.E. The risk of congestive heart failure in rheumatoid arthritis: A population-based study over 46 years. Arthritis Rheum. 2005, 52, 412–420.

13. van Halm, V.P.; Nurmohamed, M.T.; Twisk, J.W.; Dijkmans, B.A.; Voskuyl, A.E. Disease-modifying antirheumatic drugs are associated with a reduced risk for cardiovascular disease in patients with rheumatoid arthritis: A case control study. Arthritis Res. Ther. 2006, 8, R151.

4

14. Westlake, S.L.; Colebatch, A.N.; Baird, J.; Curzen, N.; Kiely, P.; Quinn, M.; Choy, E.; Ostor, A.J.; Edwards, C.J. Tumour necrosis factor antagonists and the risk of cardiovascular disease in patients with rheumatoid arthritis: A systematic literature review. Rheumatology 2011, 50, 518–531.

15. van Sijl, A.M.; van Eijk, I.C.; Peters, M.J.; Serne, E.H.; van der Horst-Bruinsma, I.E.; Smulders, Y.M.; Nurmohamed, M.T. Tumour necrosis factor blocking agents and progression of subclinical atherosclerosis in patients with ankylosing spondylitis. Ann. Rheum. Dis. 2015, 74, 119–123.

16. van Sijl, A.; Mamas, M.; Lunt, M.; Watson, K.; Symmons, D.P.; Hyrich, K.L. Incidence of Congestive Heart Failure in Subjects with Rheumatoid Arthritis Receiving Anti-Tumour Necrosis Factor Drugs: Results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. Arthritis Rheumatol. 2014, 66, S840.

17. Baniaamam, M.; Paulus, W.J.; Blanken, A.B.; Nurmohamed, M.T. The effect of biological DMARDs on the risk of congestive heart failure in rheumatoid arthritis: A systematic review. Expert Opin. Biol. Ther. 2018, 18, 585–594.

18. Anker, S.D.; Coats, A.J.S. How to RECOVER from RENAISSANCE? The significance of the results of RECOVER, RENAISSANCE, RENEWAL and ATTACH. Int. J. Cardiol. 2002, 86, 123–130.

19. Listing, J.; Strangfeld, A.; Kekow, J.; Schneider, M.; Kapelle, A.; Wassenberg, S.; Zink, A. Does tumor necrosis factor alpha inhibition promote or prevent heart failure in patients with rheumatoid arthritis? Arthritis Rheum. 2008, 58, 667–677.

20. Al-Aly, Z.; Pan, H.; Zeringue, A.; Xian, H.; McDonald, J.R.; El-Achkar, T.M.; Eisen, S. Tumor necrosis factor-alpha blockade, cardiovascular outcomes, and survival in rheumatoid arthritis. Transl. Res. 2011, 157, 10–18.

21. Cetin, S.; Mustafa, G.; Keskin, G.; Yeter, E.; Dogan, M.; Ozturk, M.A. Infliximab, an anti-TNF-alpha agent, improves left atrial abnormalities in patients with rheumatoid arthritis: Preliminary results. Cardiovasc. J. Afr. 2014, 25, 168–175.

22. Kotyla, P.J.; Owczarek, A.; Rakoczy, J.; Lewicki, M.; Kucharz, E.J.; Emery, P. Infliximab treatment increases left ventricular ejection fraction in patients with rheumatoid arthritis: Assessment of heart function by echocardiography, endothelin 1, interleukin 6, and NT-pro brain natriuretic peptide. J. Rheumatol. 2012, 39, 701–706.

23. Vizzardi, E.; Cavazzana, I.; Franceschini, F.; Bonadei, I.; Sciatti, E.; Lombardi, C.M.; Tincani, A.; Metra, M. Left ventricular function in rheumatoid arthritis during anti-TNF-alpha treatment: A speckle tracking prospective echocardiographic study. Monaldi Arch. Chest Dis. 2016, 84, 716.

24. Arnett, F.C.; Edworthy, S.M.; Bloch, D.A.; McShane, D.J.; Fries, J.F.; Cooper, N.S.; Healey, L.A.; Kaplan, S.R.; Liang, M.H.; Luthra, H.S.; et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988, 31, 315–324.

25. Prevoo, M.L.; Van't Hof, M.A.; Kuper, H.H.; Van Leeuwen, M.A.; Van De Putte, L.B.; Van Riel, P.L. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum. 1995, 38, 44–48.

26. Lang, R.M.; Badano, L.P.; Tsang, W.; Adams, D.H.; Agricola, E.; Buck, T.; Faletra, F.F.; Franke, A.; Hung, J.; de Isla, L.P.; et al. EAE/ASE recommendations for image acquisition and display using three-dimensional echocardiography. Eur. Heart J. Cardiovasc. Imaging 2012, 13, 1–46.

27. Devereux, R.B.; Reichek, N. Echocardiographic determination of left ventricular mass in man. Anatomic validation of the method. Circulation 1977, 55, 613–618.

28. Reddy, Y.N.V.; Carter, R.E.; Obokata, M.; Redfield, M.M.; Borlaug, B.A. A Simple, Evidence-Based Approach to Help Guide Diagnosis of Heart Failure with Preserved Ejection Fraction. Circulation 2018, 138, 861–870.

29. Nagueh, S.F.; Smiseth, O.A.; Appleton, C.P.; Byrd, B.F., III; Dokainish, H.; Edvardsen, T.; Flachskampf, F.A.; Gillebert, T.C.; Klein, A.L.; Lancellotti, P.; et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J. Am. Soc. Echocardiogr. 2016, 29, 277–314.

30. Tomas, L.; Lazurova, I.; Pundova, L.; Oetterova, M.; Zakuciova, M.; Petrasova, D.; Studenčan, M. Acute and long-term effect of infliximab on humoral and echocardiographic parameters in patients with chronic inflammatory diseases. Clin. Rheumatol. 2013, 32, 61–66.

31. Nauta, J.F.; Hummel, Y.M.; van der Meer, P.; Lam, C.S.P.; Voors, A.A.; van Melle, J.P. Correlation with invasive left ventricular filling pressures and prognostic relevance of the echocardiographic diastolic parameters used in the 2016 ESC heart failure guidelines and in the 2016 ASE/EACVI recommendations: A systematic review in patients with heart failure with preserved ejection fraction. Eur. J. Heart Fail. 2018, 20, 1303–1311.

32. Sharma, A.; Kaushik, R.; Kaushik, R.M.; Kakkar, R. Echocardiographic evaluation of diastolic dysfunction in rheumatoid arthritis—A case-control study. Mod. Rheumatol. 2015, 25, 552–557.

33. Targonska-Stepniak, B.; Biskup, M.; Biskup, W.; Majdan, M. Diastolic dysfunction in rheumatoid arthritis patients with low disease activity. Clin. Rheumatol. 2019, 38, 1131–1137.

34. Almeida, J.G.; Fontes-Carvalho, R.; Sampaio, F.; Ribeiro, J.; Bettencourt, P.; Flachskampf, F.A.; Leite-Moreira, A.; Azevedo, A. Impact of the 2016 ASE/EACVI recommendations on the prevalence of diastolic dysfunction in the general population. Eur. Heart J. Cardiovasc. Imaging 2018, 19, 380–386.

35. Redfield, M.M.; Jacobsen, S.J.; Burnett, J.C., Jr.; Mahoney, D.W.; Bailey, K.R.; Rodeheffer, R.J. Burden of systolic and diastolic ventricular dysfunction in the community: Appreciating the scope of the heart failure epidemic. JAMA 2003, 289, 194–202.

36. Prasad, S.B.; Holland, D.J.; Atherton, J.J.; Whalley, G. New Diastology Guidelines: Evolution, Validation and Impact on Clinical Practice. Heart Lung Circ. 2019, 28, 1411–1420.

37. Balaney, B.; Medvedofsky, D.; Mediratta, A.; Singh, A.; Ciszek, B.; Kruse, E.; Shah, A.P.; Addetia, K.; Lang, R.M.; Mor-Avi, V. Invasive Validation of the Echocardiographic Assessment of Left Ventricular Filling Pressures Using the 2016 Diastolic Guidelines: Head-to-Head Comparison with the 2009 Guidelines. J. Am. Soc. Echocardiogr. 2018, 31, 79–88.

38. Ikonomidis, I.; Tzortzis, S.; Andreadou, I.; Paraskevaidis, I.; Katseli, C.; Katsimbri, P.; Pavlidis, G.; Parissis, J.; Kremastinos, D.; Anastasiou-Nana, M.; et al. Increased benefit of interleukin-1 inhibition on vascular function, myocardial deformation, and twisting in patients with coronary artery disease and coexisting rheumatoid arthritis. Circ. Cardiovasc. Imaging 2014, 7, 619–628.

39. Obokata, M.; Kane, G.C.; Reddy, Y.N.; Olson, T.P.; Melenovsky, V.; Borlaug, B.A. Role of Diastolic Stress Testing in the Evaluation for Heart Failure with Preserved Ejection Fraction: A Simultaneous Invasive-Echocardiographic Study. Circulation 2017, 135, 825–838.

40. Huis In't Veld, A.E.; de Man, F.S.; van Rossum, A.C.; Handoko, M.L. How to diagnose heart failure with preserved ejection fraction: The value of invasive stress testing. Neth. Heart J. 2016, 24, 244–251.

41. Chamsi-Pasha, M.A.; Zhan, Y.; Debs, D.; Shah, D.J. CMR in the Evaluation of Diastolic Dysfunction and Phenotyping of HFpEF: Current Role and Future Perspectives. JACC Cardiovasc. Imaging 2020, 13 (1 Pt 2), 283–296.

42. Ikonomidis, I.; Lekakis, J.P.; Nikolaou, M.; Paraskevaidis, I.; Andreadou, I.; Kaplanoglou, T.; Katsimbri, P.; Skarantavos, G.; Soucacos, P.N.; Kremastinos, D.T. Inhibition of interleukin-1 by anakinra improves vascular and left ventricular function in patients with rheumatoid arthritis. Circulation 2008, 117, 2662–2669.

43. Ikonomidis, I.; Tzortzis, S.; Lekakis, J.; Paraskevaidis, I.; Andreadou, I.; Nikolaou, M.; Kaplanoglou, T.; Katsimbri, P.; Skarantavos, G.; Soucacos, P.; et al. Lowering interleukin-1 activity with anakinra improves myocardial deformation in rheumatoid arthritis. Heart 2009, 95, 1502–1507.

44. Kobayashi, H.; Kobayashi, Y.; Giles, J.T.; Yoneyama, K.; Nakajima, Y.; Takei, M. Tocilizumab treatment increases left ventricular ejection fraction and decreases left ventricular mass index in patients with rheumatoid arthritis without cardiac symptoms: Assessed using 3.0 tesla cardiac magnetic resonance imaging. J. Rheumatol. 2014, 41, 1916–1921.

45. Kobayashi, Y.; Kobayashi, H.; Giles, J.T.; Hirano, M.; Nakajima, Y.; Takei, M. Association of tocilizumab treatment with changes in measures of regional left ventricular function in rheumatoid arthritis, as assessed by cardiac magnetic resonance imaging. Int. J. Rheum. Dis. 2016, 19, 1169–1174.

46. Schiff, M.H. Role of interleukin 1 and interleukin 1 receptor antagonist in the mediation of rheumatoid arthritis. Ann. Rheum. Dis. 2000, 59 (Suppl. 1), i103–i108.

47.   Natriuretic Peptides Studies, C.; Willeit, P.; Kaptoge, S.; Welsh, P.; Butterworth, A.S.; Chowdhury, R.; Spackman, S.A.; Pennells, L.; Gao, P.; Burgess, S.; et al. Natriuretic peptides and integrated risk assessment for cardiovascular disease: An individual-participant-data meta-analysis. Lancet Diabetes Endocrinol. 2016, 4, 840–849.

48.   Di Angelantonio, E.; Chowdhury, R.; Sarwar, N.; Ray, K.K.; Gobin, R.; Saleheen, D.; Thompson, A.; Gudnason, V.; Sattar, N.; Danesh, J. B-type natriuretic peptides and cardiovascular risk: Systematic review and meta-analysis of 40 prospective studies. Circulation 2009, 120, 2177–2187.

49.   Provan, S.; Angel, K.; Semb, A.G.; Atar, D.; Kvien, T.K. NT-proBNP predicts mortality in patients with rheumatoid arthritis: Results from 10-year follow-up of the EURIDISS study. Ann. Rheum. Dis. 2010, 69, 1946–1950.

50.   Peters, M.J.; Welsh, P.; McInnes, I.B.; Wolbink, G.; Dijkmans, B.A.; Sattar, N.; Nurmohamed, M.T. Tumour necrosis factor - blockade reduces circulating N-terminal pro-brain natriuretic peptide levels in patients with active rheumatoid arthritis: Results from a prospective cohort study. Ann. Rheum. Dis. 2010, 69, 1281–1285.

51.   Jain, S.; Khera, R.; Corrales-Medina, V.F.; Townsend, R.R.; Chirinos, J.A. Inflammation and arterial stiffness in humans. Atherosclerosis 2014, 237, 381–390.

52.   Vlachopoulos, C.; Dima, I.; Aznaouridis, K.; Vasiliadou, C.; Ioakeimidis, N.; Aggeli, C.; Toutouza, M.; Stefanadis, C. Acute systemic inflammation increases arterial stiffness and decreases wave reflections in healthy individuals. Circulation 2005, 112, 2193–2200.

53.   Giannoni, A.; Tani, C.; Clerico, A.; Passino, C.; Tavoni, A.; d'Ascanio, A.; Bombardieri, S.; Emdin, M. When the heart is burning: Amino-terminal pro-brain natriuretic peptide as an early marker of cardiac involvement in active autoimmune rheumatic disease. Int. J. Cardiol. 2011, 148, 161–167.

54.   Moraes, J.C.; Ribeiro, A.C.; Saad, C.G.; Lianza, A.C.; Silva, C.A.; Bonfa, E. NT-proBNP levels may be influenced by inflammation in active ankylosing spondylitis receiving TNF blockers: A pilot study. Clin. Rheumatol. 2013, 32, 879–883.

Chapter 5

Clinical improvement of cardiac function in a patient with systemic lupus erythematosus and heart failure with preserved ejection fraction treated with belimumab

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Summary

We present a 51-year-old Caucasian woman, with a medical history of systemic lupus erythematosus (SLE) who had dyspnoea at exertion. The SLE was clinically quiescent but serologically active. Echocardiography showed preserved left ventricular (LV) systolic function, pseudonormal mitral inflow pattern (diastolic dysfunction grade III), absence of wall motion abnormalities and elevated E/e' at exercise. An exercise right heart catheterisation was performed, confirming the diagnosis of heart failure with preserved ejection fraction (HFpEF). In the absence of other possible causes, we assumed that HFpEF was mediated by systemic inflammation secondary to SLE. Based on the Paulus' paradigm, that systemic inflammation may lead to diastolic dysfunction, we decided to add belimumab (a biological agent against soluble B-lymphocyte stimulator protein). After 16 weeks of treatment, patient reported an improved condition. Also, cardiopulmonary exercise test and echocardiography results improved, confirming resolution of the underlying LV diastolic dysfunction. This case supports the idea that targeting inflammation has therapeutic potential in a subset of HFpEF-patients.

Background

Currently, heart failure with preserved ejection fraction (HFpEF) represents 50% of heart failure cases, and its prevalence is increasing as a result of a growing awareness and diagnosis and due to changes in population demographics [1]. Hence, if these trends continue, HFpEF may become the most prevalent form of heart failure, underscoring the importance of this growing public health problem. HFpEF is associated with several factors, including female sex, hypertension, metabolic syndrome and coronary artery disease [2]. Importantly, mortality rates in patients with heart failure with reduced ejection fraction and HFpEF are comparable. In addition, no therapy in HFpEF has yet been shown to improve survival and diuretics only give relief of symptoms [3]. The pathogenesis of HFpEF is unknown, but currently several hypotheses are available, among which increasing evidence suggests detrimental effects of systemic inflammation on the cardiac function in systemic inflammatory disease [4]. Indeed, several studies showed favourable effects of strong anti-inflammatory treatment (ie, antitumour necrosis factor (TNF) and anti-IL6 drugs) on the cardiac function as well as the prevalence and incidence of congestive heart failure in patients with rheumatoid arthritis (RA) [5].

Systemic lupus erythematosus (SLE) is a chronic autoimmune inflammatory connective tissue disease characterised by systemic inflammation targeting multiple organs. In addition, SLE is associated with an increased risk for cardiovascular disease, which is only partially explained by traditional risk factors [6]. Belimumab is a monoclonal antibody that specifically inhibits the biological activity of soluble B-lymphocyte stimulator protein [7]. This anti-inflammatory drug is indicated as adjuvant therapy in SLE patients after standard treatment failure [8].

First of all, this case report describes a case in which a patient with SLE develops HFpEF, likely to be secondary to systemic inflammation, as all traditional risk factors such as hypertension, obesity and diabetes were absent. Second, this case report describes improvement of the cardiac function in a HFpEF patient after anti-inflammatory treatment with belimumab.

We describe the first case of a patient with SLE-related HFpEF successfully managed with belimumab.

Case presentation

We present a 51-year-old Caucasian woman with a medical history of SLE, presenting with complaints of progressive exertional dyspnoea (New York Heart Association functional class II/IV). She experienced no limitations in daily life. However, during mild sport exercise or sudden exertion, she had symptoms of dyspnoea and palpitations without thoracic symptoms, which recovered in rest. These symptoms developed since more than a year and were progressive in nature. There were no complaints of coughing, sputum or other pulmonary symptoms. Furthermore, she has a slim posture and used to sport 2 times a week. The patient had been hospitalised several times due to relapsing pleuritis and pericarditis, which were successfully treated with temporary increased prednisolone treatment, in combination with several disease-modifying antirheumatic drugs and non-steroidal anti-inflammatory drugs: hydroxychloroquine, mycophenolate mofetil (later discontinued due to gastrointestinal side effects), azathioprine and ibuprofen. Except for a positive family history, she has no traditional risk factors for cardiovascular disease. During this period of dyspnoea, her SLE was in clinical remission without clinical symptoms, albeit serology was active, and she was treated with hydroxychloroquine, low-dose prednisolone and ibuprofen.

Figure 1. Cardiopulmonary exercise test
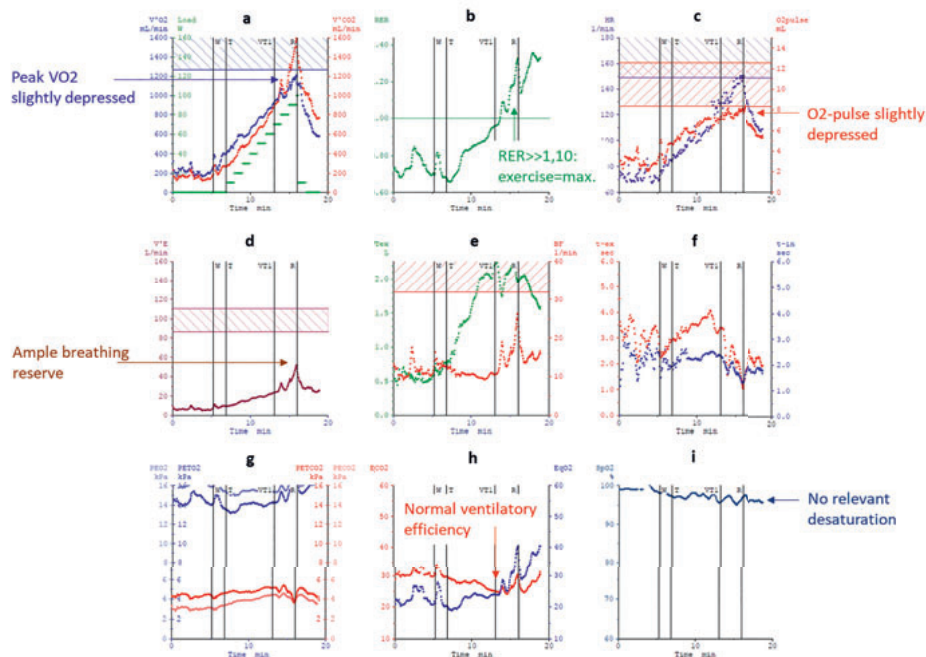
 VO2 = pulmonary uptake of oxygen per unit of time (mL/min); VCO2 = pulmonary output of carbon dioxide per unit of time (mL/min); W = Watt load; RER = respiratory exchange ratio, ratio between carbon dioxide output and oxygen uptake (VCO2/VO2); O2 pulse = oxygen uptake per heart beat (VO2/heart rate); HR = heart rate; V'E = minute ventilation (L/min), total volume of air exhaled per minute (tidal volume x breathing frequency); VTeX = expiratory tidal volume (L); BF = breathing frequency (1/min); t-ex = expiration time (sec); t-in = inspiration (sec); PE-O2 = mean partial pressure of expired oxygen (kPa); PE-CO2 = mean partial pressure of expired carbon dioxide (kPa); PET-O2 = end-tidal partial pressure of expired oxygen (kPa); PET-CO2 = end-tidal partial pressure of carbon dioxide (kPa); EqCO2 = ventilatory equivalent for carbon dioxide, number of liters of ventilation per liter of carbon dioxide output; EqO2 = ventilatory equivalent for oxygen, number of liters of ventilation per liter of carbon oxygen uptake; SpO2 = oxygen saturation (%).

Figure 2. Rest and exercise echocardiography
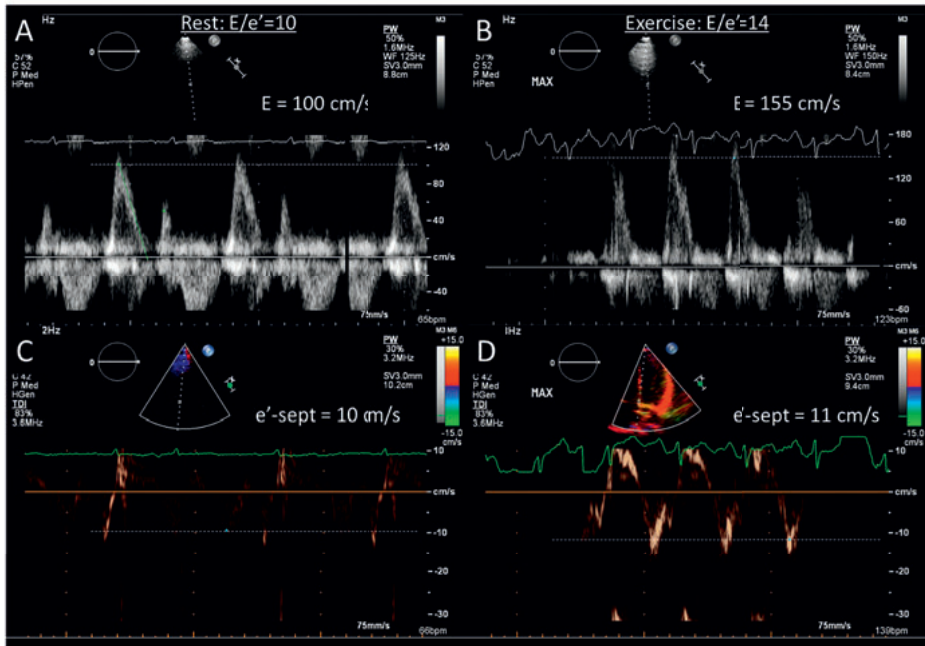
Rest and exercise echocardiography. E, peak mitral flow velocity in early diastole; E', peak mitral annular velocity during early filling; E/e', ratio approximating the left atrial pressure (normal: <14).

Investigations

The patient presented not ill and non-dyspnoeic at rest. The patient's weight was 49 kg with a length of 168 cm, body mass index of 17.4 kg/m2. Physical examination showed euvolaemia with a blood pressure of 97/57 mm Hg (normal for her) and a pulse rate of 62 bpm. Auscultation of the heart and lungs was unremarkable. ECG was normal. Laboratory tests showed a normal blood cell count, normal CK and troponin and a slightly increased N-terminal pro-brain natriuretic peptide (NT-proBNP) of 248 ng/L (ref: <125 ng/L). SLE serology showed low levels of complement C3 (0.65 g/L, ref: 0.9–1.8 g/L) and C4 (0.04 g/L, ref: 0.10–0.40 g/L) and high levels of anti-double stranded DNA (dsDNA) (118 IU/mL, ref: <15 IU/mL). Furthermore, blood samples ruled out any form of infectious, metabolic and haematological pathophysiology and any other intercurrent autoimmune disease such as thyroiditis or anti-phospholipid syndrome.

Transthoracic echocardiogram of the heart showed preserved left ventricular (LV) and right ventricular systolic function without signs of regional wall abnormalities,

pseudonormal mitral inflow pattern (diastolic dysfunction grade III) and normal valvular function. Cardiac CT angiography (CCTA) showed a calcium score of 0, no coronary plaques and no thickening of the pericardium. Cardiac magnetic resonance imaging (CMR) revealed physiological amounts of pericardial effusion, without signs of constrictive pericarditis, myocarditis and normal myocardial tissue characteristics (based on T1-, T2-mappings and late gadolinium-enhanced imaging). Holter assessment showed no signs of relevant supraventricular nor ventricular arrhythmia.

Because of a clinical suspicion for HFpEF, despite a very low H2FPEF-score (a scoring system describing the apriori chance for developing HFpEF based on traditional risk factors, in her case: 10%), [9] exercise echocardiography in combination with cardiopulmonary exercise testing was performed (see figures 1 and 2). The assessment showed normal ventilatory parameters (figure 1d–i); a peak VO2 (pulmonary oxygen uptake per minute) of 70% of predicted (>80% is normal) with a respiratory exchange ratio of 1.3 (>1.1 suggest maximal exercise) (figure 1a and b); maximal heart rate was 88% of predicted (>85% is normal) (figure 1c), but O2-pulse (a non-invasive estimate of oxygen uptake per heart beat) was 75% of predicted (>80% is normal; figure 1c). In conclusion, the results showed a normal pulmonary function with exercise limitation suggestive for cardiac impairment. Exercise echocardiography showed relevant LV diastolic dysfunction, as E/e' increased to 14 (<14 is normal) (figure 2). For definitive diagnosis, an exercise right heart catheterisation was performed (figure 3), which revealed normal haemodynamics at rest, but a significant increase in pulmonary capillary wedge pressure (PCWP) of 29 mm Hg during exercise (≥25 mm Hg=diagnostic; exercise PCWP is considered the gold standard), [9] indicating increased LV filling pressure, which in this context is secondary to diastolic impairment, as LV ejection fraction was >50% without signs of valvular disease. Thus, the diagnosis of (early-stage) HFpEF was confirmed.

Figure 3. Rest and exercise right heart catheterization
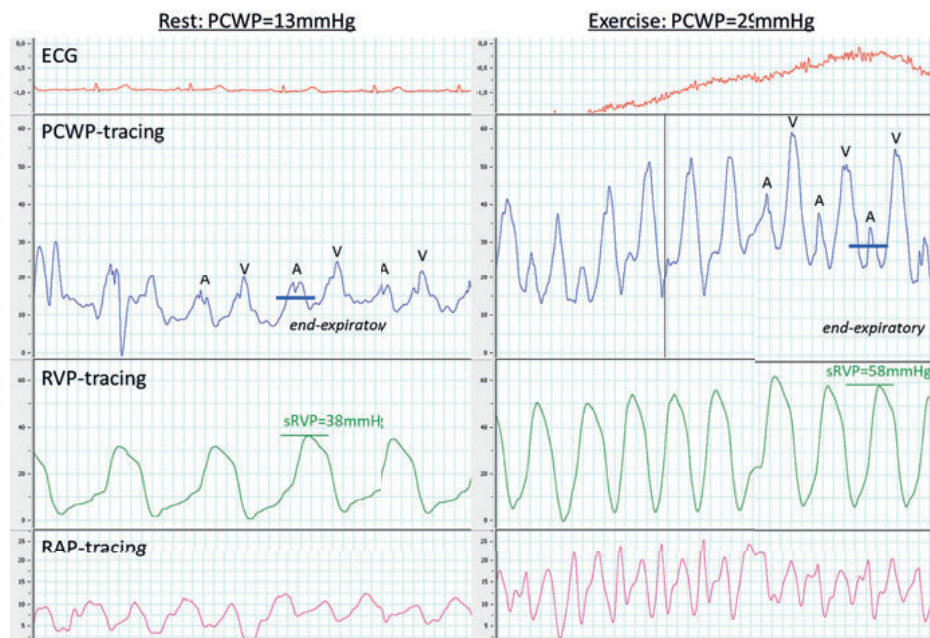
ECG = electrocardiogram; PCWP = pulmponary capillary wedge pressure; RVP = right ventricular pressure; RAP = right atrial pressure

Differential diagnosis

In the differential diagnosis, SLE-related and non-SLE-related causes resulting in HFpEF were considered. With respect to non-SLE-related causes, traditional risk factors for HFpEF were not present, that is, metabolic syndrome including diabetes, hypertension and obesity. Furthermore, CCTA ruled out coronary disease. In the light of SLE-related causes, cardiac imaging (CCTA and CMR) ruled out pericardial involvement, despite recurrent pericarditis in the past. Also, no evidence was found for an underlying cardiac structural or infiltrative cardiomyopathy. Furthermore, we considered whether in theory HFpEF might have been hydroxychloroquine-induced. However CMR was normal, and a myocardial biopsy was refused by the patient when the potential risks of this diagnostic procedure were explained in relation to the relative low diagnostic yield in her specific case. As all probable causes were ruled out, we hypothesised, based on the Paulus paradigm, that the underlying LV diastolic dysfunction in this patient could be related to her systemic inflammation secondary to SLE. This was substantiated by the low complement levels in combination with high dsDNA levels, suggesting active SLE despite the absence of

other clinical signs of active disease. The Paulus paradigm describes the role of systemic inflammation in the development of HFpEF, in this case circulating cytokines, which leads to endothelial activation, interstitial fibrosis and stiff cardiomyocytes resulting in diastolic dysfunction and in severe cases, such as this, HFpEF [4].

Treatment

Considering that systemic inflammation in this patient played a pivotal role in the development of HFpEF, strong anti-inflammatory treatment was proposed as a possible treatment. After ruling out important differential diagnoses, exercise echocardiography and cardiopulmonary exercise testing were indicative but not conclusive for significant diastolic impairment. Furthermore, although active serology was indicative for active systemic inflammation, the patient did not fulfil all criteria for high disease activity to justify strong inflammatory treatment with belimumab yet, as the SLE, without the assessment by right heart catheterisation, was considered in clinical remission. Thus, certainty was required on the presence of diastolic dysfunction to confirm SLE was not clinically in remission, assuming HFpEF/diastolic dysfunction was secondary to SLE-induced systemic inflammation. In our case, we judged that the additional value of right heart catherisation assessment (certainty of diagnosis with direct clinical consequences) outweighed the potential risks of an invasive diagnostic procedure. Eventually, after HFpEF was confirmed, we decided to start additional anti-inflammatory therapy with belimumab, and closely monitored clinical response. Belimumab is monoclonal antibody that specifically inhibits the biological activity of soluble B-lymphocyte stimulator protein, thereby suppressing immunological activity. Belimumab is a relatively new biological treatment and is only initiated in patients with SLE with active disease activity after failure of standard therapy.8 Subsequent to consent with the patient treatment with belimumab 200 mg/week subcutaneously was started.

Outcome and follow-up

The patient experienced a significant improvement of physical condition after 4 months belimumab treatment and she could now perform all physical exercises as before. Cardiopulmonary exercise test in combination with exercise echocardiography was repeated after 4 months, showing normalisation in peak VO2, O2-pulse and E/e' at exercise. SLE stayed in full remission and improving serology (C3/C4 from 0.65/0.04 g/L to 0.98/0.10 g/L, respectively, and anti-dsDNA from 118 IU/mL to 70 IU/mL). NT-proBNP reduced to 167 ng/L. Until today (1.5 years after initiation), patient remains in good physical health and has no complaints of exertional dyspnoea nor physical limitation

under belimumab. At the start of her treatment she experienced mild injections site reactions and flare of arthritis which disappeared after 4 weeks. Furthermore, after 4 months of treatment she had ophthalmic herpes zoster for which was belimumab was temporarily stopped, without detrimental permanent effects. After 4 weeks belimumab was resumed and until now, she remains in good clinical condition without any symptoms.

Patient's perspective

Since the year 2000 I have experienced several exacerbations of SLE with polymyositis, pericarditis, pleuritis, meningitis and mastitis. All of them were treated with a temporary high dose prednisolone among some other immune suppressive drugs like azathioprine and hydroxychloroquine.

In 2005 suspicion of developing pulmonary hypertension after another period of pericarditis/pleuritis was the reason for consulting the pulmonary doctor. During that time I experienced irregular heart rates and some small physical limitations during high exercise which were confirmed by the lung function test which showed that during high exercise my heart was not pumping enough blood and oxygen around. It was thought that this was caused by scarring tissue in the pericardium after several inflammations of the pericardium and that the heart was therefore limited in space to extent in volume. On the hindsight I believe that these were the first mild signs of later complaints that got more severe over time.

During 2010–2015 the SLE was in remission. I was on a daily dose of 7 mg prednisolone, azathioprine, and 200 mg hydroxychloroquine. I only experienced some mild SLE complaints like fatigue and stiff, sometimes painful, joints. Especially hands and knees. I was able to work for 75% besides being a mother of two. In my spare time I performed sports twice a week and I enrolled in a study in basic medicine for 3 years.

In 2015 I noticed on a more frequent base that I was not able to perform physical exercise at the level I used to. Running up the stairs for two levels, biking over a bridge or running for more than 100 metres already gave me the feeling of being out of breath and I felt very fast runs of heartbeats while I did not have the feeling that my physical condition or muscle strength was the limiting factor. I felt that something was not right, but still the medical explanation for my complaints was the scar tissue of the pericardium and pleura. In 2016, after a few months of active SLE, I was in the emergency room again with suspicion of another pericarditis. I told the cardiologist on call about my complaints of the fast heartbeats during exercise and told him this was probably caused by the scar

tissue of the pericardium. He asked me if this had ever been examined, but I told him this was not the case, it was an assumption.

The cardiologist was very determined to find out what caused this problem and performed several examinations and tests. The result of those examinations (in rest) was that everything with my heart and the pericardium was fine. So, the condition or thickness of the pericardium was not the problem.

I was then transferred to a cardiologist specialised in heart failure. Many examinations like echo's, exercise tests, holter assessments, MRI etc. followed. The most difficult examination of all was the physical exercise where I was lying horizontally on a bed and having to bicycle to the max while, at the same time, an intravenous catheter was inside my heart (exercise right heart catheterisation)... This was a very unpleasant and scary feeling. But above all I was VERY scared of the outcome.

The minutes between the end of the test and the outcome took forever. Unfortunately, the outcome was not good. I was diagnosed with heart failure... My world collapsed. I cried and I was very worried.

The next months were terrible for me and my family. I cried a lot and I was terrified with the prognosis and I was worried for my family, especially for my children. I was very afraid to die in a few years. This cannot happen, children need their mom!

However I was told by the cardiologist that I did not have the risk factors for heart failure and therefor probably a better prognosis. I tried to hang on to that. The cardiologist also told me about the theory of Professor Paulus that heart failure might be caused by the chronic systematic inflammation of the SLE. My cardiologist suggested that it would be helpful for me to talk with Prof. Paulus and set up a meeting with Prof. Paulus for me and my husband. In this meeting Prof. Paulus answered our many questions and explained his theory. He emphasised that it was very important to suppress the chronic inflammation. With this advise and the knowledge that there is a biological (belimumab) especially developed for SLE with high success rates to bring SLE to rest, my husband and I went to the rheumatologist. However, my situation did not meet the requirements for starting belimumab. Finally my case was discussed in a group of rheumatologists and because there was no other medicine to treat the heart failure, an exception was made and the belimumab treatment was approved. I was so relieved... Finally, after months, hope was given back to me.

I started belimumab in August 2018, but after 2 weeks (second dose) I experienced side effects. The location of the injection became a large red, swollen and hot circle. My hands, fingers and wrist were very painful and swollen. And my right arm was so painful, I could not lift it. It was clear there was a negative reaction to the belimumab. I

was so sad, because belimumab was my only hope and I was afraid that the belimumab treatment had to be stopped. But I did not want to give up on the belimumab, so I continued the treatment. Surprisingly the side effects diminished and were gone after 4 weeks. Somewhere half October, beginning of November, I started to feel improvement; my overall condition improved, I noticed I could do more and longer exercises without getting out of breath and I had less irregular heartbeats. This was also confirmed by the function and echo tests under exercise. I was very happy and relieved. Then in December there was another complication and disappointment. The belimumab had suppressed my immune system so much that a herpes zoster infected my left eye. I was hospitalised for a week, got anti-viral treatment and the belimumab had to be stopped. I felt very hopeless, because if this was a recurring side effect, I had to stop the belimumab... After 2 months I was allowed to restart the belimumab again and so far no side effects anymore and my heart is doing very well! I am very grateful towards my doctors and want to thank them for thinking 'out of the box' and to reverse the problem of the heart filling by supressing the SLE activity. I think it is very important for other doctors all over the world to learn that HFpEF can be caused by chronic inflammation and the solution for treating HFpEF could be treating the inflammation.

Discussion

To date, there are no published cases of HFpEF secondary to SLE treated with anti-inflammatory therapy, in this specific case belimumab.

The differential diagnosis of exertional dyspnoea is broad. In this particular case, we needed extensive diagnostic testing to demonstrate that underlying LV diastolic dysfunction was the reason for her symptoms. The pretest likelihood chance of HFpEF (H2FpEF score), in the absence of the metabolic risk factors for HFpEF, was very low. In addition, it is well known that measurements at rest (electrocardiography, echocardiography, cardiac markers for heart failure) are very insensitive to detect relevant LV dysfunction, especially at the earlier stage of the condition [9, 10]. Therefore, in these cases, haemodynamic measurements during exercise are obligatory, although these advanced diagnostic tools are only available at centres of expertise. Furthermore, for adequate management all possible pathogenetic mechanisms of HFpEF were considered. As described in the differential diagnosis section, all probable causes including traditional risk factors for HFpEF were ruled out. Therefore, in this case, presenting a patient with SLE with active serology, systemic inflammation-induced LV diastolic dysfunction seemed as the remaining plausible pathogenetic cause and this assumption was confirmed by successful anti-inflammatory treatment.

As presented in this case, the pathogenesis of HFpEF is not yet fully understood. However, mounting evidence postulate an important role of systemic inflammation in the development and maintenance of diastolic dysfunction [1, 11, 12]. This substantiates the Paulus paradigm describing a pivotal role of chronic systemic inflammation in myocardial remodelling and the development of diastolic dysfunction and in severe cases HFpEF. In this model, circulating inflammatory mediators, including TNF-a and IL-6, result in myocardial microvascular dysfunction. Subsequently, it assumed endothelial activation leads to deposition of collagen with subsequent stiffness and hypertrophy of cardiomyocytes and decreased ability to relax of the myocardium, which can evolve in HFpEF [4].

Several studies investigated the effect of anti-inflammatory strategies on the cardiac function in patients with HFpEF. Though anti-inflammatory strategies in animal models with HFpEF have shown promising results, studies in human HFpEF patients are conflicting. In the D-HART study, a randomised, double-blind, placebo-controlled, cross-

over pilot trial of 12 stable HFpEF patients treated with anakinra (an anti-interleukin (IL)-1 drug), patients showed improvement in ventilatory efficiency [13]. The subsequent D-HART2 trial, a randomised placebo-controlled blinded trial, sought to confirm the D-HART trial results on exercise tolerance in HFpEF. This study among 28 patients showed reduction in C reactive protein and NT-proBNP levels, however, failed to improve ventilatory efficiency at 12 weeks [14]. Importantly, the patients in these studies had no secondary auto-immune disease. Therefore, the pathophysiology of HFpEF in these cohorts may differ in patients with HFpEF secondary to autoimmune disease induced systemic inflammation. That is to say, if significant systemic inflammation secondary to autoimmune disease is the driving factor in the development of HFpEF, anti-inflammatory therapy may be of therapeutic value. One study investigated concurrent SLE or systemic autoimmune connective tissue disorders in patients with (unexplained) HFpEF. In 5 of 44 cases of HFpEF, the investigators were able to diagnose an underlying autoimmune disease, suggesting a link between systemic inflammation and HFpEF [15]. In RA, several studies investigated the effect of anti-inflammatory treatment on the cardiac function. Ikonomidis et al. showed in patients with RA treated with anakinra, improvement of the diastolic function (E/e') 3 hours to 30 days after administration [16]. In addition, Cetin et al. [17] demonstrated improvement of diastolic function (E/e') in RA patients after 3 months treatment with infliximab (anti-TNF). However, the latter two studies were performed in patients with no HFpEF. To our knowledge, to date, no cases of patients with SLE or any other auto-immune disease complicated with HFpEF and treated with anti-inflammatory agents have been reported, yet.

The patient presented in this case started with belimumab with the aim to improve HFpEF and exertional dyspnoea symptoms in the context of subclinical systemic inflammation (low complement levels and high dsDNA levels). There was significant improvement of physical fitness after treatment with belimumab, confirmed by improved echocardiographic and cardiopulmonary exercise results as well as improvement of serological parameters and cardiac markers for heart failure at follow-up.

This case offers opportunities in the limited treatment of patients with HFpEF secondary to autoimmune diseases. Possibly, if systemic inflammation has a considerable role in HFpEF, anti-inflammatory treatment could be of therapeutic value in a wider range of HFpEF patients with underlying inflammation of any cause. Therefore, further investigation is advocated to assess the therapeutic potential of anti-inflammatory agents in systemic inflammatory diseases and HFpEF.

References

1. Shah SJ, Kitzman DW, Borlaug BA, van Heerebeek L, Zile MR, Kass DA, et al. Phenotype-Specific Treatment of Heart Failure With Preserved Ejection Fraction: A Multiorgan Roadmap. Circulation. 2016;134(1):73-90.

2. Lam CS, Donal E, Kraigher-Krainer E, Vasan RS. Epidemiology and clinical course of heart failure with preserved ejection fraction. Eur J Heart Fail. 2011;13(1):18-28.

3. Hollan I, Meroni PL, Ahearn JM, Cohen Tervaert JW, Curran S, Goodyear CS, et al. Cardiovascular disease in autoimmune rheumatic diseases. Autoimmun Rev. 2013;12(10):1004-15.

4. Paulus WJ, Tschope C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. J Am Coll Cardiol. 2013;62(4):263-71.

5. Baniaamam M, Paulus WJ, Blanken AB, Nurmohamed MT. The effect of biological DMARDs on the risk of congestive heart failure in rheumatoid arthritis: a systematic review. Expert Opin Biol Ther. 2018;18(5):585-94.

6. Esdaile JM, Abrahamowicz M, Grodzicky T, Li Y, Panaritis C, du Berger R, et al. Traditional Framingham risk factors fail to fully account for accelerated atherosclerosis in systemic lupus erythematosus. Arthritis Rheum. 2001;44(10):2331-7.

7. Navarra SV, Guzman RM, Gallacher AE, Hall S, Levy RA, Jimenez RE, et al. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. Lancet. 2011;377(9767):721-31.

8. Fongen C, Halvorsen S, Dagfinrud H. High disease activity is related to low levels of physical activity in patients with ankylosing spondylitis. Clin Rheumatol. 2013;32(12):1719-25.

9. Reddy YNV, Carter RE, Obokata M, Redfield MM, Borlaug BA. A Simple, Evidence-Based Approach to Help Guide Diagnosis of Heart Failure With Preserved Ejection Fraction. Circulation. 2018;138(9):861-70.

10. Huis In 't Veld AE, de Man FS, van Rossum AC, Handoko ML. How to diagnose heart failure with preserved ejection fraction: the value of invasive stress testing. Neth Heart J. 2016;24(4):244-51.

11. Buss SJ, Wolf D, Korosoglou G, Max R, Weiss CS, Fischer C, et al. Myocardial left ventricular dysfunction in patients with systemic lupus erythematosus: new insights from tissue Doppler and strain imaging. J Rheumatol. 2010;37(1):79-86.

12. Plazak W, Kopec G, Tomkiewicz-Pajak L, Rubis P, Dziedzic H, Suchon E, et al. Heart structure and function in patients with generalized autoimmune diseases: echocardiography with tissue Doppler study. Acta Cardiol. 2011;66(2):159-65.

13. Van Tassell BW, Arena R, Biondi-Zoccai G, Canada JM, Oddi C, Abouzaki NA, et al. Effects of interleukin-1 blockade with anakinra on aerobic exercise capacity in patients with heart failure and preserved ejection fraction (from the D-HART pilot study). Am J Cardiol. 2014;113(2):321-7.

14. Van Tassell BW, Buckley LF, Carbone S, Trankle CR, Canada JM, Dixon DL, et al. Interleukin-1 blockade in heart failure with preserved ejection fraction: rationale and design of the Diastolic Heart Failure Anakinra Response Trial 2 (D-HART2). Clin Cardiol. 2017;40(9):626-32.

15. Blasco Mata LM, Acha Salazar O, Gonzalez-Fernandez CR, Robledo FN, Perez-Llantada Amunarriz E. Systemic lupus erythematosus and systemic autoimmune connective tissue disorders behind recurrent diastolic heart failure. Clin Dev Immunol. 2012;2012:831434.

16. Ikonomidis I, Lekakis JP, Nikolaou M, Paraskevaidis I, Andreadou I, Kaplanoglou T, et al. Inhibition of interleukin-1 by anakinra improves vascular and left ventricular function in patients with rheumatoid arthritis. Circulation. 2008;117(20):2662-9.

17. Çetin S, Süha Çetin, Mustafa G, et-al. Infliximab, an anti-TNF-alpha agent, improves left atrial abnormalities in patients with rheumatoid arthritis: preliminary results. Cardiovasc J Afr 2014;25:168–243.

Part II

Systemic inflammation and cardiac diseases in ankylosing spondylitis patients

Unexpected high aortic valve regurgitation prevalence in a contemporary large cohort Dutch ankylosing spondylitis patients - the CARDAS study

Chapter

6

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Abstract

Objectives – The aim of the present study was to determine the prevalence of specific cardiac manifestations, i.e. conduction disorders, valvular disease and diastolic left ventricular (LV) dysfunction, in a large cross-sectional controlled cohort of Ankylosing Spondylitis (AS)-patients.

Methods – This cross-sectional study assessed the prevalence of valvular disease, conduction disorders and LV dysfunction in 193 randomly selected AS–patients compared with 74 osteoarthritis (OA) controls aged 50-75 years. Patients underwent conventional and tissue Doppler echocardiography in combination with clinical and laboratory assessments. Multivariate regression analyses were performed to compare the risk of mitral valve regurgitation (MVR) and aortic valve regurgitation (AVR) between AS-patients and OA controls. Associations between disease duration, disease activity and use of anti-tumour necrosis factor (anti-TNF) drugs and valvular disease were also investigated.

Results – The prevalence of AVR was significantly higher in AS-patients compared to the controls, respectively 23% (9% trace, 12% mild, 1% moderate, 1% severe, 1% prosthesis) vs 11%, p=0.04. After correcting for age, sex and CV risk factors AS-patients had an odds ratio of 4.5 (95%CI 1.1-13.6) for AVR compared to the controls. Prevalence of MVR, conduction disorders and diastolic LV dysfunction were comparable between AS-patients and controls. Furthermore, disease duration, disease activity and use of anti-TNF drugs were not significantly associated with cardiac manifestations in AS-patients.

Conclusion – The prevalence of conduction disorders and diastolic LV dysfunction were seldomly found and similar in AS-patients and controls. However, AS-patients had an up to five times increased risk to develop AVR compared to controls. Therefore, echocardiographic screening of elderly (50-75 years) AS patients should be considered.

Introduction

Ankylosing spondylitis (AS) is an inflammatory joint disease associated with extra-articular manifestations including cardiac disease [1, 2]. Previous studies have shown an increased mortality in AS-patients compared to the general population with cardiovascular diseases as leading cause of death [3, 4]. Chronic inflammation in AS contributes considerably to this excess cardiovascular risk, besides progression of atherosclerosis, it may lead to structural changes of the heart thereby causing cardiac disease [5, 6]. Indeed, previous studies suggest that AS-patients are at increased risk to develop aortic valve regurgitation (AVR), conduction disorders and diastolic left ventricular (LV) dysfunction. Although some of previous studies suggested that these cardiac manifestations occur more frequently in AS-patients, results varied and altogether inconclusive [7-15]. Furthermore, therapeutic treatment in AS has significantly improved in the last decades and this may have altered the CV burden. As recent data regarding the prevalence of cardiac manifestations in AS are lacking, clear guidelines regarding cardiovascular screening of AS-patients are still absent. Hence, current cardiovascular risk management guidelines make no distinction between AS patients and healthy persons, and the EULAR only recommends to make a CVD risk assessment once per 5 years [16]. Therefore, the aim of the present study was to determine the current prevalence of diastolic LV dysfunction (primary objective), cardiac valve regurgitation and conduction disorders (secondary objectives) in a large cohort of AS-patients, and compare these results to findings in controls without an inflammatory joint disease i.e. osteoarthritis (OA) patients. As cardiac disease is more prominent with older age we assessed the prevalence of cardiac disease in subjects between 50-75 years.

Methods

Study population
A cross-sectional controlled study was conducted in randomly selected AS-patients and age, sex and smoking status matched controls in a 2:1 ratio. Control patients with OA were selected as they also suffer from joint problems and subsequent mobility issues (physical activity) however without auto-inflammatory characteristics. Subjects were randomly recruited between March 2014 and February 2020 at a large rheumatology outpatient clinic (Reade) in Amsterdam, the Netherlands.

Patients were eligible for inclusion if they were between 50-75 years of age. AS-patients needed to be diagnosed according to the 1984 modified New York [17] criteria and OA-controls with active hip-, knee- or polyosteoarthritis had to be diagnosed by a general practitioner or rheumatologist. Patients with a history of chemotherapy (for malignant disease) were excluded due to presence of potential cardiotoxicity.

All patients gave written consent prior to inclusion in the study. This study was conducted in accordance with the Helsinki Declaration, and the protocol (NL44202.048.13) was approved by the medical ethics committee of the Slotervaart hospital and Reade, Amsterdam, the Netherlands.

Echocardiography
Transthoracic echocardiography (TTE) was performed by certified echo technicians at the European Society of Cardiology (ESC)-certified department of echocardiography of the Amsterdam University medical center, location VUmc, using a Philips ultrasound system (Epiq 7 or IE 33). Furthermore, the echo technicians were not informed about to the clinical diagnosis of the subject. To exclude inter-observer variability, all recordings of echocardiographic images and data were assessed afterwards by an experienced cardiologist of the VUmc specialized in echocardiography (TK). The cardiologist graded diastolic dysfunction, AVR and MVR. TTE was performed according to the guidelines provided by the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI) [18]. Furthermore, the severity of AVR and MVR was graded according to the EACVI guidelines [19, 20].

Left atrial-volume (LA–volume; ml)-index and left ventricular mass (LVM; g)-index were calculated with body surface area (BSA; m^2) LA-volume or LVM / BSA; g/m^2).

The aortic root was measured at sinuses of Valsalva during diastole. Furthermore, aortic root diameter was corrected for BSA according to the Dubois method (aortic root index) [21]. An aortic root index of $\geqslant 2.1$ cm/m^2 was considered as aortic root dilatation [22, 23].

Electrocardiography
Electrocardiography (ECG) was performed using standard 12-lead ECGs, recorded at 25mm/s paper speed. ECGs were analysed by a single cardiologist (TK) whom was blinded to the clinical status of all patients.

Disease specific parameters
The following disease specific parameters were collected.

In AS: HLA-B27 status, extra-articular manifestations, disease activity (Bath AS Metrology Index (BASMI), Bath AS Disease Activity Index (BASDAI), AS Disease Activity Score-C-reactive protein (ASDAS-CRP). In AS, high disease activity was defined as an ASDAS-score of ≥2.1.

In OA: disease severity was assessed with the Western Ontario and McMaster Universities Osteoarthritis index (WOMAC) questionnaire [24].

Cardiovascular history and risk factor parameters
Cardiovascular risk factors were assessed including smoking status, body mass index (BMI), hypertension, hypercholesterolemia, diabetes mellitus type II and family history for cardiovascular disease. Furthermore, data history for cardiovascular disease was collected, i.e. angina pectoris, myocardial infarction, congestive heart failure, stroke (cerebrovascular accident (CVA) and/or transient ischemic attack (TIA)), peripheral ischemia and coronary arterial bypass grafting (CABG).

Other study parameters
Anthropometric data including length, weight, waist/hip ratio and blood pressure were assessed during physical examination. Demographic data were collected, i.e. age, race, ethnicity and sex. Blood sample measurements (non-fasting) consisted of standard haematological assessment, erythrocyte sedimentation rate (ESR), CRP, triglyceride, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL) and HLA-B27 status. Furthermore, medical history, current and historic medication use and disease specific data (i.e. year of onset, disease duration) were documented.

Definitions
Systolic LV dysfunction
Systolic LV dysfunction was defined as a left ventricular ejection fraction (LVEF) less than 50%.

Diastolic LV dysfunction
Diastolic LV dysfunction was evaluated according to the 2009 ASE/EACVI recommendations and 2016 ASE/EACVI recommendations, and both categorized in 4

grades: normal diastolic LV function and grade I-III (or intermediate) [25, 26]. Regarding the 2016 ASE/EACVI recommendations, for patients with a preserved ejection fraction, four variables were evaluated; average mitral E/e' velocity, septal and lateral e' velocity, tricuspid regurgitation-velocity (TR-velocity; cm/s) and LA-volume index. Patients with at least three aberrant values were diagnosed with diastolic LV dysfunction. Patients with more than one missing variable were not classified.

Hypertension

Patients were diagnosed with hypertension when they had a systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg measured during the physical examination, or when they were using antihypertensive medication.

Family history

A positive family history for cardiovascular events or cerebrovascular events was defined as having a first degree female relative under 65 years old or a male relative under 55 years old diagnosed with angina pectoris / myocardial infarction or TIA / CVA respectively.

Cardiovascular diseases

A positive history of cardiovascular disease was defined as a history of angina pectoris, myocardial infarction, coronary artery bypass grafting (CABG), congestive heart failure, CVA/TIA and/or peripheral ischemia.

Obesity

BMI ≥ 30 kg/m^2.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD) for normally distributed variables or median (interquartile range) for non-normally distributed variables. Differences were compared between subjects using independent samples t-test for normally distributed variables and a Mann-Whitney U test for non-normally distributed variables. Dichotomous and categorical data are presented as frequencies (percentages). These variables were compared using a Chi-square test or Fisher's exact test where applicable.

Logistic multivariate regression analyses were performed to investigate the association between AS and valve regurgitation. In addition, subgroup analyses using linear or

logistic multivariate regression analyses were performed to investigate the relationship of disease duration, disease activity and anti-tumour necrosis factor (TNF) with valve regurgitation. All statistical analyses were performed using SPSS software, version 23.0.

Results

Patient characteristics

Baseline characteristics are shown in table 1. A total of 193 AS-patients and 74 matched controls were included in the study. Matching was done in the best way possible within logistical limitations. The mean age of the AS-patients and the controls was respectively 60 (±7) years and 62 (±7) years and 72% and 58% were male, respectively. AS-patients had a lower BMI and BSA than controls, respectively 26.6 ± 4.1 vs. 28.6 ± 5.5 kg/m^2 and 1.9 ± 0.20 vs. 2.0 ± 0.2 m^2. Furthermore, obesity and hypercholesterolemia were seen less often in AS-patients compared to controls, respectively 22% vs 30% and 19% vs 30%. AS-patients used more antihypertensives compared to controls, respectively 44% vs 27%. The prevalence of other cardiovascular diseases, comorbidities and risk factors were comparable in both groups.

Table 1. Patient characteristics of AS and OA-controls

	AS-patients (n = 193)	OA-controls (n = 74)
Patient characteristics		
Gender, male (n, %)	138 (72)	43 (58)
Age, years (mean ± SD)	60 ± 7	62 ± 7
Race, Caucasian (n, %)	162 (84)	65 (88)
BMI, kg/m^2 (mean ± SD)	26.6 ± 4.1	28.6 ± 5.5
BSA, m^2 (mean ± SD)	1.9 ± 0.2	2.0 ± 0.2
Blood pressure, mmHg		
Systolic (mean ± SD)	134 ± 16	133 ± 17
Diastolic (mean ± SD)	84 ± 8	82 ± 9
CVD risk factors		
Smoking status		
current (n, %)	39 (20)	15 (20)
ever (n, %)	98 (51)	35 (47)
never (n, %)	55 (29)	24 (32)
pack years (median, IQR)	28 (14 – 37)	12 (6 – 31)
Obesity (n, %)	42 (22)	26 (35)
Hypertension (n, %)	118 (61)	45 (61)
Hypercholesterolemia (n, %)	36 (19)	22 (30)

Table 1. Continued.

	AS-patients (n = 193)	OA-controls (n = 74)
Diabetes Mellitus type II (n, %)	22 (11)	10 (14)
Total history CVD (n, %)	21 (11)	8 (11)
Angina Pectoris (n, %)	5 (3)	2 (3)
Myocardial infarction (n, %)	12 (6)	4 (5)
Stroke		
TIA (n, %)	4 (2)	3 (4)
CVA (n, %)	3 (2)	0 (0)
Peripheral ischemia (n, %)	1 (1)	1 (1)
CABG (n, %)	8 (4)	2 (3)
Family history (first degree)		
AP / MI (n, %)	24 (12)	11 (15)
Stroke / TIA (n, %)	14 (7)	6 (8)
Laboratory		
LDL, mmol/l	3.3 ± 0.9	3.5 ± 1.1
HDL, mmol/l	1.5 ± 0.4	1.3 ± 0.4
Cholesterol/HDL ratio	3.8 ± 1.6	4.2 ± 1.7
ESR, mm/hr	7.5 (4.0-10.0)	5.0 (2.0-11)
CRP, mg/l	2.8 (1.1-7.8)	1.6 (0.8-3.1)
Medication		
Antihypertensives (n, %)	85 (44)	20 (27)
Lipid modifying drugs (n, %)	40 (21)	19 (26)
NSAIDs (n, %)	108 (56)	37 (50)
Anti-TNF drugs		
current (n, %)	70 (36)	N.A.
ever (n, %)	13 (7)	N.A.
naive (n, %)	110 (57)	N.A.

Values are displayed as mean ± standard deviation (SD), median with corresponding interquartile range (IQR) or frequencies with corresponding percentages (%). AS = ankylosing spondylitis, OA = osteoarthritis, BMI = body mass index, BSA = body surface area, CVD = cardiovascular disease, TIA = transient ischemic attack, CVA = cerebrovascular attack, CABG = coronary artery bypass graft, AP = angina pectoris, MI = myocardial infarction, NSAIDs = non-steroidal anti-inflammatory drugs, anti-TNF = anti-tumour necrosis factor, N.A.= not applicable.

Disease characteristics

Disease characteristics are shown in table 2. A total of 82% of the AS-patients were HLA-B27+. AS-patients had a moderate to high disease activity with a mean ASDAS-CRP of 2.1 (±1.0) and a mean disease duration of 22 (±12) years. Most of the OA controls had knee osteoarthritis (82%) and/or polyosteoarthritis (81%) compared to hip osteoarthritis (24%). Disease duration (since diagnosis) was 5 (2-8) years. OA-patients had median a WOMAC score of 42 (±23).

Table 2. Disease characteristics of AS and OA-controls

Ankylosing spondylitis	n = 193
HLA-B27 positive (n, %)	156 (82)
Disease activity and severity	
ASDAS-CRP (mean ± SD)	2.1 ± 1.0
BASMI (mean ± SD)	4.1 ± 1.8
BASFI (mean ± SD)	3.7 ± 2.4
BASDAI (median; IQR)	3.1 (1.6 – 5.0)
Time since diagnosis, years (mean ± SD)	22 ± 12
Osteoarthritis	**n = 74**
Affected joints	
Knee (n, %)	61 (82)
Hip (n, %)	18 (24)
Polyosteoarthritis (n, %)	60 (81)
Prosthesis (n, %)	15 (20)
WOMAC (mean ± SD)	42 (23)
Time since diagnosis (median; IQR)	5 (2-8)

Values are displayed as mean ± standard deviation (SD), median with corresponding interquartile range (IQR) or frequencies with corresponding percentages (%). AS = ankylosing spondylitis, OA = osteoarthritis, HLA = Human leukocyte antigen, ASDAS-CRP = Ankylosing Spondylitis Disease Activity Score-C-reactive protein, BASMI = Bath Ankylosing Spondylitis Metrology Index, BASFI = Bath Ankylosing Spondylitis Functional Index, BASDAI = Bath Ankylosing Spondylitis Disease Activity Index, WOMAC = Western Ontario and McMaster Universities Osteoarthritis.

Electrocardiography

Electrocardiographic results are shown in table 3. No differences were found in conduction disorders between AS-patients and controls.

Table 3. Electrocardiographic results

	AS patients (N = 193)	OA-controls (N = 74)	*p* Value [a]
Atrial fibrillation (n, %)	3 (2)	4 (5)	0.10
Atrial flutter (n, %)	0 (0)	0 (0)	1.0
AV-block degree			
1st degree (n, %)	2 (1)	1 (1)	0.62
2nd degree, Mobitz type 1 (n, %)	0 (0)	0 (0)	1.0
2nd degree, Mobitz type 2 (n, %)	0 (0)	0 (0)	1.0
3rd degree (n, %)	0 (0)	0 (0)	1.0
LBBB (n, %)	2 (1)	0 (0)	1.0
LAFB (n, %)	2 (1)	0 (0)	1.0
RBBB (n, %)	2 (1)	3 (4)	1.0
iRBBB (n, %)	13 (7)	5 (7)	1.0
Pathologic Q waves (n, %)	3 (2)	4 (5)	0.10
LVH (n, %)	9 (5)	0 (0)	0.11
Nonspecific IVCD (n, %)	2 (1)	1 (1)	1.0
Pacemaker (n, %)	2 (1)	0 (0)	1.0
Other (n, %)	5 (3)	0 (0)	0.33
Total (n, %)	44 (23)	18 (24)	

Values are displayed as frequencies with corresponding percentages (%). AS = ankylosing spondylitis, OA = osteoarthritis, AV block = atrioventricular block, LBBB = left bundle branch block, LAFB = left anterior fascicular block, RBBB = right bundle branch block, iRBBB = incomplete right bundle branch block, LVH = left ventricular hypertrophy, IVCD = intraventricular conduction delay. a p values of chi-square test. * Significance level of $p < 0.05$.

Echocardiography

Table 4 provides an overview of echocardiographic parameters. An increased aortic root index was seen in AS-patients compared to controls, though both in the normal range, respectively 1.74 (±0.20) cm/m^2 vs 1.68 (±0.22) cm/m^2, p=0.08. The prevalence of aortic root dilatation (⩾ 2.1 cm/m2) was comparable in both groups with a prevalence of 7% in AS-patients and 4% in controls, p=0.53. Furthermore, AS-patients had more often AVR compared to controls, 41 (23%) vs 8 (11%), p=0.04. No difference was observed in MVR between AS-patients and controls.

The prevalences of systolic and diastolic LV dysfunction (both 2009 and 2016 ESE/EACVI grading criteria) were low and comparable between AS-patients and controls.

Table 4. Echocardiographic results

Cardiac structures	AS patients (N = 193)	OA-controls (N = 74)	p Value [a]
Aortic root index, cm/m² (mean ± SD)	1.74 ± 0.20	1.68 ± 0.22	0.08
Aortic root dilatation, ⩾ 2.1 cm/m² (n, %)	12 (7)	2 (4)	0.53
**Mitral valve regurgitation			0.46
Mild (n, %)	65 (34)	23 (32)	
Moderate (n, %)	4 (2)	0 (0)	
Severe (n, %)	0 (0)	0 (0)	
Prosthesis (n, %)	0 (0)	0 (0)	
Aortic valve regurgitation			0.04*
Trace (n, %)	16 (9)	1 (1)	
Mild (n, %)	23 (12)	7 (10)	
Moderate (n, %)	1 (1)	0 (0)	
Severe (n, %)	1 (1)	0 (0)	
Prosthesis (n, %)	1 (1)	0 (0)	
Cardiac function			
LV mass index, g/m² (mean ± SD)	75 ± 20	76 ± 19	0.79
LA volume index, ml/m² (mean ± SD)	29 ± 9	32 ± 13	0.11
EDV index, ml/m² (mean ± SD)	62 ± 15	55 ± 18	0.01*
ESV index, ml/m² (mean ± SD)	27 ± 8	22 ± 10	<0.01*
Ejection fraction (mean ± SD)	57 ± 6	60 ± 8	0.02*
E/e' average, cm/s (mean ± SD)	8.5 ± 2.5	8.0 ± 2.1	0.16
E-max, cm/s (mean ± SD)	69 ± 17	65 ± 17	0.06
A-max, cm/s (mean ± SD)	71 ± 17	71 ± 17	0.95
E/A ratio (mean ± SD)	1.0 ± 0.3	0.9 ± 0.2	0.03*
MV deceleration time, m/s (mean ± SD)	0.22 ± 0.05	0.22 ± 0.04	0.83
Septal e' velocity, cm/s (mean ± SD)	7.8 ± 1.9	7.4 ± 1.7	0.12
Lateral e' velocity, cm/s (mean ± SD)	9.5 ± 2.7	9.5 ± 2.2	0.94
TR velocity, cm/s (mean ± SD)	219 ± 26	229 ± 30	0.23
Systolic LV dysfunction (n, %)	10 (5)	2 (3)	0.74
Diastolic LV dysfunction – 2016			0.88
Grade I (n, %)	6 (3)	2 (3)	
Grade II (n, %)	1 (1)	0 (0)	
Grade III (n, %)	0 (0)	0 (0)	
Diastolic LV dysfunction – 2009			0.59
Grade I (n, %)	60 (32)	17 (25)	
Grade II (n, %)	39 (21)	16 (24)	
Grade III (n, %)	0 (0)	0 (0)	

Values are displayed as mean ± standard deviation (SD) or frequencies with corresponding percentages (%). Indexed values are corrected for BSA. AS = ankylosing spondylitis, OA = osteoarthritis, BSA = body surface index, LVMI = left ventrical mass index, LV = left ventricular, EDV = end diastolic volume, ESV = end systolic volume, MV = mitral valve, TR = tricuspid regurgitation. a p values of Student's t-test or chi-square test. * Bold, significance level of p ⩽ 0.05. ** A trace MVR is considered as physiological regurgitation and is therefore not added in the table.

Results of regression analyses
Results of logistic and linear multivariate regression analyses are presented in table 5. The relationship between AVR and AS was statistically significant and became more pronounced after adjusting for age, sex and CV risk factors. It revealed that AS-patients had an increased risk of AVR compared to controls, OR: 4.5; 95% CI: 1.1 – 13.6. In contrast, AS-patients did not have an increased risk of MVR compared to controls, OR: 1.9; 95% CI: 0.8 – 4.5. Lastly, subgroup analyses in AS showed no significant relationship between disease duration, ASDAS-CRP and anti-TNF drugs and the presence of AVR or MVR (data not shown).

Table 5. Association of AS with valve regurgitation.

	Crude model	Adjusted model [a]	Fully adjusted model [b]
Aortic valve regurgitation	2.3 (1.0 – 5.3) *	2.9 (1.3 – 6.8) *	4.5 (1.1 – 13.6) *
Mitral valve regurgitation	1.2 (0.7 – 2.2)	1.4 (0.8 – 2.5)	1.9 (0.8 – 4.5)

Values are displayed as odds ratio with corresponding 95% confidence interval.
[a] Adjusted for age and gender. [b] Adjusted for age, gender, current smoking status, pack years, systolic blood pressure, diastolic blood pressure, hypercholesterolemia, BMI, Diabetes Mellitus type 2, family history of cardiovascular diseases.
* Significance level of $p \leq 0.05$.

Discussion

The results of this study revealed that AS-patients had an up to five times increased risk of AVR compared to OA controls. Disease activity, disease duration and use of TNF-inhibitors were not associated with AVR. In addition, conduction disorders and diastolic LV dysfunction, based on the 2016 criteria of the ASE/EACVI, were rare in both AS-patients and controls, and the prevalence was comparable for both groups.

Aortic valve regurgitation
We found a prevalence of 23% of AVR in AS-patients and thus a 4-5 times increased risk for AVR in comparison to controls. Previous echocardiographic studies showed varying prevalences of AVR in AS-patients, ranging from 6 to 31% [6, 8-10, 27, 28]. However, as the presence of AVR is associated with age and cardiovascular risk factors, and these differed greatly between the available studies, these prevalence data are not well comparable. Overall, the AS patients of these cohort studies were younger, had a shorter disease duration and one study did not include trace AVR, thus likely underestimating the prevalence of AVR. Brunner et al. observed that AVR was present

in 10% of AS-patients, but they included patients aged 32 – 86 years and did not assess CV risk factors or comorbidities [8]. And again, trace regurgitation was not taken into account likely leading to a considerable underestimation of the prevalence.

Our most important observation was that elderly AS-patients (50-75 years) have an up to five times increased risk of having AVR compared to controls after correction for age, sex and CV risk factors. In addition, OA patients have an increased CV burden due to increased CV comorbidities, the increased risk that we observed in AS patients is probably an underestimation compared to when healthy subjects would have been used as controls [22].

In this study we observed a significant difference in the prevalence of AV regurgitation between AS patients and controls, but manifestations were mostly mild. Nevertheless, chronic AVR is a slow progressive disease, and the chronic state of inflammation that is present in AS patients may further accelerate progression . Moreover, the American Heart Association/American College of Cardiology (AHA/ACC) and the European Association of Cardiovascular Imaging (EACVI) state that regurgitation of the aortic valve is pathological, regardless of its grade [29, 30]. Hence, echocardiographic follow-up once per 3 – 5 years for trace or mild regurgitation, once per 1 – 2 years for moderate regurgitation and once per 0.5 – 1 year for severe regurgitation is recommended. Severe AR and rapid progression of the disease can be treated by valve replacement if recognized timely.

The current hypothesis on the valve involvement in AS is that entheses, the region where ligaments and tendons attach to bones, are the structures where inflammatory processes in AS mainly take place [31]. Pro-inflammatory cytokines, such as Interleukin (IL)- 23 and IL-17 have an important role in this inflammatory process and IL-23 stimulates IL-17 production by Th17-cells that further amplifies this inflammation [32-34]. The relevance for cardiac involvement in AS, is that entheses and the part of the aortic valve that inserts into the aortic root are histologically similar [34]. Sherlock et al. demonstrated in mice that both, entheses and this part of the aortic root, contain IL-23 receptor positive T-cells that can induce local inflammation after systemic exposure to Il-23 [34]. In the aortic root, inflammation may cause root dilatation and the inflammation may extend to the annulus, resulting in basal thickening and downward retraction of the cusps, also resulting in AVR [27, 35, 36]. The thickening of the annulus itself could also disturb the laminar blood flow resulting deterioration of valve function. In line with the increased

prevalence of AVR in AS-patients, we observed a trend towards a significantly greater aortic root index compared to OA controls, respectively 1.74 ±0.20 cm/m^2 vs 1.68 ± 0.22 cm/m^2, p=0.08. This is consistent with small-sized studies of Roldan et al. and Yildirir et al. as they also showed increased aortic root diameter, as well as increased prevalence of AVR in AS patients compared to controls [27, 37].

Conduction disorders

Major electrical conduction elements, such as the atrial-ventricular (AV) node and the bundle branches (BBs) are located in very close proximity to the heart valves. In addition to the aortic root and the cusps of the aortic valve, in AS the inflammatory process therefore may extend to the atrial ventricular node (AV-node) and interventricular septum, leading to AR, AV-blocks and bundle branch blocks (BBB's) [27]. However, most of the existing studies regarding conduction disturbances in AS-patients were relatively small, some lack controls and the results are inconsistent [8, 11, 12, 28, 38]. Our study assessed the clinically relevant and significant conduction disturbances in a large cohort AS-patients. We found a very low prevalence of, mostly mild, conduction disturbances with limited clinical relevance in the AS population comparable to the controls which is in contrast to the existing literature [11, 12, 38]. A Swedish prospective, nationwide populations-based cohort showed AS-patients have a two-fold increased risk to develop an AV-block. However, the clinical relevance of this result is limited as this corresponds with an AV-block prevalence of 0.5% in AS patients compared to 0.4% in healthy subjects after a follow-up duration of 6 years [11]. Two other studies performed by Forsblad-d'Elia et al. and Dik et al. demonstrated in clinical trials that first degree AV-blocks and BBB's are common in AS-patients [12, 38]. However, both studies had no control group to compare their results to, and after specifying the type of BBB, the total prevalence of BBB's dropped under 10% with both studies reporting primarily incomplete BBB's. In fact Dik et al. demonstrated only 0.8% (1) of the AS patients with a complete right BBB and none with a complete Left BBB or left hemi block [38], though, their subjects were younger. Therefore, based on our results and in context of existing literature, we conclude that conduction disturbances are mostly mild with limited clinical relevance, and conduction disorders do not occur more frequently in AS-patients compared to controls.

Diastolic LV dysfunction

It is hypothesized that development of diastolic LV dysfunction may result from coronary endothelium activation caused by systemic inflammation [39]. The activated endothelial cells cause cardiomyocytes to hypertrophy and stiffen, but also enable monocytes to

enter cardiac tissue where they trigger collagen production. The combined effect of these processes may lead to microvascular rarefaction, interstitial fibrosis and stiff cardiomyocytes, which impairs relaxation of the ventricles and thus induces diastolic LV dysfunction [39, 40].

The current literature supports evidence for an increased risk of diastolic LV dysfunction in AS-patients, albeit that varying prevalences have been reported (9-45%) [14, 15]. Three studies assessed diastolic LV dysfunction using the combined set of parameters as recommended by the ASE/EACVI in 2009 ranging from 12-45%, though cut-off values of single parameters differed slightly between studies [15, 41, 42]. Other studies reported prevalences ranging from 20% to 49%, but those studies were not specifically designed to assess diastolic LV dysfunction or only used a single or few echocardiographic parameter for assessing diastolic LV dysfunction, which differs from the ASE/EACVI guidelines [8, 14, 26, 43-46]. Nowadays, the most appropriate way, recommended by American and European echocardiography organizations (ASE and EACVI) to asses diastolic LV dysfunction, is to combine specific echocardiographic parameters [47]. Thus far there have been no studies assessing diastolic LV function in AS patients with the updated ASE/EACVI 2016 guidelines.

However, the 2009 algorithms were considered too complex and had a substantial inter-observer variability, which possibly caused the wide variation in the observed prevalence of diastolic LV dysfunction. Therefore, the guidelines to assess diastolic LV dysfunction were upgraded in 2016 by the ASE/EACVI with the purpose of simplifying the approach [48]. It has been shown that the 2016 algorithm is superior to the 2009 algorithm with regards to specificity, correlation with clinical outcomes and inter-observer variability, but had a lower sensitivity [49]. The above-mentioned studies mostly used the 2009 criteria and when using the 2009 algorithm we found a prevalence of diastolic LV dysfunction of 53% in AS-patients and 46% in OA-patients, respectively. When applying the 2016 criteria, these prevalences, declined to 3.8% and 3.3%, respectively. Moreover, eight of the nine patients with diastolic LV dysfunction also had systolic LV dysfunction. According to the 2016 criteria, all patients with systolic LV dysfunction are defined to have also diastolic LV dysfunction. For our study this means that only one patient in the entire cohort was diagnosed with diastolic LV dysfunction because of aberrant echocardiographic Doppler values. Altogether, our results indicate that diastolic LV dysfunction in AS-patients is infrequent and that previous studies overestimated the

prevalence of impaired diastolic LV function in AS-patients due to the low accuracy of the diagnostic/grading tool.

Strengths and limitations

Our study has several strengths and limitations. First, to our knowledge, this is the largest study undertaken in AS-patients assessing LV function by echocardiography. Second, this is the first study to assess diastolic LV dysfunction in AS-patients based on the 2016 guidelines of the ASE/EACVI.

Nonetheless, there are also limitations of the present study. First of all, due to the cross-sectional study design, the described associations found in this study are not necessarily causal. We were therefore unable to determine long-term consequences of the cardiac manifestations we observed in our patients. Secondly, complete matching of groups on a ratio of 2:1 based on age, sex and current smoking status, was not completely achieved, introducing minor differences in patient characteristics. Therefore, we adjusted for these variables in our regression analyses, thereby limiting the consequences thereof.

Conclusions

In conclusion, AS-patients have an up to five times increased risk of AVR, although this was mostly mild. However, it is important to realize that any stage of AVR is considered to be pathological as mild regurgitation may progress and result into severe complications. When timely recognized it can be treated adequately (aortic valve replacement). Therefore, our findings indicate that echocardiographic screening of elderly AS patients (50-75 years) should be considered. Obviously, prospective studies should assess the cost-effectiveness of screening of all AS patients as well as the long-term complications of AVR in AS patients. In contrast, AS-patients did not have an increased risk of conduction disorders nor LV diastolic dysfunction compared to controls.

References

1. Braun J, Sieper J. Ankylosing spondylitis. Lancet. 2007;369(9570):1379-90.
2. El Maghraoui A. Extra-articular manifestations of ankylosing spondylitis: prevalence, characteristics and therapeutic implications. Eur J Intern Med. 2011;22(6):554-60.
3. Exarchou S, Lie E, Lindstrom U, Askling J, Forsblad-d'Elia H, Turesson C, et al. Mortality in ankylosing spondylitis: results from a nationwide population-based study. Annals of the rheumatic diseases. 2016;75(8):1466-72.
4. Haroon NN, Paterson JM, Li P, Inman RD, Haroon N. Patients With Ankylosing Spondylitis Have Increased Cardiovascular and Cerebrovascular Mortality: A Population-Based Study. Annals of internal medicine. 2015;163(6):409-16.
5. Heeneman S, Daemen MJ. Cardiovascular risks in spondyloarthritides. Curr Opin Rheumatol. 2007;19(4):358-62.
6. Ozkan Y. Cardiac Involvement in Ankylosing Spondylitis. J Clin Med Res. 2016;8(6):427-30.
7. Schilder DP, Harvey WP, Hufnagel CA. Rheumatoid spondylitis and aortic insufficiency. N Engl J Med. 1956;255(1):11-7.
8. Brunner F, Kunz A, Weber U, Kissling R. Ankylosing spondylitis and heart abnormalities: do cardiac conduction disorders, valve regurgitation and diastolic dysfunction occur more often in male patients with diagnosed ankylosing spondylitis for over 15 years than in the normal population? Clin Rheumatol. 2006;25(1):24-9.
9. Klingberg E, Svealv BG, Tang MS, Bech-Hanssen O, Forsblad-d'Elia H, Bergfeldt L. Aortic Regurgitation Is Common in Ankylosing Spondylitis: Time for Routine Echocardiography Evaluation? Am J Med. 2015;128(11):1244-50.e1.
10. Soroush M, Mominzadeh M, Ghelich Y, Soroosh S, Pasha MA. Investigation of Cardiac Complications and their Incidence in Patients with Ankylosing Spondylitis. Med Arch. 2016;70(1):35-8.
11. Bengtsson K, Forsblad-d'Elia H, Lie E, Klingberg E, Dehlin M, Exarchou S, et al. Risk of cardiac rhythm disturbances and aortic regurgitation in different spondyloarthritis subtypes in comparison with general population: a register-based study from Sweden. Ann Rheum Dis. 2018;77(4):541-8.
12. Forsblad-d'Elia H, Wallberg H, Klingberg E, Carlsten H, Bergfeldt L. Cardiac conduction system abnormalities in ankylosing spondylitis: a cross-sectional study. BMC Musculoskelet Disord. 2013;14:237.
13. Longo B, Kirchner LA, Simioni J, Campos APB, Skare TL. Electrocardiographic changes in spondyloarthritis and use of anti-TNF-alpha drugs: a retrospective study with 100 patients. Einstein (Sao Paulo). 2019;17(2):eAO4539.
14. Heslinga SC, Van Dongen CJ, Konings TC, Peters MJ, Van der Horst-Bruinsma IE, Smulders YM, et al. Diastolic left ventricular dysfunction in ankylosing spondylitis--a systematic review and meta-analysis. Seminars in arthritis and rheumatism. 2014;44(1):14-9.

15. Svealv BG, Tang MS, Klingberg E, Forsblad-d'Elia H, Bergfeldt L. Prevalence of diastolic dysfunction in patients with ankylosing spondylitis: a cross-sectional study. Scand J Rheumatol. 2015;44(2):111-7.

16. Agca R, Heslinga SC, Rollefstad S, Heslinga M, McInnes IB, Peters MJ, et al. EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 update. Ann Rheum Dis. 2017;76(1):17-28.

17. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum. 1984;27(4):361-8.

18. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2015;16(3):233-70.

19. Lancellotti P, Tribouilloy C, Hagendorff A, Moura L, Popescu BA, Agricola E, et al. European Association of Echocardiography recommendations for the assessment of valvular regurgitation. Part 1: aortic and pulmonary regurgitation (native valve disease). Eur J Echocardiogr. 2010;11(3):223-44.

20. Lancellotti P, Moura L, Pierard LA, Agricola E, Popescu BA, Tribouilloy C, et al. European Association of Echocardiography recommendations for the assessment of valvular regurgitation. Part 2: mitral and tricuspid regurgitation (native valve disease). Eur J Echocardiogr. 2010;11(4):307-32.

21. Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. 1916. Nutrition. 1989;5(5):303-11; discussion 12-3.

22. Wang H, Bai J, He B, Hu X, Liu D. Osteoarthritis and the risk of cardiovascular disease: a meta-analysis of observational studies. Sci Rep. 2016;6:39672.

23. Evangelista A, Flachskampf FA, Erbel R, Antonini-Canterin F, Vlachopoulos C, Rocchi G, et al. Echocardiography in aortic diseases: EAE recommendations for clinical practice. Eur J Echocardiogr. 2010;11(8):645-58.

24. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol. 1988;15(12):1833-40.

25. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. Eur J Echocardiogr. 2009;10(2):165-93.

26. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, 3rd, Dokainish H, Edvardsen T, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2016;17(12):1321-60.

6

27. Roldan CA, Chavez J, Wiest PW, Qualls CR, Crawford MH. Aortic root disease and valve disease associated with ankylosing spondylitis. J Am Coll Cardiol. 1998;32(5):1397-404.

28. Ward MM. Lifetime Risks of Valvular Heart Disease and Pacemaker Use in Patients With Ankylosing Spondylitis. J Am Heart Assoc. 2018;7(20):e010016.

29. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, 3rd, Guyton RA, et al. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129(23):e521-643.

30. Joint Task Force on the Management of Valvular Heart Disease of the European Society of C, European Association for Cardio-Thoracic S, Vahanian A, Alfieri O, Andreotti F, Antunes MJ, et al. Guidelines on the management of valvular heart disease (version 2012). Eur Heart J. 2012;33(19):2451-96.

31. Ball J. Enthesopathy of rheumatoid and ankylosing spondylitis. Annals of the rheumatic diseases. 1971;30(3):213-23.

32. Lubberts E. The IL-23-IL-17 axis in inflammatory arthritis. Nature reviews Rheumatology. 2015;11(7):415-29.

33. Sherlock JP, Buckley CD, Cua DJ. The critical role of interleukin-23 in spondyloarthropathy. Molecular immunology. 2014;57(1):38-43.

34. Sherlock JP, Joyce-Shaikh B, Turner SP, Chao CC, Sathe M, Grein J, et al. IL-23 induces spondyloarthropathy by acting on ROR-gammat+ CD3+CD4-CD8- entheseal resident T cells. Nature medicine. 2012;18(7):1069-76.

35. Bulkley BH, Roberts WC. Ankylosing spondylitis and aortic regurgitation. Description of the characteristic cardiovascular lesion from study of eight necropsy patients. Circulation. 1973;48(5):1014-27.

36. Davidson P, Baggenstoss AH, Slocumb CH, Daugherty GW. CARDIAC AND AORTIC LESIONS IN RHEUMATOID SPONDYLITIS. Proceedings of the staff meetings Mayo Clinic. 1963;38:427-35.

37. Yildirir A, Aksoyek S, Calguneri M, Oto A, Kes S. Echocardiographic evidence of cardiac involvement in ankylosing spondylitis. Clin Rheumatol. 2002;21(2):129-34.

38. Dik VK, Peters MJ, Dijkmans PA, Van der Weijden MA, De Vries MK, Dijkmans BA, et al. The relationship between disease-related characteristics and conduction disturbances in ankylosing spondylitis. Scand J Rheumatol. 2010;39(1):38-41.

39. Paulus WJ, Tschope C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. J Am Coll Cardiol. 2013;62(4):263-71.

40. Paulus WJ. Unfolding Discoveries in Heart Failure. N Engl J Med. 2020;382(7):679-82.

41. Okan T, Sari I, Akar S, Cece H, Goldeli O, Guneri S, et al. Ventricular diastolic function of ankylosing spondylitis patients by using conventional pulsed wave Doppler, myocardial performance index and tissue Doppler imaging. Echocardiography. 2008;25(1):47-56.

42. Acar G, Sayarlioglu M, Akcay A, Sokmen A, Sokmen G, Altun B, et al. Assessment of atrial electromechanical coupling characteristics in patients with ankylosing spondylitis. Echocardiography. 2009;26(5):549-57.

43. Emren SV, Gercik O, Ozdemir E, Solmaz D, Eren N, Simsek EC, et al. Evaluation of subclinical myocardial dysfunction using speckle tracking echocardiography in patients with radiographic and non-radiographic axial spondyloarthritis. Eur J Rheumatol. 2020;7(1):9-15.

44. Turkmen S, Askin L, Uzel KE, Nacar H, Kavalci V, Akturk E, et al. Association of High-Sensitivity Troponin T With Left Ventricular Dysfunction in Ankylosing Spondylitis. J Clin Rheumatol. 2020;26(3):87-93.

45. Brewerton DA, Gibson DG, Goddard DH, Jones TJ, Moore RB, Pease CT, et al. The myocardium in ankylosing spondylitis. A clinical, echocardiographic, and histopathological study. Lancet. 1987;1(8540):995-8.

46. Crowley JJ, Donnelly SM, Tobin M, FitzGerald O, Bresnihan B, Maurer BJ, et al. Doppler echocardiographic evidence of left ventricular diastolic dysfunction in ankylosing spondylitis. Am J Cardiol. 1993;71(15):1337-40.

47. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2012;14(8):803-69.

48. Lang RM, Badano LP, Tsang W, Adams DH, Agricola E, Buck T, et al. EAE/ASE recommendations for image acquisition and display using three-dimensional echocardiography. Eur Heart J Cardiovasc Imaging. 2012;13(1):1-46.

49. Prasad SB, Holland DJ, Atherton JJ, Whalley G. New Diastology Guidelines: Evolution, Validation and Impact on Clinical Practice. Heart Lung Circ. 2019;28(9):1411-20.

Chapter 7

Aortic root diameter is associated with HLA-B27: identifying the patient with ankylosing spondylitis at risk for aortic valve regurgitation

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Abstract

Objective

To assess the association between the aortic root diameter in HLA-B27 positive (+) and HLA-B27 negative (-) ankylosings spondylitis (AS) patients from the CARDAS cohort.

Methods

The CARDAS study is a cross-sectional study in AS patients between 50-75 years who were recruited from a large rheumatology outpatient clinic. Patients underwent cardiovascular screening including echocardiography, with 2D, spectral and color flow Doppler measurements. The aortic root was measured at sinuses of Valsalva during diastole. The aortic root diameter was adjusted for body surface area (BSA) (aortic root index, cm/m²).

Results

193 Consecutive AS patients were included of whom 158 (82%) were HLA-B27 positive. The aortic root index was significantly higher in HLA-B27+ patients compared to HLA-B27- patients, respectively 1.76 cm ± 0.21 vs. 1.64 cm ± 0.14, p<0.001. No difference was seen in the prevalence of aortic valve regurgitation (AVR), p=0.8. Regression analysis showed a significant association between HLA-B27 and aortic root index corrected for age, sex and cardiovascular risk factors (β 0.091, 95%CI 0.015-0.168, p=0.02). Especially, male HLA-B27+ patients had a significantly increased aortic root index compared to male HLA-B27- AS patients, respectively 1.76 cm (1.63-1.88) and 1.59 cm (1.53-1.68), p<0.001.

Conclusion

We found an increased aortic root index in elderly HLA-B27+ AS patients compared to HLA-B27- AS patients, especially in male patients. No difference was seen in the prevalence of AVR. However, as AVR can be progressive, echocardiographic monitoring in elderly male HLA-B27+ AS might be considered.

Introduction

Ankylosing spondylitis (AS) is an inflammatory joint disease associated with cardiac involvement. Aortic valve regurgitation (AVR) is a well-known cardiac complication described in AS patients [1, 2]. Inflammation of the aortic root might weaken aortic wall strength with subsequent dilatation of the aortic root causing fibrotic thickening of the aortic cusps. In combination with shortening of the aortic cusps this might ultimately lead to AVR [3-5]. In the majority of patients with AVR, the disease course is chronic and slowly progressive and in severe cases can lead to congestive heart failure, arrhythmia and sudden death [6-8]. The American Heart Association/American College of Cardiology (AHA/ACC) and the European society of cardiology (ESC) state that AVR is pathological, regardless of its grade of severity [8, 9]. Timely intervention with life style changes, pharmaceutical and/or surgical treatment of the aortic valve reduces the risk for severe complications [10]. Hence, follow up is indicated in all cases of AVR [8, 9]. In this light, some advocate regular echocardiographic screening for AS patients [11]. However, the cost-benefit of echocardiographic screening in AS is currently unknown and to what extent AS specific (subclinical) cardiac pathology leads to clinically overt cardiovascular morbidity and mortality remains to be elucidated. Therefore, it is needed to identify a specific at risk AS population that might benefit from routine echocardiographic monitoring.

HLA-B27 genotype is associated with AS. Eighty to 90% of AS patients in the Western World, carry the HLA-B27 allele compared to the a 5% prevalence in the general Western population [12]. Interestingly, the HLA-B27 genotype has also been associated with cardiac diseases including AVR in non-rheumatic patients [4, 5]. The question rises whether the increased risk for cardiac diseases in AS patients is linked to the HLA-B27 genotype. Therefore, the presence of the HLA-B27 genotype may be a screening feature to identify AS patients at risk for AVR. Hence, we hypothesized that HLA-B27 positive (+) AS patients have a higher risk of developing AVR compared to HLA-B27 negative (-) AS patients.

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Patients and Methods

Study population

Data of AS patients of the Cardiac disease in Ankylosing Spondylitis (CARDAS) cohort were used. The CARDAS cohort included AS patients aged between 50 and 75 years old who had a comprehensive cardiovascular screening. Subjects were consecutively recruited between March 2014 and September 2019 from the Rheumatology department of Reade, Amsterdam, and the Netherlands. All patients fulfilled the 1984 Modified New York criteria for AS [13]. This study was conducted in accordance with the Helsinki Declaration and the approval was obtained from the ethics committee of the Slotervaart Hospital and Reade, Amsterdam, The Netherlands (NL44202.048.13). All participating patients gave written consent.

Patient and disease characteristics

All patients underwent a complete AS workup and cardiovascular screening including transthoracic echocardiographic (TTE) screening. Medical history was obtained by questionnaires and medical charts, including medication use, cardiovascular risk factors including smoking, hypertension and dyslipidemia and history of cardiovascular disease. Hypertension was defined as present if a patient was treated with antihypertensive medication, had a systolic blood pressure ≥ 140mmHg or a diastolic blood pressure ≥ 90mmHg measured during physical examination. Furthermore, physical examination included height, weight and blood pressure measurements. Body mass index (BMI) was calculated. Blood sample measurements included standard hematological assessment, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Disease activity was measured with the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), and the Ankylosing Spondylitis Disease Activity Score - CRP (ASDAS-CRP).

Transthoracic echocardiography

TTE was performed by experienced echo technicians at the Amsterdam UMC, location VUmc, a European Society of Cardiology certified echo-lab. To exclude inter-observer variability, all recordings of echocardiography data from both AS patients and controls were stored digitally and were afterwards analysed offline by a single cardiologist (T.C.K.). TTE was performed according to the protocol based on the guidelines provided by European Association of Echocardiography. Evaluation of cardiac function consisted of 2D, spectral and color flow Doppler recordings. 2D recordings were performed in

parasternal long- and short-axis views, and apical four-, three- and two-chamber views. The aortic root was measured at sinuses of Valsalva during diastole. The aortic root diameter was corrected for body surface area (BSA) according to the Dubois method (aortic root index) [14]. An aortic root index of ⩾ 2.1 cm/m^2 was considered as aortic root dilatation [15, 16].

Statistical analysis
For data analysis SPSS Version 24.0 (IBM Corp., Armonk, New York) was used. Demographic and disease characteristics were summarized using descriptive statistics. Distribution of data was displayed by histograms. Values are expressed as mean ± standard deviation (SD), median (interquartile range, IQR) or numbers (percentages, %) where appropriate. Independent samples t-tests were used for comparisons of normally distributed continuous variables and the Mann-Whitney U-test for non-normally distributed variables. The Chi-square test or Fisher's exact test (n<10) was performed on dichotomous variables. Echocardiographic data were analysed using the unpaired samples t-test or the Mann-Whitney U test, where appropriate. A level of p<0.05 was considered statistically significant.

Results

Patient characteristics
In total, 193 consecutive AS patients were included of whom 158 were HLA-B27+ and 35 HLA-B27-. AS patients had respectively a mean age of 60 (±7) years and 61 (±7) years and 44 (28%) and 11 (31%) were female, respectively (Table 1). Both groups had a comparable disease duration (time since diagnosis), 36 (±11) and 30 (±14) years, and a moderate disease activity assessed with the ASDAS-CRP, 2.1 (±1.0) and (2.3 ±1.0) (table 1). Furthermore, obesity and diabetes type II were more common in HLA-B27- AS patients, respectively 18% vs 40% and 9% vs 20%. History for cardiovascular disease was similar in both groups.

Table 1. Baseline characteristics

Patient characteristics	HLA-B27 +	HLA-B27 -
n	158	35
Age, years (mean ±SD)	60 ±7	61 ±7
Sex, female (n, %)	44 (28)	11 (31)
BSA, m² (mean ±SD)	1.91 ±0.19	2.00 ±0.20
BMI, m²/kg (mean ±SD)	26.2 ±4.1	28.7 ±3.9
Systolic blood pressure, mmHg (mean ±SD)	133 ±16	136 ±15
Diastolic blood pressure, mmHg (mean ±SD)	83 ±7	86 ±8
Disease activity and severity		
Disease duration, years (mean ±SD)	36 ±11	30 ±14
ESR, mm/hr (median; IQR)	7 (4-14)	9 (5-17)
CRP, mg/L (mean ±SD)	2.7 (1.2-7.6)	3.3 (1.1-8.1)
ASDAS-CRP (mean ±SD)	2.1 ±1.0	2.3 ±1.0
BASDAI (mean ±SD)	3.3 ±2.2	4.0 ±2.4
BASFI (mean ±SD)	3.6 ±2.4	4.0 ±2.6
Cardiovascular risk factors		
Smoking		
Current (n, %)	33 (21)	6 (17)
Ever (n, %)	111 (70)	23 (66)
pack years, years (mean ±SD)	26.2 ±14.0	26.4 ±16.8
Hypertension		
Criteria (n, %)	93 (59)	25 (71)
Patient history (n, %)	59 (37)	17 (49)
Obesity (n, %)	28 (18)	14 (40)
Hypercholesterolemie (n, %)	28 (18)	8 (23)
Diabetes type II (n, %)	15 (9)	7 (20)
History of cardiovascular disease		
Angina Pectoris (n, %)	2 (1)	3 (9)
Myocardial infarction (n, %)	10 (6)	2 (6)
Stroke (n, %)	5 (3)	2 (6)
TIA (n, %)	3 (2)	1 (3)
CVA (n, %)	2 (1)	1 (3)
Peripheral ischemia (n, %)	1 (1)	0 (0)
CABG (n, %)	6 (4)	2 (6)
Family history (first degree)		
AP / MI (n, %)	19 (12)	5 (14)
CVA/TIA (n, %)	11 (7)	3 (9)
Medication		
Lipid modifying drug (n, %)	29 (18)	9 (26)
Antihypertensives (n, %)	68 (43)	17 (49)
Biologic DMARDs (anti-TNF) (n, %)	58 (37)	12 (34)

Values are displayed as mean ± standard deviation (SD), median (IQR) or frequencies with corresponding percentages (%). BSA=body surface area, BMI=body mass index, ESR=erythrocyte sedimentation rate, CRP=C-reactive protein, ASDAS=ankylosing spondylitis disease activity score, BASDAI=bath ankylosing spondylitis disease activity score, BASFI=bath ankylosing spondylitis functional index, TIA=transient ischemic attack, CVA=cerebral vascular accident, CABG=coronary artery bypass graft, AP=angina pectoris, MI=myocardial infarction. * Significance level of $p \leq 0.05$.

Aortic root Measurement and valvular disease

The median aortic root index was significantly higher in HLA-B27+ patients compared to HLA-B27- patients: 1.76 (±0.21) cm/m² vs 1.64 (±0.14) cm/m², p<0.001. Furthermore, HLA-B27+ AS patients compared to HLA B27- AS patients had more often aortic root dilatation (≥2.1 cm/m²), 11 (8%) and 1 (3%), p=0.3, respectively (table 2). The presence of aortic root dilatation in HLA-B27+ AS patients was seen significantly more often in patients with aortic valve regurgitation, p=0.003. The single case of aortic root dilatation in the HLA-B27- cohort had a mild AVR. Of the eleven cases of aortic root dilatation in HLA-B27+ AS patients four had no AVR, one had AVR, five had mild AVR, one severe AVR and in one AS patient had an aortic valve prosthesis. None of the AS patients had aortic valve stenosis and one AS patient had mitral valve stenosis.

Table 2. Echocardiographic parameters

	HLA-B27 +	HLA-B27 -	p value
Echocardiography			
Aortic root, cm (mean ±SD)	3.35 ±0.43	3.25 ±0.28	0.12
Aortic root index, cm/m² (mean ±SD)	1.76 ±0.21	1.64 ±0.14	<0.001*
Aortic root dilatation (≥2,1 cm/m²) (n, %)	11 (8)	1 (3)	0.5
Aortic valve regurgitation (n, %)	34 (22)	8 (24)	0.8
Trace (n, %)	13 (8)	3 (9)	
Mild (n, %)	18 (12)	5 (15)	
Moderate (n, %)	4 (3)	0	
Severe (n, %)	1 (1)	0	
Prothesis (n, %)	1 (1)	0	
Mitral valve regurgitation (n, %)	52 (34)	17 (49)	0.25
Mild (n, %)	49 (32)	16 (46)	
Moderate (n, %)	3 (2)	1 (3)	
Severe (n, %)	0 (0)	0 (0)	
Prothesis (n, %)	0 (0)	0 (0)	

Values are displayed as mean ± standard deviation (SD) or frequencies with corresponding percentages (%). No cases of aortic valve stenosis and only one case of mitral valve stenosis were assessed. * Significance level of $p \leq 0.05$.

Association between HLA-B27 and aortic root index

The results of the linear regression analysis (crude, adjusted and fully adjusted) are presented in table 3. The relation between HLA-B27 genotype and the aortic root index remained significant in the fully adjusted model corrected for age, sex and cardiovascular risk factors, B 0.091 (95%CI 0.091-0.168), p=0.02.

Table 3. Association of HLA-B27 genotype with the aortic root index

	Crude model		**Adjusted model**[a]		**Fully adjusted model**[b]	
	Beta	p value	Beta	p value	Beta	p value
Aortic root index, cm/m²	0.121 (0.045-0.198)	0.002	0.123 (0.048-0.199)	0.002	0.091 (0.015-0.168)	0.02

Values are displayed as odds ratio with corresponding 95% confidence interval. BSA=body surface area. - Adjusted for age and gender. - Adjusted for age, gender, systolic blood pressure, diastolic blood pressure, hypercholesterolemia, BMI, Diabetes Mellitus type 2 and family history of cardiovascular diseases. * Significance level of p ≤ 0.05.

Aortic root index, HLA-B27 genotype and sex

The differences in aortic root index and sex and HLA-B27 genotype are shown in table 4. Male HLA-B27+ patients had a significant increased aortic root index compared to male HLA-B27- AS patients, respectively 1.76 (1.63-1.88) and 1.59 (1.53-1.68), p<0.001. No difference was seen in female HLA-B27+ and HLA-B27- AS patients, respectively 1.66 (1.53-1.92) and 1.64 (1.54-1.83), p=0.91. Furthermore, male HLA-B27+ AS patients also had an increased aortic root index compared to female HLA-B27+ AS patients.

Table 4. Gender differences in aortic root index, aortic root dilatation and aortic valve regurgitation

	Male		p value	**Female**		p value
	HLA-B27 +	HLA-B27 -		HLA-B27 +	HLA-B27 -	
n=	114	24		44	11	
Aortic root index, cm/m² (median; IQR)	1.76 (1.63-1.88)	1.59 (1.53-1.68)	<0.001	1.66 (1.53-1.92)	1.64 (1.54-1.83)	0.91
Aortic root dilatation, n (%)	7 (7)	0	0.35	4 (11)	1 (10)	1.00
Aortic valve regurgitation, n (%)	23 (20)	5 (23)	0.80	11 (26)	3 (27)	0.94

Values are displayed as median (IQR) or frequencies with corresponding percentages (%). No cases of aortic valve stenosis and only one case of mitral valve stenosis. * Significance level of p ≤ 0.05.

Discussion

In the present study, the association between HLA-B27 genotype and aortic root diameter in AS patients was investigated. HLA-B27+ AS patients had a significantly increased aortic root index compared to HLA-B27- AS patients. This association was not explained by difference in age, sex nor cardiovascular risk factors. The prevalence of AVR was however similar in both groups. Furthermore, aortic dilatation was seen more often in HLA-B27+ AS patients, albeit this reached no statistical significance. Finally, our data suggest a sex and HLA-B27 genotype linked difference in aortic root index as male HLA-B27+ patients had an increased aortic root index compared to the HLA-B27- male patients and the overall female AS patients.

The HLA-B27 antigen is assumed to misfold causing an unfolded protein response (UPR). This might result in IL-23 upregulation by macrophages and lamina propria mononuclear cells and leading to activation of the IL-23/IL-17 inflammatory pathway, increasing susceptibility to AS [17-19]. Pathology studies have shown that IL-23– Dependent -/- T-Cells (IL23+ T-cell) are specifically expressed in entheseal organs such as entheses (the primary inflammatory target in AS), ciliary body of the eye, and aortic root and aortic valves [17, 20]. Entheseal organs are avascular in their fibrocartilaginous regions, however microdamages of entheseal tissue due to continuous exposure to mechanical forces are common and appear to be associated with tissue repair responses and vessel ingrowth [21, 22]. It is assumed that enthesis-resident IL23+ T-cells have a homeostatic role in entheseal tissue repair. However, enthesis-resident IL23+ T-cells can also trigger a pro-inflammatory cascade as IL-23 binding induces IL-17 and IL-22 production leading to inflammation, bone loss and ossification [17, 23]. Therefore, IL-23 upregulation possibly also results in activation of in situ IL23+ T-cells in aortic root and valves leading to local inflammation with subsequently inflammation of the aortic root and valves. In fact, murine studies have shown inflammation of entheses and aortic root and valves after infusion with IL-23 [20].

Our study partially confirms our hypothesis as HLA-B27+ AS patients didn't not have an increased prevalence of aortic valve disease as was expected. However, HLA-B27+ AS patients did have an increased aortic root index and had more often aortic root dilatation. To our knowledge, this finding has not been reported before. Our results may be indicative for the preclinical state of aortic valve disease in HLA-B27+ AS patients. At an older age HLA-B27+ AS patients may have a higher risk at developing aortic

valve disease as inflammation of the aortic root and valves is progressive of nature [7]. Klingberg et al. found also no relation between HLA-B27 genotype and aortic valve regurgitation [11]. However, in this study assessment of this relation was not the primary objective and the AS subjects were 10 years younger. Moreover, Huppert et al. found, in HLA-B27+ juvenile arthritis patients, a higher prevalence of aortic valve regurgitation compared to HLA-B27- non-rheumatic controls, respectively 10% (4/40) vs 0% (0/40) [24]. However, this study was performed in children <18 years of age and the control group consisted of non-rheumatic HLA-B27- subjects.

Our data suggest a sex and HLA-B27 genotype linked difference in aortic root index in disadvantage for male HLA-B27+ patients. In this light, the findings of Bergfeldt et al. are important as they showed that patients needing a pacemaker due to severe conduction disturbances were primarily male HLA-B27+ patients [25].

Our study did have some limitations. Firstly, due to the cross-sectional study design, the associations found in this study are not necessarily causal. Therefore, the (potential) long-term consequences of the cardiac manifestations we observed in our patients still need to be demonstrated. AS is predominant in male AS patients therefore the female subgroup was relatively small what could have masked differences between HLA-B27 + and HLA-B27 women.

In conclusion, our study demonstrated an increased aortic root index in elderly HLA-B27+ AS patients, especially in male patients. This did not already translated in an increased prevalence of aortic valve regurgitation in this subgroup. However, this finding is important as inflammation of the aortic root and valve in chronic inflammatory disease are progressive and may evolve in severe complications. Therefore, to recognize the AS patients at risk for this cardiac disease, echocardiographic monitoring, particularly in elderly male HLA-B27+ AS subjects should be considered. Obviously, prospective studies should determine the long term outcomes as well the cost effectiveness of echocardiographic screening in this subgroup.

References

1. Roldan CA, Chavez J, Wiest PW, Qualls CR, Crawford MH. Aortic root disease and valve disease associated with ankylosing spondylitis. J Am Coll Cardiol. 1998;32(5):1397-404.

2. Palazzi C, S DA, Lubrano E, Olivieri I. Aortic involvement in ankylosing spondylitis. Clin Exp Rheumatol. 2008;26(3 Suppl 49):S131-4.

3. Bulkley BH, Roberts WC. Ankylosing spondylitis and aortic regurgitation. Description of the characteristic cardiovascular lesion from study of eight necropsy patients. Circulation. 1973;48(5):1014-27.

4. Bergfeldt L, Insulander P, Lindblom D, Moller E, Edhag O. HLA-B27: an important genetic risk factor for lone aortic regurgitation and severe conduction system abnormalities. Am J Med. 1988;85(1):12-8.

5. Bergfeldt L. HLA-B27-associated cardiac disease. Ann Intern Med. 1997;127(8 Pt 1):621-9.

6. Rigolin VH, Bonow RO. Hemodynamic characteristics and progression to heart failure in regurgitant lesions. Heart Fail Clin. 2006;2(4):453-60.

7. Flint N, Wunderlich NC, Shmueli H, Ben-Zekry S, Siegel RJ, Beigel R. Aortic Regurgitation. Curr Cardiol Rep. 2019;21(7):65.

8. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, 3rd, Guyton RA, et al. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129(23):e521-643.

9. Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Baron-Esquivias G, Baumgartner H, et al. Guidelines on the management of valvular heart disease (version 2012): the Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur J Cardiothorac Surg. 2012;42(4):S1-44.

10. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2017;38(36):2739-91.

11. Klingberg E, Svealv BG, Tang MS, Bech-Hanssen O, Forsblad-d'Elia H, Bergfeldt L. Aortic Regurgitation Is Common in Ankylosing Spondylitis: Time for Routine Echocardiography Evaluation? Am J Med. 2015;128(11):1244-50 e1.

12. Reveille JD. HLA-B27 and the seronegative spondyloarthropathies. Am J Med Sci. 1998;316(4):239-49.

13. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum. 1984;27(4):361-8.

14. Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. 1916. Nutrition. 1989;5(5):303-11; discussion 12-3.

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15. Saura D, Dulgheru R, Caballero L, Bernard A, Kou S, Gonjilashvili N, et al. Two-dimensional transthoracic echocardiographic normal reference ranges for proximal aorta dimensions: results from the EACVI NORRE study. Eur Heart J Cardiovasc Imaging. 2017;18(2):167-79.

16. Evangelista A, Flachskampf FA, Erbel R, Antonini-Canterin F, Vlachopoulos C, Rocchi G, et al. Echocardiography in aortic diseases: EAE recommendations for clinical practice. Eur J Echocardiogr. 2010;11(8):645-58.

17. Reinhardt A, Yevsa T, Worbs T, Lienenklaus S, Sandrock I, Oberdorfer L, et al. Interleukin-23-Dependent gamma/delta T Cells Produce Interleukin-17 and Accumulate in the Enthesis, Aortic Valve, and Ciliary Body in Mice. Arthritis Rheumatol. 2016;68(10):2476-86.

18. DeLay ML, Turner MJ, Klenk EI, Smith JA, Sowders DP, Colbert RA. HLA-B27 misfolding and the unfolded protein response augment interleukin-23 production and are associated with Th17 activation in transgenic rats. Arthritis Rheum. 2009;60(9):2633-43.

19. Colbert RA, Navid F, Gill T. The role of HLA-B*27 in spondyloarthritis. Best Pract Res Clin Rheumatol. 2017;31(6):797-815.

20. Sherlock JP, Joyce-Shaikh B, Turner SP, Chao CC, Sathe M, Grein J, et al. IL-23 induces spondyloarthropathy by acting on ROR-gammat+ CD3+CD4-CD8-entheseal resident T cells. Nat Med. 2012;18(7):1069-76.

21. Benjamin M, McGonagle D. The enthesis organ concept and its relevance to the spondyloarthropathies. Adv Exp Med Biol. 2009;649:57-70.

22. Bridgewood C, Sharif K, Sherlock J, Watad A, McGonagle D. Interleukin-23 pathway at the enthesis: The emerging story of enthesitis in spondyloarthropathy. Immunol Rev. 2020;294(1):27-47.

23. Gravallese EM, Schett G. Effects of the IL-23-IL-17 pathway on bone in spondyloarthritis. Nat Rev Rheumatol. 2018;14(11):631-40.

24. Jimenez-Balderas FJ, Garcia-Rubi D, Perez-Hinojosa S, Arellano J, Yanez P, Sanchez ML, et al. Two-dimensional echo Doppler findings in juvenile and adult onset ankylosing spondylitis with long-term disease. Angiology. 2001;52(8):543-8.

25. Bergfeldt L, Moller E. Pacemaker treated women with heart block have no increase in the frequency of HLA-B27 and associated rheumatic disorders in contrast to men--a sex linked difference in disease susceptibility. J Rheumatol. 1986;13(5):941-3.

Part III

Beyond the heart

Chapter 8

Microvascular changes of the retina in Ankylosing Spondylitis, and the association with cardiovascular disease – the Eye for a Heart study.

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Abstract

Objective

Ankylosing spondylitis (AS) is associated with an increased risk of cardiovascular disease (CVD). Microvasculature changes can precede overt CVD, but have been studied poorly in AS. The retinal vasculature is easily accessible and changes are associated with CVD (e.g. arteriolar narrowing, venular widening, loss of tortuosity). This proof of concept study compared the retinal microvasculature of AS patients with healthy controls, and the influence of gender.

Methods

Cross-sectional case-control study comparing AS patients with healthy controls. Main inclusion criteria were: age 5075 years, no diabetes mellitus and, for AS, fulfillment of the modified New York criteria. All subjects underwent fundus photography, analyzed with Singapore I Vessel Assessment software, and Optical Coherence Tomography Angiography (OCTA). Subjects were compared with generalized estimating equations (GEE). Multivariable analyses were adjusted for demographics and cardiovascular risk, and stratified for gender.

Results

Fifty-nine AS patients and 105 controls were included (50% women). Controls were significantly older than patients (68 versus 60, p<0.01), but did not differ in cardiovascular profile. Patients had a lower retinal arteriolar tortuosity (b--0.1, 95%CI [-0.2; -0.01], p = 0.02), and higher vessel density (b 0.5, 95% CI [0.1; 0.9], p = 0.02). In addition, male AS patients showed a lower arteriovenular ratio compared to male controls (b -0.03, p = 0.04, 95%CI [-0.05; -0.001]). There were no differences found between women with and without AS.

Conclusion

This study detected several retinal microvascular changes, in AS patients compared to controls, which have been associated with CVD. Retinal imaging might be an interesting tool for future CVD screening.

Introduction

Patients with ankylosing spondylitis (AS) have an 1.5 times increased risk of cardiovascular comorbidity and mortality.(1-3) Current research suggests that chronic systemic inflammation contributes to the development of cardiovascular risk factors, such as hypertension and dyslipidaemia, and ischemic heart disease.(1, 4-6) Changes in the microvasculature can precede clinically overt cardiovascular disease (CVD), but have been studied poorly in AS. The retinal vasculature is easily accessible and may provide an unique opportunity to timely recognize microvascular changes in AS patients.

Microvascular abnormalities, such as endothelial dysfunction and vascular remodeling, can precede macrovascular CVD and systemic endothelial dysfunction can reveal CVD. (7, 8) In addition, microvascular disease itself is increasingly recognized as an important contributor to myocardial ischaemia.(9, 10) Mounting evidence has pointed out the importance of microvascular abnormalities in relation to CVD in women, aside from macrovascular disease.(11, 12) Interestingly, this pathophysiology was also suggested for patients with rheumatic diseases.(4, 9)

In AS, several studies have demonstrated increased signs of macrovascular abnormalities (atherosclerosis) but the literature on microvascular changes is limited.(13) The few studies available so far, have shown an impairment of the microcirculation in structure and function.(13-15) These studies mostly use experimental methodology, such as capillary microscopy and laser Doppler fluxmetry, which are influenced by blood pressure and temperature.(14, 15) In contrast, the retinal blood flow is mostly auto-regulated and is easily accessible for non-invasive visualization, which is part of standard care.(16, 17)

Retinal vascular parameters, measured through fundus photography and ocular coherence tomography angiography (OCT-A), could provide interesting biomarkers of (early) CVD in AS. Several large population studies have described associations between retinal vascular changes and CVD. In particular, changes of vascular diameter (narrower arterioles and wider venules), a lower tortuosity of the arterioles, a lower fractal dimension and a lower vessel density were reported in this context.(16, 18-22) Some studies describe the abovementioned diameter changes to be especially associated with CVD in women, independent of other risk factors.(11, 16, 23) In the few studies in rheumatic diseases (not AS), similar vascular diameter changes were found, with widening of the venules being particularly associated with systemic inflammation.(24-

28) The vascular tortuosity, -fractal dimension and vessel density have not yet been studied in patients with rheumatic diseases.

In AS, many patients visit the ophthalmologist multiple times in their lives, due to Acute Anterior Uveitis attacks (this does not involve the posterior part of the eye, which contains the retinal vasculature). Consequently, using ophthalmic evaluation, such as retinal imaging, for early recognition of CVD might be a good opportunity. However, currently, there are no reports available on the retinal vasculature in AS specifically. The primary aim of this study was to investigate the differences between the retinal vessels of AS patients compared with healthy controls, and whether this differs for men and women. Secondary, it evaluates the association of the retinal vasculature with disease activity and other cardiovascular risk factors in AS patients.

Materials and methods

Design and study population
This cross sectional, case-control study is a proof of concept study which applied two retinal imaging modalities: fundus photography (vascular morphology) and optical coherence tomography angiography (OCT-A; retinal vessel density). Both AS patients and healthy control subjects were included, with an equal male-to-female ratio, and aged between 50-75 years, to increase the chance of detecting CVD associated vascular changes.

AS patients were consecutively recruited from the Rheumatology outpatient clinics of the Amsterdam Rheumatology and immunology Centre (ARC) locations Reade and Amsterdam UMC-VUmc, the Netherlands. Patients had to fulfil the 1984 modified New York criteria, and auto-immune disorders other than AS-related (e.g. psoriasis, inflammatory bowel disease) were excluded.(29)

Healthy control subjects were selected from the two year follow up visit of the Dutch EMIF-AD PreClinAD cohort of the Amsterdam UMC-VUmc, that contains cognitively healthy, monozygotic twins of ≥60 years, from the "Netherlands Twin Registry".(30) Control group data were collected previously.(30) Controls were eligible if they did not have a history of any rheumatic disease (including inflammatory bowel disease or psoriasis) and had undergone at least one ophthalmologic examination (fundus photography or OCT-A).

Exclusion criteria for all subjects were conditions interfering with ocular evaluation (diabetes mellitus, current anterior uveitis, glaucoma, significant cataract or eye surgery ⩽6 months ago) and cerebrovascular events resulting in permanent disabilities (pre-existing exclusion criterion of the control group). Current use of non-steroidal anti-inflammatory drugs (NSAIDs) and biologicals was allowed, but corticosteroids (systemic/topical ocular corticosteroids, or injections in the previous three months) were not permitted.

All subjects underwent fundus photography and OCT-A, preferably of both eyes. Study procedures were performed consecutively on the same day, at the Amsterdam University Medical Centre (UMC) VUmc. The protocol (NL66784.048.18) was approved by the medical ethics committee of the Slotervaart hospital & Reade, Amsterdam, the Netherlands. All patients gave written informed consent according to the Helsinki Declaration.

Study parameters

Retinal vasculature assessment
Imaging was performed after application of tropicamide 0.5% eye drops for pupil dilation.

Retinal vessel morphology
Fundus photos (508 field of view, centred on the optic nerve head; Topcon TRC 50DX type IA) were analysed with Singapore I Vessel Assessment (SIVA) software (version 3.0; National University of Singapore, Singapore). SIVA automatically identifies retinal arterioles and venules, in the zone 0.5-2 disc diameters around the optic nerve head (Figure 1). An experienced grader examined the traced vessels and made manual corrections if necessary (same grader for all subjects; intra-observer intra-class correlation, absolute agreement, of >0.80 (31)). Ungradable images were excluded. SIVA analyses resulted in: vascular diameter (central retinal arterioles, venules; and arteriovenous ratio), vascular curvature tortuosity (of the arterioles and venules) and fractal dimension. The latter is a measure of the branching complexity of the retinal vessels. SIVA skeletonizes the retinal vessels and uses a box-counting method to calculate the fractal dimension.

Retinal vessel density
OCT-A (Zeiss Meditec, Inc, Germany) registers the retinal microvascular network through movement detection of blood cells, enabling calculation of the vessel density

(vessel area versus total area). Macula images (6x6 mm area around the fovea) were analysed automatically with accompanying software (Cirrus 5000 Angioplex, version 11), applying an ETDRS grid (three rings of 1 mm, 3 mm and 6 mm centred around the fovea). This divides the macula in a central foveal region, an inner and outer region, to calculate two parameters: macular inner- and outer region vessel density (mm/mm^2). The image quality was evaluated based on the software reported quality score (0-10; ≥8=potentially eligible) and visual inspection. Images of insufficient quality, and ocular diseases interfering with OCT-A quality or vessel density (e.g. severe cataract/ametropia, glaucoma, epiretinal membrane) were excluded.

Cardiovascular history

Cardiovascular risk factors were recorded: Body Mass Index (BMI), current smoking, and history of dyslipidemia and hypertension. In addition, the history of previous CVD (myocardial infarction, coronary disease, peripheral artery disease, transient ischemic attack) was recorded.

Other study parameters

During the study visit, data were collected on demographics (gender, age), hip- and waist circumference, blood pressure, medication (daily use of NSAIDs, nonsteroidal anti-inflammatory drugs; DMARDs, conventional disease modifying antirheumatic drugs; biologicals) and lipid profile. The latter was collected for AS patients within 12 months, and for healthy controls within 24 months prior to the study visit.

In addition, for AS patients, data were collected on disease duration, HLA-B27, extra-articular manifestations, C-reactive protein (during or within 3 months prior/after study visit) and disease activity (Bath AS Disease Activity Index (BASDAI), AS Disease Activity Score (ASDAS). High disease activity was defined as an ASDAS-score of ≥2.1 or, if unavailable, a BASDAI of ≥4.

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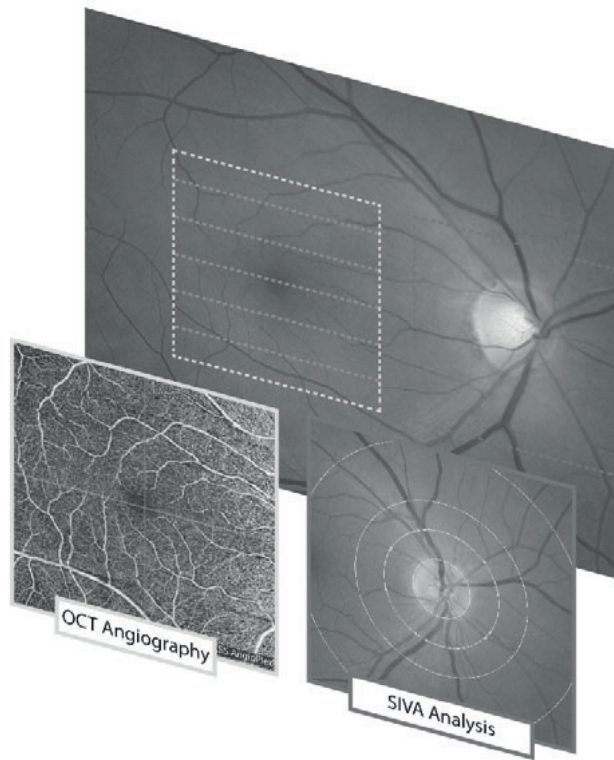
Figure 1. Overview of the imaging modalities for the evaluation of the retinal vasculature*. Retinal vascular parameters were derived from fundus photography analysed with SIVA software (Singapore I Vessel analysis, resulting in vascular morphology parameters) and Optical Coherence Tomography Angiography (OCT-A; resulting in capillary density parameters). *Image adapted, with permission, from Haan et al. (32).
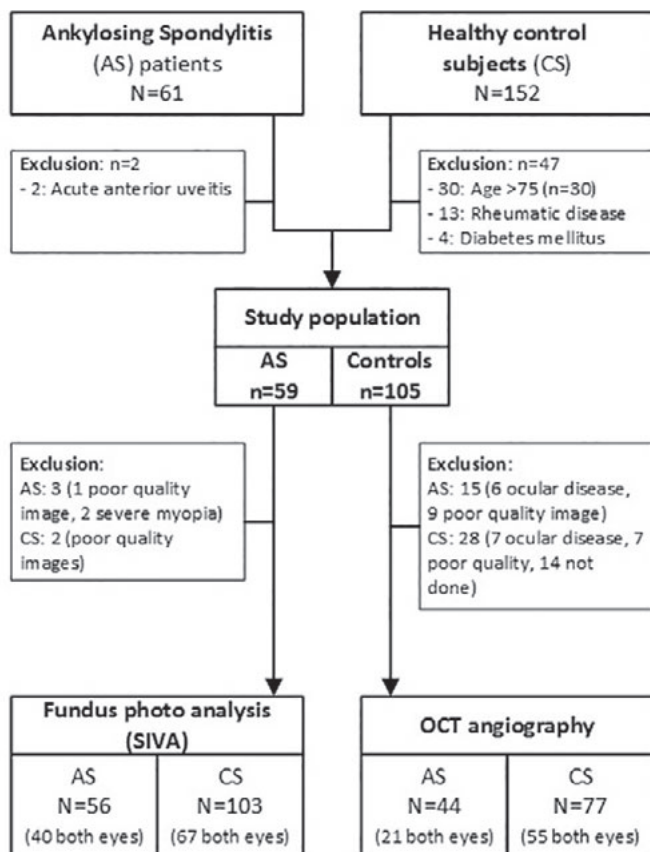
Figure 2. Flowchart study population (AS patients and healthy controls). As, Ankylosing Spondylitis; CS, healthy control subjects; OCT, Optical Coherence Tomography; SIVA, Singapore I Vessel Assessment software.

Statistical analyses

Data are presented as mean (standard deviation, SD), number (with percentage) or percentage only. Non-normally distributed variables were presented as median (interquartile range, IQR) and transformed with the natural logarithm (Ln) for further analyses. For all retinal parameters, the mean of both eyes was used. If only one eye was available (due to unavailability, failed imaging or ocular disease), only data of the available eye was used.

Differences between AS patients and healthy controls were tested with Generalized Estimating Equations (GEE) analyses, correcting for genetic relatedness within twin-pairs of the control group. AS patients and controls were compared in univariable

and multivariable analyses, with stepwise addition of cardiovascular risk factors: demographics and lifestyle (model 1: age, gender, BMI and current smoking status), and factors that could also be part of the pathophysiological pathway between AS and CVD (model 2: model 1 plus hypertension and dyslipidaemia). In addition, OCT-A data were always corrected for software-reported scan quality, as scan quality can significantly influence the vessel density measurement. Next, the influence of gender on the differences between AS and controls in retinal parameters was evaluated by including a cross-product interaction term (gender*patient) as independent variable in the final multiple regression model (model 2). For parameters with an interaction term of p < 0.10, the gender-specific regression coefficients were reported as well. Last, within the AS population, the association between retinal parameters and disease parameters (ASDAS, high disease activity, biological use) or cardiovascular risk (hypertension, dyslipidemia, previous cardiovascular disease) was evaluated with linear or logistic regression, corrected for age and gender.

RESULTS

Study population
Sixty-one AS patients were recruited, of whom two were excluded because of active anterior uveitis (Figure 2). The control population consisted of 152 healthy subjects, of whom 47 did not meet the inclusion criteria, resulting in 105 eligible subjects.

Demographic characteristics are depicted in Tables 1 and 2. The control group was significantly older than AS patients (68 (SD4) years, versus 60 (SD6) years, p<0.001, respectively). However, there were no significant differences in the presence of cardiovascular risk factors or previous CVD (Table 2).

Table 1. Disease characteristics Ankylosing Spondylitis patients (n=59)

Women, n (%)	30	(51)
Age in years, mean (SD)	60	(6)
AS disease duration since diagnosis, in years, mean (SD)	24	(11)
HLA-B27 positive, n (%)	43	(78)
Extra-articular manifestations, n (%)		
Anterior uveitis	29	(49)
Inflammatory Bowel disease	3	(5)
Psoriasis	6	(10)

Table 1. Continued.

Current AS medication, n (%)	
Biologicals	29 (49)
DMARDs	6 (10)
NSAIDs	24 (41)
Disease activity parameters	
CRP in mg/L, median (IQR)	3 (2-4)
ESR in mm/hr, median (IQR)	11 (2-15)
ASDAS-CRP/BSE, mean (SD)	2.1 (0.9)
BASDAI, mean (SD)	4 (2)
High disease activity (ASDAS≥2.1)*, n (%)	27 (46)
BASFI score, mean (SD)	4 (2)

Values are depicted as number of patients (%), mean (standard deviation) or median (Q1-Q3). AS, Ankylosing Spondylitis; ASDAS, AS disease activity score; BASDAI, Bath AS disease activity index; BASFI, Bath AS functional index; CRP, C-reactive protein; DMARDs, disease modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; NSAIDs, nonsteroidal anti-inflammatory drugs. Biologicals: mostly TNF inhibitors (n = 27; secukinumab n = 2). *If ASDAS was unavailable, a BASDAI _4 was defined as high disease activity.

In AS patients, the average disease duration was 36 (SD 12) years, the mean ASDAS-CRP/ESR-score 2.1 (SD 0.9), 41% used NSAIDs, 10% a DMARD and 49% received biological treatment, mainly TNF inhibitors (Table 1). No subject used corticosteroids, as this was an exclusion criterion. Men and women with AS did not differ significantly in disease activity, medication use or disease duration (data not shown). Among the healthy controls, only 6% used a NSAID, and no one used a conventional DMARD or biological agent.

Table 2. Demographics and cardiovascular profile AS and healthy control subjects.

	AS patients	Healthy controls [a]	p-value
	(n=59)	*(n=105)*	
Women, n (%)	30 (51)	52 (50)	0.87
Age in years, mean (SD)	60 (6)	68 (4)	**<0.001**
Smoking currently, n (%)	11 (19)	8 (8)	0.06
Hypertension and/or dyslipidemia, n (%)	26 (44)	44 (42)	0.98
Hypertension	23 (39)	39 (37)	0.91
Dyslipidemia	9 (15)	18 (17)	0.78
History of cardiovascular disease, n (%)	9 (15)	15 (14)	0.89
Body mass index, mean (SD)	26 (4)	26 (3)	0.51
Waist-to-hip-ratio, mean (SD)	0.9 (0.1)	0.9 (0.1)	0.46
Systolic blood pressure, mean (SD)	143 (17)	143 (15)	0.98
Diastolic blood pressure, mean (SD)	83 (9)	81 (8)	0.30
Cholesterol-HDL ratio, mean (SD)	4 (1)	4 (1)	0.58

Values were depicted as mean (standard deviation) or number of patients (percentage of total). a. 43 twin pairs and 19 singletons. AS, Ankylosing Spondylitis.

Comparison of the retinal vasculature of AS patients with healthy controls

Retinal vessel morphology (fundus photography)

Fundus photos of at least one eye were available in 56 (95%) AS patients and 103 (98%) healthy controls (Figure 2). On a group level, in crude analyses, only fractal dimension differed between AS and healthy controls (higher in AS: β 0.01, 95% CI [0.0; 0.03], p = 0.04, Table 3), but this effect disappeared after correction for age (Table 4). Interestingly, crude analyses only showed a non-significant, lower arteriolar tortuosity in AS patients, but this association became stronger after correction for age and gender, and even more after correction for cardiovascular risk factors (Table 4; (Ln transformation of) arteriolar tortuosity: β -0.1, 95%CI [-0.2; -0.01], p = 0.02, Table 4; 11% lower). A positive history of anterior uveitis was not a confounder in these analyses.

The comparison of gender specific differences between AS patients and healthy controls, revealed that gender was only a significant effect modifier for the association between AS and vascular diameter (retinal arteriovenous ratio, AVR; p<0.01; Table 4). Stratified analyses showed that men with AS had a significantly lower AVR (β-0.03, 95%CI [-0.05; -0.001], p = 0.04) than men without AS, whereas this parameter did not differ significantly between women with and without AS.

Table 3. Retinal vascular parameters of the AS patients and Healthy controls.

		AS Patients (n=59)	Healthy Controls[b] (n=105)	*p-value*
Vascular morphology (Fundus photography)				
Number of patients		*56*	*103*	
Diameter	Arteriolar (μm)	125 (11)	124 (10)	0.37
	Venular (μm)	197 (20)	191 (14)	0.08
	Arteriovenous ratio (AVR)	0.64 (0.06)	0.65 (0.04)	0.43
Tortuosity	Arteriolar, x10^{-5} [a]	-9.8 (0.2)	-9.7 (0.2)	0.19
	Venular, x10^{-5} [a]	-9.7 (0.2)	-9.7 (0.2)	0.61
Complexity	Fractal dimension	1.19 (0.04)	1.18 (0.03)	**0.04**
Vessel density (OCT-angiography)				
Number of patients		*44*	*77*	
Vessel density	Inner ring macula, mm/mm^2	18.4 (0.7)	17.6 (1.1)	**<0.001**
	Outer ring macula, mm/mm^2	18.4 (0.6)	17.8 (1.1)	**<0.001**

Values are depicted as mean (standard deviation, SD). a. analyses were performed on log-transformed variable, because of a nonparametric distribution. b. 43 twin pairs and 19 singletons. AS, Ankylosing Spondylitis.

Retinal vessel density (OCT-Angiography)
OCT-A images were available for 75% of the AS patients (n = 44; both eyes in n = 21) and 73% of the healthy controls (n = 77; both eyes in n = 55; Figure 2). In this subgroup, AS patients were also significantly younger than healthy controls (59 (SD 6) versus 68 years (SD 4) respectively, p<0.01). When comparing subjects with and without OCT-A: AS patients with OCT-A were significantly younger (58 (SD5) versus 66 (SD5) years, p<0.01), used more NSAIDs (66% versus 33%, p = 0.03) and had less often hypertension (30% versus 67%, p = 0.01), than AS patients without OCT-A. Healthy controls in whom OCT-A was performed did not differ significantly from controls without.

On a group level, univariable analyses suggested that AS patients had a significantly higher retinal vessel density in both the inner and outer region of the macula (Table 3), compared to healthy controls. After correction for demographics, lifestyle-factors, hypertension and dyslipidemia, this difference persisted for the inner macula region (higher in AS: β 0.5, 95%CI [0.1; 0.9], p = 0.02, Table 4).

Gender was only a significant effect modifier for the association between AS and capillary density of the outer macula (p<0. 01; Table 4). Gender stratified analysis showed that male AS patients had a significantly higher vessel density in the outer macula (β 0.6, 95%CI [0.1; 1.0], p = 0.03), compared to men without AS. Again, this parameter did not differ between women with and without AS.

Disease activity, cardiovascular history and retinal parameters in AS patients.

Disease activity and retinal characteristics
The mean ASDAS was 2.1 (SD 0.9), with 27 AS patients (49%) reporting a high disease activity (Table 1). Biologicals were used less often by patients showing a high disease compared to patients with low disease activity, respectively 44% versus 50% (not significant).

AS patients with high disease activity showed a significantly higher venular diameter (β 10, 95%CI [0; 21], p = 0.05; corrected for age and gender), compared to patients with low disease activity. Interestingly, in contrast, in AS patients who used biologicals, a significantly higher arteriole diameter was found compared to patients without this treatment, regardless of disease activity, age and gender (β 8, 95%CI [2; 14], p<0.01).

Retinal parameters and cardiovascular history in AS patients

Cardiovascular risk factors were often present in AS patients: 39% had hypertension and 15% dyslipidemia. In addition, 15% reported a history of CVD. Hypertension and CVD were both significantly associated with a higher venule diameter in AS patients, also after correction for age and gender: hypertension, β 11 (95%CI [4; 25], p<0.01) and CVD: β 16 (95%CI [1; 31], p = 0.03). Other retinal parameters did not show any associations with CVD, hypertension or dyslipidaemia. In contrast, in controls, CVD were associated with a higher arteriolar diameter and AVR (data not shown).

Table 4. Retinal vascular parameters, differences between AS versus Control subjects.

Retinal vascular parameters		Crude		Model 1 Adjusted for: Demographics, lifestyle (age, gender, BMI, smoking)[A]		Model 2 Adjusted for: Demographics, lifestyle + hypertension, dyslipidemia [A]		Effect modification by sex[B]
		β (95%CI)	p	β (95%CI)	p	β (95%CI)	p	p
Diameter	Arteriolar	1.6 (-2.0, 5.2)	0.37	0.15 (-4.5, 4.8)	0.94	-0.2 (-4.8, 4.4)	0.92	0.60
	Venular	5.4 (-0.66, 11.5)	**0.08**	2.9 (-5.0, 10.8)	0.47	2.5 (-5.4, 10.4)	0.53	0.17
	Arteriovenular ratio	-0.01 (-0.03, 0.01)	0.43	-0.01 (-0.03, 0.01)	0.56	-0.01 (-0.03, 0.02)	0.65	**<0.01**
Tortuosity	**Arteriolar** [a]	-0.05 (-0.12, 0.03)	0.19	**-0.08 (-0.18, 0.00)**	**0.05**	**-0.1 (-0.2, -0.01)**	**0.02**	0.14
	Venular [a]	0.02 (-0.05, 0.08)	0.61	-0.01 (-0.09, 0.08)	0.88	-0.02 (-0.01, 0.1)	0.67	0.10
Complexity	**Fractal dimension**	0.01 (0.00, 0.03)	**0.04**	0.00 (-0.02, 0.02)	0.78	0.0 (-0.02, 0.02)	0.88	0.16
Vessel Density	**Inner ring**	**0.8 (0.5, 1.1)**	**<0.001**	**0.5 (0.03, 0.9)**	**0.04**	**0.5 (0.1, 0.9)**	**0.02**	0.18
	Outer ring	**0.7 (0.4, 1.0)**	**<0.001**	0.2 (-0.3, 0.6)	0.49	0.2 (-0.2, 0.6)	0.42	**<0.01**

Legend: GEE analyses, with retinal parameters as the dependents. BMI, body mass index; CI, confidence interval; GEE, generalized estimating equation. a. analyses performed on log-transformed variable. A. Vessel density (OCT-A) analyses were corrected additionally for software-reported scan quality. B. Effect modification by sex was tested for model 2 and further described in the paper. β, regression coefficient; p, p-value.

Discussion

This study showed several retinal microvascular changes in AS patients, compared to healthy controls, of which some have been associated with cardiovascular risk. The most prominent changes in AS patients consisted of straighter arterioles and a higher vessel density. In addition, male AS patients showed a decreased arteriovenular ratio compared to male controls, whereas no specific changes were found in women with AS. In AS, high disease activity and previous CVD were associated with wider venules, whereas treatment with biologicals was related to wider arterioles.

This proof of concept study is the first to report on the microvasculature of the retina specifically in AS patients. The results are mostly in line with the expectations based on other populations. Large population studies demonstrated CVD to be associated with arterial narrowing, venular widening (or a decreased arteriovenular ratio), reduced arteriolar tortuosity and reduced complexity.(18, 20, 22, 32-34) The few studies in other rheumatic diseases, primarily including rheumatoid arthritis, psoriatic arthritis and systemic lupus erythematosus, found the same vascular diameter changes as reported for CVD (arteriolar narrowing, venular widening) in patients, compared to controls. (24-28) Only one study included a small number of AS patients (n = 26) together with other rheumatic diseases, and reported no differences with controls. However, the AS patients included in that study were younger compared to our study, and the majority of controls suffered from hypertension which is known to influence the retinal vasculature. (35) None of the studies in rheumatic patients evaluated the tortuosity or vessel density.

The current results are mostly in line with the expectations based on the abovementioned studies. Most prominently, the retinal arteriolar tortuosity was significantly decreased in AS patients, which is associated with an increased risk of CVD based on large population studies.(22, 32, 34) This decreased tortuosity appears to be due to AS itself as the association became stronger after correction for cardiovascular risk factors. In addition, there was a trend of an increased venular diameter and decreased arteriolar diameter and, consequently, decreased arteriovenular ratio (AVR), in AS patients. Although these diameter differences were not significant on a group level (only male AS patients had a significantly decreased AVR compared to controls), this combination of changes has been repeatedly reported to be associated with CVD.(20, 22) Also in the current study, within the AS population, venular widening was associated with CVD. In

contrast with other population studies, and the AS patients in this study, the controls in our study with CVD had wider arterioles.(20, 22, 23)

OCT-A imaging, which had not yet been described for rheumatic diseases, revealed an increased retinal vessel density in AS patients. In addition, in male AS patients, this was found for a more extensive area. This is a novel finding. Until now, only one study studied the vessel density, in patients with coronary heart disease, and found a decreased density, compared to controls.(21) However, this study focused on macrovascular CVD, whereas an early disease state with primarily microvascular damage might have different hemodynamic states. An alternative hypothesis is that the increased vessel density found in the AS patients, is related with systemic inflammation, causing an increased capillary flow (in AS patients, a higher CRP was associated with a higher vessel density, although not significant; β 0.01, 95%CI [-0.1; 0.13], p = 0.83). Nevertheless, the association between vessel density and microvasculopathy needs to be further explored.

Microvascular changes in women were of particular interest, as increasing evidence supports the importance of microvasculopathy, including retinal vascular diameter changes, in the risk of CVD.(10, 11, 23, 36) It was expected that, in particular in AS women, microvascular changes would be observed. However, in this study, differences between AS and controls were found only on a group level, and additionally in men, when stratified for gender. The fact that microvascular changes were not specifically detected in women, cannot be explained by more systemic inflammation in men, because disease activity parameters and treatment (ASDAS, biologicals, NSAIDs) did not differ between AS men and women.

A higher AS disease activity was associated with wider retinal venules, in accordance with studies in other rheumatic diseases.(14, 25, 28) Although the pathophysiological process is not fully understood, wider venules are associated with metabolic disturbances (diabetes mellitus, obesity, dyslipidemia), inflammation, smoking and CVD, and is therefore considered unfavourable.(16) In contrast, biologicals were associated with a more favourable arteriolar morphology (wider diameter, instead of narrowing, which is associated with CVD), and this was independent of disease activity. The main target of the biological, tumour necrosis factor alpha, hampers nitro oxide release. Studies in AS patients initiating a TNFi have shown to improve the vascular status, such as the endothelial function, intima media thickness and pulse wave velocity.(14, 15, 37) The

current findings are in accordance with the theory that TNFi have a beneficial effect on the vessel wall.

As this was a proof of concept study, there were a few limitations. Firstly, the healthy control group was significantly older than the AS patients. Therefore, analyses were adjusted for age, limiting this influence, but also for other cardiovascular risk factors that are considered to influence the microvasculature. Secondly, 43 of the control subjects were genetically related to another subject (twin). Alternatively, only one of the twin pairs could have been selected, but this would have resulted in a much smaller control group. Therefore, to increase statistical power, all available subjects were included, with adjustment for genetic relatedness. Thirdly, it was not possible to link the retinal vasculature directly to the current cardiac vessels conditions, as cardiac imaging data were not available. However, as this was a secondary aim, retinal parameters were compared with the presence of CVD, a clinically important endpoint. Fourthly, it is unclear how NSAIDs (and biologicals) could have had a confounding influence on the differences between AS and controls, but the use of NSAIDs is very common in AS, and an AS group without NSAIDs would not be representative. In addition, the potential influence of exercise should be considered in future studies. Fifthly, 49% of the AS patients had a history of anterior uveitis (AAU), which is comparable with the prevalence reported for patients with a long disease duration (43%).(38) Unfortunately, whether a previous history of AAU influences these retinal parameters is unknown. However, AAU in AS is typically a short-term inflammation of the anterior eye segment, that generally does not involve the posterior segment and is, therefore, unlikely to affect the retinal vessels. In addition, patients with active AAU at the time of the study were excluded and a positive history of AAU was not a confounder in the analyses. Lastly, because this is a proof of concept study, the study population size was limited, rendering it potentially underpowered to detect more microvascular changes. In this perspective, no additional correction for multiple testing was applied. However, this is the first study focusing on AS and, furthermore, the first that also evaluated the vascular tortuosity and density, which had not yet been described before for patients with rheumatic diseases in general.

In conclusion, this study was the first to report on the retinal microvasculature in a large group of AS patients, in comparison with healthy controls. It supports the hypothesis that AS causes microvascular changes, which were found more extensively in men. Importantly, the results might indicate a retinal vascular profile in AS patients that has also been demonstrated to be associated with CVD, whereas the value of a novel finding

(increased vessel density) needs to be explored further. By all means, this proof of concept study indicates that retinal imaging techniques might be useful for the detection of microvascular changes in AS patients. Importantly, these techniques are non-invasive and easily accessible in daily clinical practice, in contrast with other microvascular assessments. If longitudinal follow up further demonstrates its opportunities and predictive value, these techniques might provide a great future opportunity for the early recognition of CVD in AS.

References

1. Liew JW, Ramiro S, Gensler LS. Cardiovascular morbidity and mortality in ankylosing spondylitis and psoriatic arthritis. Best Pract Res Clin Rheumatol. 2018;32(3):369-89.

2. Eriksson JK, Jacobsson L, Bengtsson K, Askling J. Is ankylosing spondylitis a risk factor for cardiovascular disease, and how do these risks compare with those in rheumatoid arthritis? Ann Rheum Dis. 2017;76(2):364-70.

3. Haroon NN, Paterson JM, Li P, Inman RD, Haroon N. Patients With Ankylosing Spondylitis Have Increased Cardiovascular and Cerebrovascular Mortality: A Population-Based Study. Ann Intern Med. 2015;163(6):409-16.

4. Faccini A, Kaski JC, Camici PG. Coronary microvascular dysfunction in chronic inflammatory rheumatoid diseases. Eur Heart J. 2016;37(23):1799-806.

5. Chou CH, Lin MC, Peng CL, Wu YC, Sung FC, Kao CH, et al. A nationwide population-based retrospective cohort study: increased risk of acute coronary syndrome in patients with ankylosing spondylitis. Scand J Rheumatol. 2014;43(2):132-6.

6. Nurmohamed MT, van der Horst-Bruinsma I, Maksymowych WP. Cardiovascular and cerebrovascular diseases in ankylosing spondylitis: current insights. Curr Rheumatol Rep. 2012;14(5):415-21.

7. Bonetti PO, Pumper GM, Higano ST, Holmes DR, Jr., Kuvin JT, Lerman A. Noninvasive identification of patients with early coronary atherosclerosis by assessment of digital reactive hyperemia. J Am Coll Cardiol. 2004;44(11):2137-41.

8. Rubinshtein R, Kuvin JT, Soffler M, Lennon RJ, Lavi S, Nelson RE, et al. Assessment of endothelial function by non-invasive peripheral arterial tonometry predicts late cardiovascular adverse events. Eur Heart J. 2010;31(9):1142-8.

9. Bordy R, Totoson P, Prati C, Marie C, Wendling D, Demougeot C. Microvascular endothelial dysfunction in rheumatoid arthritis. Nat Rev Rheumatol. 2018;14(7):404-20.

10. Murthy VL, Naya M, Taqueti VR, Foster CR, Gaber M, Hainer J, et al. Effects of sex on coronary microvascular dysfunction and cardiac outcomes. Circulation. 2014;129(24):2518-27.

11. Jones E, Eteiba W, Merz NB. Cardiac syndrome X and microvascular coronary dysfunction. Trends Cardiovasc Med. 2012;22(6):161-8.

12. Pepine CJ, Anderson RD, Sharaf BL, Reis SE, Smith KM, Handberg EM, et al. Coronary microvascular reactivity to adenosine predicts adverse outcome in women evaluated for suspected ischemia results from the National Heart, Lung and Blood Institute WISE (Women's Ischemia Syndrome Evaluation) study. J Am Coll Cardiol. 2010;55(25):2825-32.

13. Peters MJ, van Eijk IC, Smulders YM, Serne E, Dijkmans BA, van der Horst-Bruinsma IE, et al. Signs of accelerated preclinical atherosclerosis in patients with ankylosing spondylitis. J Rheumatol. 2010;37(1):161-6.

8

14. Batko B, Maga P, Urbanski K, Ryszawa-Mrozek N, Schramm-Luc A, Koziej M, et al. Microvascular dysfunction in ankylosing spondylitis is associated with disease activity and is improved by anti-TNF treatment. Sci Rep. 2018;8(1):13205.

15. van Eijk IC, Peters MJ, Serne EH, van der Horst-Bruinsma IE, Dijkmans BA, Smulders YM, et al. Microvascular function is impaired in ankylosing spondylitis and improves after tumour necrosis factor alpha blockade. Ann Rheum Dis. 2009;68(3):362-6.

16. Sun C, Wang JJ, Mackey DA, Wong TY. Retinal vascular caliber: systemic, environmental, and genetic associations. Surv Ophthalmol. 2009;54(1):74-95.

17. Flammer J, Mozaffarieh M. Autoregulation, a balancing act between supply and demand. Can J Ophthalmol. 2008;43(3):317-21.

18. Ikram MK, de Jong FJ, Bos MJ, Vingerling JR, Hofman A, Koudstaal PJ, et al. Retinal vessel diameters and risk of stroke: the Rotterdam Study. Neurology. 2006;66(9):1339-43.

19. Ikram MK, Witteman JC, Vingerling JR, Breteler MM, Hofman A, de Jong PT. Retinal vessel diameters and risk of hypertension: the Rotterdam Study. Hypertension. 2006;47(2):189-94.

20. Wong TY, Kamineni A, Klein R, Sharrett AR, Klein BE, Siscovick DS, et al. Quantitative retinal venular caliber and risk of cardiovascular disease in older persons: the cardiovascular health study. Arch Intern Med. 2006;166(21):2388-94.

21. Wang J, Jiang J, Zhang Y, Qian YW, Zhang JF, Wang ZL. Retinal and choroidal vascular changes in coronary heart disease: an optical coherence tomography angiography study. Biomed Opt Express. 2019;10(4):1532-44.

22. Wang SB, Mitchell P, Liew G, Wong TY, Phan K, Thiagalingam A, et al. A spectrum of retinal vasculature measures and coronary artery disease. Atherosclerosis. 2018;268:215-24.

23. Wong TY, Klein R, Sharrett AR, Duncan BB, Couper DJ, Tielsch JM, et al. Retinal arteriolar narrowing and risk of coronary heart disease in men and women. The Atherosclerosis Risk in Communities Study. JAMA. 2002;287(9):1153-9.

24. Aissopou E.K. PAD, Papaioannou T.G., Tektonidou M, Tentolouris N., Theodossiadis P.G., Stehouwer C.D.A., Kitas G.D., Sfikakis P.P. Retinal vascular calibers in contemporary patients with chronic systemic inflammatory diseases: The Greek REtinal Microcirculation (GREM) study. Artery Research, 2017 18: p 1-6.

25. Anyfanti P, Triantafyllou A, Gkaliagkousi E, Koletsos N, Athanasopoulos G, Zabulis X, et al. Retinal vessel morphology in rheumatoid arthritis: Association with systemic inflammation, subclinical atherosclerosis, and cardiovascular risk. Microcirculation. 2017;24(8).

26. Lee JH, Kim SS, Kim GT. Microvascular findings in patients with systemic lupus erythematosus assessed by fundus photography with fluorescein angiography. Clin Exp Rheumatol. 2013;31(6):871-6.

27. Okada M, Wong TY, Kawasaki R, Baharuddin NB, Colville D, Buchanan R, et al. Retinal venular calibre is increased in patients with autoimmune rheumatic disease: a case-control study. Curr Eye Res. 2013;38(6):685-90.

28. Van Doornum S, Strickland G, Kawasaki R, Xie J, Wicks IP, Hodgson LA, et al. Retinal vascular calibre is altered in patients with rheumatoid arthritis: a biomarker of disease activity and cardiovascular risk? Rheumatology (Oxford). 2011;50(5):939-43.

29. Rudwaleit M, van der Heijde D, Landewe R, Listing J, Akkoc N, Brandt J, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis. 2009;68(6):777-83.

30. Konijnenberg E, Carter SF, Ten Kate M, den Braber A, Tomassen J, Amadi C, et al. The EMIF-AD PreclinAD study: study design and baseline cohort overview. Alzheimers Res Ther. 2018;10(1):75.

31. van de Kreeke JA, Nguyen HT, Konijnenberg E, Tomassen J, den Braber A, Ten Kate M, et al. Retinal and Cerebral Microvasculopathy: Relationships and Their Genetic Contributions. Invest Ophthalmol Vis Sci. 2018;59(12):5025-31.

32. Witt N, Wong TY, Hughes AD, Chaturvedi N, Klein BE, Evans R, et al. Abnormalities of retinal microvascular structure and risk of mortality from ischemic heart disease and stroke. Hypertension. 2006;47(5):975-81.

33. Kirin M, Nagy R, MacGillivray TJ, Polasek O, Hayward C, Rudan I, et al. Determinants of retinal microvascular features and their relationships in two European populations. J Hypertens. 2017;35(8):1646-59.

34. Cheung CY, Zheng Y, Hsu W, Lee ML, Lau QP, Mitchell P, et al. Retinal vascular tortuosity, blood pressure, and cardiovascular risk factors. Ophthalmology. 2011;118(5):812-8.

35. Aissopou E.K. PAD, Papaioannou T.G., Tektonidou M, Tentolouris N., Theodossiadis P.G., Stehouwer C.D.A., Kitas G.D., Sfikakis P.P. Retinal vascular calibers in contemporary patients with chronic systemic inflammatory diseases: The Greek REtinal Microcirculation (GREM) study. Artery Research. 2017;18:1-6.

36. Kawamoto KR, Davis MB, Duvernoy CS. Acute Coronary Syndromes: Differences in Men and Women. Curr Atheroscler Rep. 2016;18(12):73.

37. Arida A, Protogerou AD, Kitas GD, Sfikakis PP. Systemic Inflammatory Response and Atherosclerosis: The Paradigm of Chronic Inflammatory Rheumatic Diseases. Int J Mol Sci. 2018;19(7).

38. Zeboulon N, Dougados M, Gossec L. Prevalence and characteristics of uveitis in the spondyloarthropathies: a systematic literature review. Ann Rheum Dis. 2008;67(7):955-9.

The effect of anti-TNF treatment on body composition and insulin resistance in patients with rheumatoid arthritis

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ABSTRACT

Introduction
Given the link between systemic inflammation, body composition and insulin resistance (IR), anti-inflammatory therapy may improve IR and body composition in inflammatory joint diseases. This study assesses the IR and beta cell function in rheumatoid arthritis (RA) patients with active disease compared to osteoarthritis (OA) patients and investigates the effect of anti-TNF treatment on IR, beta cell function and body composition in RA.

Methods
28 Consecutive RA patients starting anti-TNF treatment (adalimumab), and 28 age, and sex-matched patients with OA were followed for 6 months. Exclusion criteria were use of statins, corticosteroids, and cardiovascular or endocrine co-morbidity. Pancreatic beta cell function and IR, using the Homeostasis Model Assessment (HOMA2), and body composition, using Dual-energy X-ray Absorptiometry (DXA) were measured at baseline and 6 months.

Results
At baseline, IR [1.5 (1.1-1.8) vs. 0.7 (0.6-0.9), 100/%S] and beta cell function (133% vs. 102%) were significantly (p<0.05) higher in RA patients with active disease as compared to OA patients. After 6 months of anti-TNF treatment IR [1.5 (1.1-1.8) to 1.4 (1.1-1.7), p=0.17] slightly improved and beta cell function [133% (115-151) to 118 (109–130), p<0.05] significantly improved. Improvement in IR and beta cell function was most pronounced in RA patients with highest decrease in CRP and ESR.

Conclusion
Our observations indicates IR and increased beta cell function are more common in RA patients with active disease. Anti-TNF reduced IR and beta cell function especially in RA patients with highest decrease in systemic inflammation and this effect was not explained by changes in body composition.

Introduction

In healthy persons, normoglycaemia is maintained by a balanced interaction between insulin action (insulin sensitivity (IS) and insulin secretion (pancreatic beta cell function). Insulin resistance (IR) is more prevalent in rheumatoid arthritis (RA) and is associated with endothelial dysfunction and with increased CVD[1-3]. Already in 1949, generalized muscle wasting and hyperglycaemia, both characteristics of IR, were identified in patients with RA[4]. Previous studies demonstrated that RA patients have peripheral IR that is correlated with inflammatory markers and normalizes after reduction of inflammation with glucocorticoid treatment[5-7]. Previous studies in non-diabetic RA patients found pancreatic beta cell function to be impaired[8, 9].

Increasing evidence arises that body composition, particularly body fat distribution and the quantity and characteristics of (visceral) adipose tissue, is an important factor contributing to enhanced CV risk in inflammatory diseases[3]. Cachectic obesity, defined as a loss of body cell mass without weight loss, but with concomitant increased fat mass, is a prominent feature of RA, and associated with increased circulating tumor necrosis factor (TNF) levels[10].

A clear link between obesity and chronic (low grade) inflammation was established when TNF-α, a pro-inflammatory cytokine, was found to be overexpressed in the adipose tissue of obese mice [11]. TNF-α is also overexpressed in adipose and muscle tissues of obese humans[12] and exogenous TNF-α administration leads to IR[13].

Nowadays, TNF antagonists are widely used to treat several inflammatory diseases, including RA. A recent systematic review and meta-analysis suggests that anti-TNF treatment improved IR in RA patients[14]. However, the underlying inflammatory mechanisms affecting IR in relation with body composition have not yet been fully elucidated.

To investigate the role of systemic inflammation and body composition in the development of IR we compared RA patients, starting anti-TNF treatment, with matched osteoarthritis (OA) patients. We hypothesize that decrease in systemic inflammation and change in body composition (secondary to decrease in systemic inflammation) will positively affect IR in RA patients treated with anti-TNF. The objectives of the present investigation were 1) to investigate the body composition and IR in RA to sex and age matched OA patients 2) to investigate correlations between IR, inflammation and body

composition and 3) to study if and to what extent IR and body composition are influenced by anti-TNF treatment.

Methods

Study population and design

For this prospective study 69 consecutive subjects, 36 RA and 33 OA patients were recruited from the outpatient rheumatology clinic at Reade, Center for Rehabilitation and Rheumatology, Amsterdam, the Netherlands. RA patients fulfilled the American College of Rheumatology criteria of 1987 for RA[15]. The RA patients with active disease were biological naive and were included when they were eligible for Anti-TNF therapy according to the Dutch consensus statement on the initiation of Anti-TNF therapy [16]. All patients started with adalimumab 40 mg every two weeks. The OA patients, not treated with anti-TNF, were matched for sex and age to the RA patients and they all had OA of the hands according to the American College of Rheumatology criteria of 1990 for osteoarthritis of the hand[17]. We chose OA patients as controls because they have substantially less systemic inflammation but many similarities to RA patients in terms of life style, physical inactivity, frequent use of non-steroidal anti-inflammatory drugs (NSAIDs) and obesity. Patients, with a medical history of CVD, diabetes mellitus or hypothyroidism and/or used glucose or cholesterol lowering medication, were excluded. Also, patients, who used systemic (oral or intramuscular) corticosteroids within a month before inclusion, were excluded from analyses. All patients were followed for 6 months and measurements were performed at t=0 (before start of Anti-TNF therapy and at t=6 months (after start of therapy). Non-steroidal anti-inflammatory drugs (NSAIDs) were allowed to be discontinued during follow up. When patients altered the use of Anti-TNF or disease modifying anti-inflammatory drugs (DMARDs) or started using corticosteroids, glucose or cholesterol-lowering medication during the follow up period, they were excluded from the follow up analyses. This study was approved by the Ethics committee of the Slotervaart Hospital/Reade (NL19944.048.07) and prior to inclusion written informed consent from all patients was obtained.

Patient characteristics

At baseline and after 6 months of treatment all patients were interviewed to record details about history of co-morbidity, medication use and disease characteristics.

Special attention was paid to history of cardiovascular risk factors like hypertension, hypercholesterolemia, overweight, diabetes mellitus (DM), and smoking.

A physical examination was performed by experienced research nurses to assess blood pressure, heart rate, waist and hip circumference, length, weight, and body mass index (BMI).

Blood pressure and heart rate were measured twice (left and right) in sitting position after 5 minutes of rest. Hypertension was defined as a mean systolic blood pressure (SBP) ⩾ 140 mmHg and/or a mean diastolic blood pressure (DBP) ⩾ 90 mmHg and/or the use of antihypertensive drugs. Hypercholesterolemia was defined as total cholesterol (TC) level of ⩾ 6.5 mmol/L.

Waist circumference was measured at the level of the navel, hip circumference was measured at the level of the trochanter major of the hip bone (widest circumference). The ratio of these two measurements was determined as waist-hip-ratio (WHR).

Height and weight were measured using the same portable weight scale and height meter, without shoes but with clothes on. Overweight was defined as a BMI ⩾ 25 kg/m^2 and obesity as a BMI ⩾ 30 kg/m^2.

RA disease activity was assessed with the disease activity score of 28 joints (DAS28)[18] and the Health Assessment Questionnaire (HAQ)[19], a questionnaire measuring daily functioning in RA patients.

After the physical examination an Oral Glucose Tolerance Test (OGTT) was performed. Patients were asked to drink a solution of 250 ml of water with 75 grams of glucose within 5 minutes. Patients were not allowed to exercise or come out of the chair for the next 2 hours. Two hours (plus minus 15 minutes) after the glucose intake blood samples were drawn to measure the glucose level.

Blood tests

Fasting blood samples were collected to measure erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), cholesterol levels (including apolipoprotein-A and B), and fasting glucose levels. All the above tests were performed the same day that blood was drawn in a single laboratory at Reade in Amsterdam. Furthermore, serum and plasma were stored at −20 degrees Celsius to measure C-peptide and insulin batch-wise after all the samples were collected.

Insulin resistance and beta cell function

The updated Homeostasis Model Assessment (HOMA2) computer model, available from www.OCDEM.ox.ac.uk, was used to estimate insulin resistance (HOMA2-IR), and

pancreatic beta cell function (HOMA2-%B)[20]. This model calculates IR and beta cell function from fasting plasma insulin and glucose concentrations and correlates well with insulin clamp method which is considered the gold standard in the assessment of insulin action in vivo[21]. This latest developed computer model has non-linear solutions as it accounts for variations in hepatic and peripheral glucose resistance and also other organs and tissues involved in glucose regulation. Pancreatic beta cell function is expressed as percentage of a normal reference population, where 100% is normal. However, HOMA2-%B measures first of all beta cell activity, not beta cell health or pathology. Therefore, the outcomes of HOMA2-%B have to be interpreted together with HOMA2-IR. Insulin resistance is expressed as 100/ %insulin sensitivity (100/%S) and a normal IR is 1. The HOMA2-IR is race and age dependent of which cut-off values for abnormal insulin resistance range from 1.6-3.8[22, 23]. For IR simultaneously drawn fasting plasma glucose and insulin values were used. For beta cell function instead of insulin, C-peptide values from the same blood sample were used[24].

Body composition
Next to the WHR and the BMI, specific body composition data, including total, gynoid (hip area) and android (abdominal area) fat percentage, lean body mass (LBM) and visceral adipose tissue (VAT) mass calculations were obtained using Dual-energy X-ray Absorptiometry (DXA) Whole Body Composition. (GE Healthcare Lunar iDXA and enCORE software version 13.6)[25].

Statistical analysis
 The sample size calculation was based on the results of the of HOMA-IR measurements by Dessein et al[26]. Based on a power analysis with alpha 0.05 and power >85% resulted in a sample size of 25 per group.

Results are expressed as mean ± standard deviation (SD) when normally distributed, as median (interquartile range) when not normally distributed or as number and percentage. When variables were not normally distributed, the (natural) logarithms of these variables were calculated and used for analyses. Unpaired sample *t* tests were used to observe differences in baseline variables between RA and OA. For comparisons of paired continuous variables between baseline and follow up with normal distribution paired t-test were used. In case of non-normal distribution we used the Wilcoxon signed-ranks test or log transformation. Pearson or Spearman correlation coefficients were determined to look for correlations between IR, IS, beta cell function, body composition

measurements and inflammatory markers. To assess the effect of change in systemic inflammation on IR and beta cell function patients were stratified in tertiles for ΔCRP, ΔESR and ΔDAS28. Mann-Whitney U tests were used to determine changes of variables after 6 months between groups. Two sided p-values less than 0.05 were considered statistically significant. All analyses were performed by IBM SPSS Statistics version 18.0.

Results

Study population
From the 69 patients, who were initially screened for study inclusion, 13 patients were excluded at baseline, mostly due to the exclusion criteria and again 9 patients were excluded at follow up, because of discontinuation of adalimumab or loss to follow up (figure 1). Baseline patient characteristics are displayed in table 1.

Figure 1. Flowchart of study inclusion
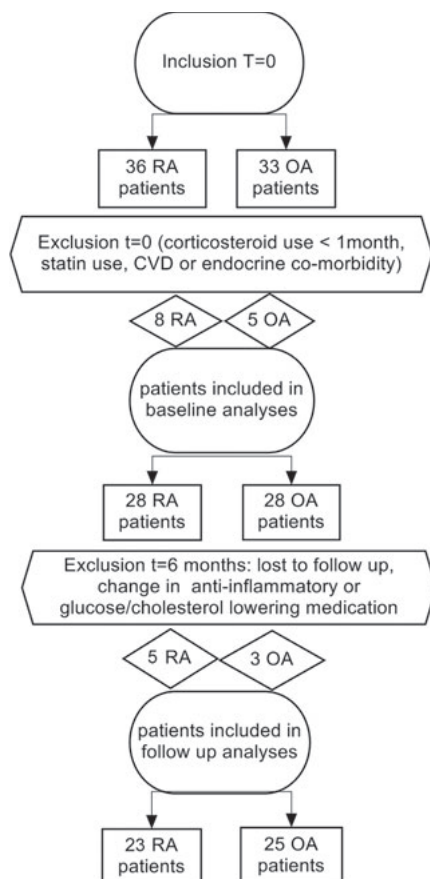
Table 1. Baseline characteristics

	RA	OA
Demographics	n=28	n=28
Females	20 (71)	19 (68)
Age, years	53±10	55±11
Cardiovascular risk factors		
Impaired glucose tolerance[a]	3 (11)	4 (14)
Diabetes mellitus[a]	0	1 (4)
Metabolic syndrome (NCEP ATP III)	3 (11)	4 (14)
Hypertension	4 (14)	4 (14)
Antihypertensive drug use	3 (11)	4 (14)
Hypercholesterolemia	3 (10)	8 (28)

Table 1. Continued.

	RA	OA
Smoking		
Current smoker	5 (18)	10 (36)
Past smoker	14 (50)	6 (21)
Never smoker	9 (32)	12 (43)
Disease characteristics		
Disease duration, years	4 (1-14)	1 (1-2)
Orthopedic surgery	5 (19)	8 (30)
Anti-inflammatory medication use		
NSAID use	14 (50)	10 (36)
DMARD use	25 (89)	0
Rheumatoid arthritis specific characteristics		
Rheumafactor positive	22 (82)	N/A
Anti-CCP positive	24 (92)	N/A
Erosive disease	15 (56)	N/A
Disease activity score of 28 joints	4.34±1.35	N/A
Health Assesment Questionnaire	1.0±0.6	N/A

RA= rheumatoid arthritis, OA= osteoarthritis, n= number, NSAID= non- steroidal anti-inflammatory drugs, DMARD= disease modifying anti- rheumatic drugs, DAS28= Disease activity score of 28 joints, HAQ= Health assessment questionnaire, N/A= not applicable. [a] according to the WHO criteria for OGTT [35]. Results are presented as mean and standard deviation (SD), median and interquartile range (IQR) or number and percentage (%).

Baseline measurements in patients with rheumatoid arthritis and osteoarthritis

Table 2 presents the results of the baseline measurements in RA and OA patients. There were no significant differences in the anthropometric characteristics or blood pressure between the groups. The prevalence of metabolic syndrome determined by the NCEP ATP III guidelines[27] was 11% in the RA group and 18% in the OA group. One matched OA patient with diabetes was included erroneously but was left in according to the intention-to-treat principle. Furthermore, leaving this patient out did not affect our results. Moreover, this did not hamper our analyses of the effect of anti-TNF on the insulin resistance as subjects did not receive any treatment and were only used as age and sex-matched controls. As expected, both ESR and CRP levels were significantly higher in the RA group. Baseline insulin levels, IR and beta cell function were all significantly higher in RA patients compared to OA patients (figure 2). Fasting glucose was significantly lower in RA patients compared to OA patients (p<0.05). The percentage of gynoid fat was significantly higher in RA patients compared to OA patients (p<0.05). LBM and VAT mass were not significantly different between the groups. Total cholesterol, LDL-cholesterol and apolipoprotein B were significantly lower in RA patients compared to OA patients (Fig. 3).

Table 2. Results of measurement changes after six months comparing rheumatoid arthritis patients with anti-TNF treatment to osteoarthritis patients without anti-TNF treatment

|	RA group n=28 t=0	RA group n=23 t=6 months	p (difference paired values)	OA group n=28 t= 0	OA group n=25 t= 6 months	p (difference paired values)	p (difference baseline values)
Physical examination							
Systolic blood pressure, mmHg	126±17	123±16	0.19	122±12	118±11	0.14	0.26
Diastolic blood pressure, mmHg	76±9	72±8	<0.01*	72±9	70±8	0.21	0.18
Waist Hip Ratio	0.88±0.07	0.87±0.07	0.63	0.87±0.07	0.87±0.076	0.69	0.40
Body Mass Index, kg/m2	26.2±4.0	25.7±3.5	0.80	25.3±4.9	25.7±5.1	0.12	0.41
DAS28	4.34±1.35	2.76±0.94	<0.001*	-	-	-	-
Health Assessment Questionnaire	1.1 (0.4-1.5)	0.5 (0-1.3)	0.001*	-	-	-	-
Inflammatory markers							
ESR, mm/hour	17 (11-32)	14 (6-17)	<0.01*	7 (3-11)	5 (4-9)	0.25	<0.001*
CRP, mg/l	5 (3-9)	2 (2-4)	<0.01*	2 (1-3)	2 (1-3)	0.62	<0.01*
Glucose and insulin measurements							
Fasting glucose, mmol/l	4.9 (4.7-5.1)	4.9 (4.6-5.4)	0.32	5.2 (4.8-5.4)	5.2 (4.9-5.5)	0.94	<0.05*
Glucose 2 hours after 75 gram glucose, mmol/l	5.6 (4.5-6.5)	5.6 (4.2-6.8)	0.87	5.0 (4.2-5.7)	4.7 (4.2-5.8)	0.85	0.14
C-peptide nmol/l	0.71 (0.58-0.80)	0.64 (0.51-0.76)	<0.05*	0.52 (0.46-0.71)	0.56 (0.44-0.68)	0.55	0.10
Insulin, μU/ml	12.0 (8.4-13.7)	9.8 (6.2-11.5)	0.14	5.7 (4.3-7.0)	4.9 (4.17-6.82)	0.71	<0.01*
Insulin resistance (100/%S)	1.5 (1.1-1.8)	1.4 (1.1-1.7)	0.17	0.7 (0.6-0.9)	0.64 (0.55-0.9)	0.75	<0.01*
Beta cell function, % (Cpep)	133 (115-151)	118 (109-130)	<0.05*	102 (91-133)	100 (90-125)	0.3	<0.01*

Table 2. Continued.

|	RA group n=28 t=0	RA group n=23 t=6 months	p (difference paired values)	OA group n=28 t= 0	OA group n=25 t= 6 months	p (difference paired values)	p (difference baseline values)
Body composition whole body DXA							
Fat percentage whole body	37±11	37±8	0.52	35 (29-43)	35 (27-45)	0.18	0.77
Gynoid fat percentage	43±11	41±10	0.01*	37±10	37±10	0.75	<0.05*
Android fat percentage	43±12	41±10	0.20	38 (31-49)	40 (29-49)	0.13	0.13
Visceral adipose tissue mass, grams	888 (492-1436)	870 (473-1350)	0.93	722 (435-1098)	785 (455-1249)	<0.05*	0.68
Lean body mass whole body, kilograms	46.1±7.6	46.7±7.7	0.25	46.1±9.7	46.5±9.6	0.92	0.99
Lipid profile							
Total cholesterol, mmol/l	5.02±0.95	5.47±1.00	<0.01*	5.88±1.01	5.70±0.99	<0.05*	<0.01*
Triglycerides, mmol/l	1.13±0.50	1.20±0.56	0.49	1.09 (0.94-1.54)	1.17 (0.89-1.55)	0.47	0.12
LDL-cholesterol, mmol/l	3.04±0.87	3.33±0.92	<0.05*	3.76±0.96	3.64±0.90	<0.05*	<0.01*
HDL-cholesterol, mmol/l	1.48±0.34	1.66±0.54	<0.05*	1.53±0.41	1.49±0.34	0.60	0.59
Total cholesterol/HDL ratio	3.69±1.17	3.58±1.18	0.41	4.10±1.24	4.02±1.13	0.26	0.17
Apolipoprotein A, g/l	1.67±0.29	1.83±0.48	<0.05*	1.73±0.28	1.68±0.25	0.17	0.47
Apolipoprotein B, g/l	0.92±0.27	0.99±0.26	0.084	1.07±0.24	1.07±0.26	1.0	<0.05*

RA= rheumatoid arthritis, OA=osteoarthritis, n=number, NCEP ATPIII= National Cholesterol Education Program Adult Treatment Panel III (US 2001), DXA= Dual-Energy X-ray absorptiometry.

Results are presented as mean and standard deviation (±SD), median and interquartile range (IQR) or number percentage, * significance level of p<0.05.

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Figure 2. Insulin resistance and pancreatic beta cell function at baseline and after 6 months in patients with rheumatoid arthritis and osteoarthritis
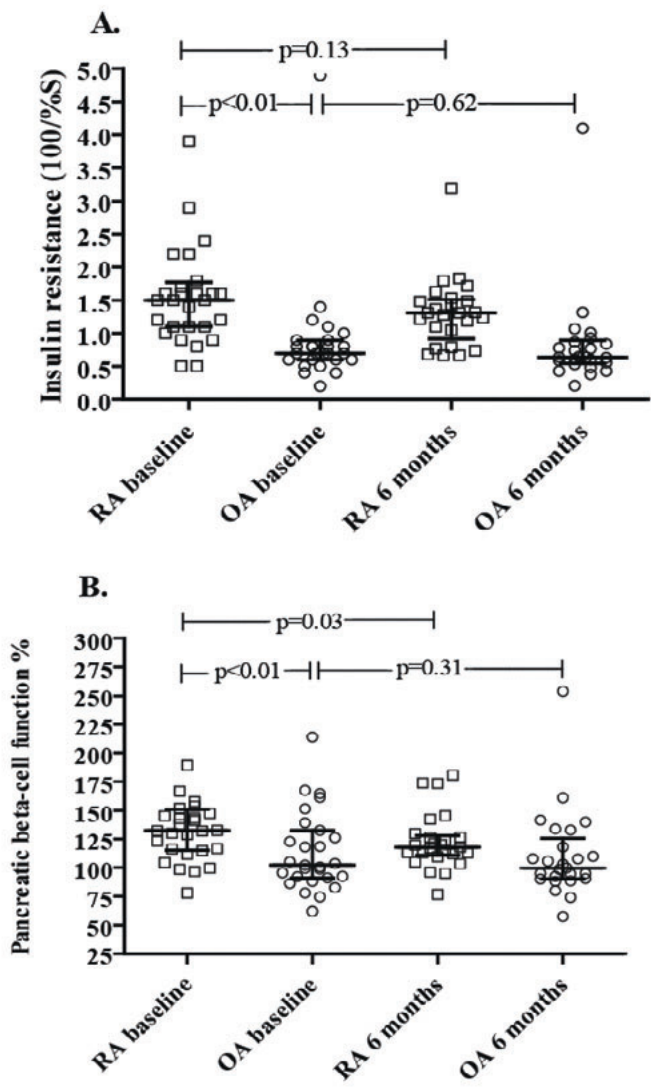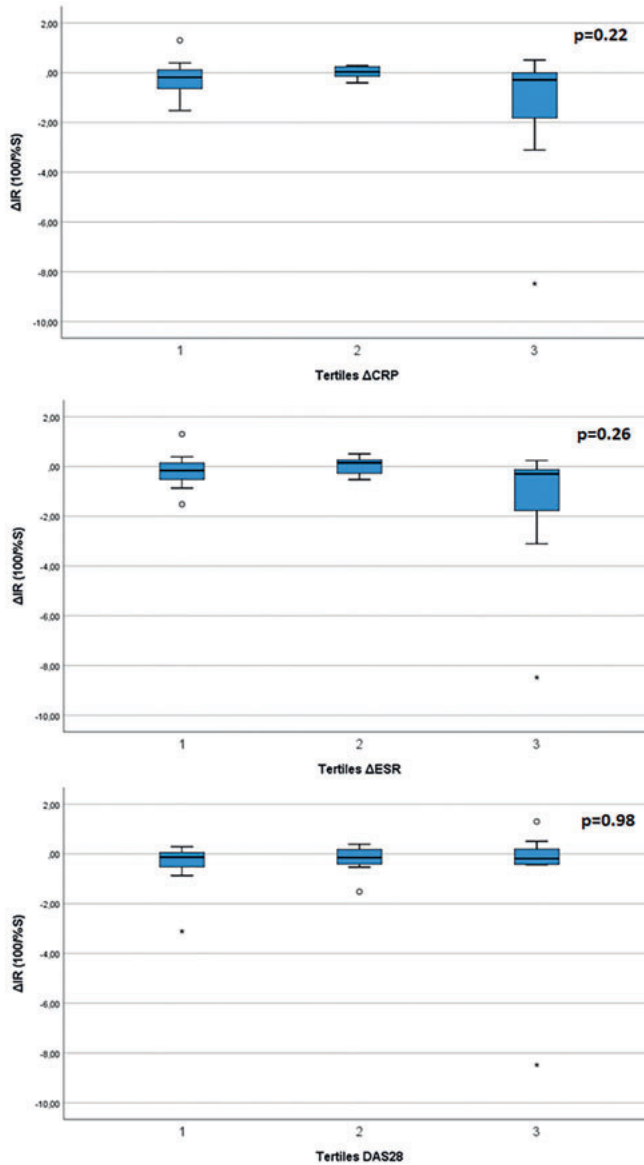
Figure 3. Associations between body mass index and insulin resistance and pancreatic beta cell function in rheumatoid arthritis patients (RA) and osteoarthritis patients (OA).
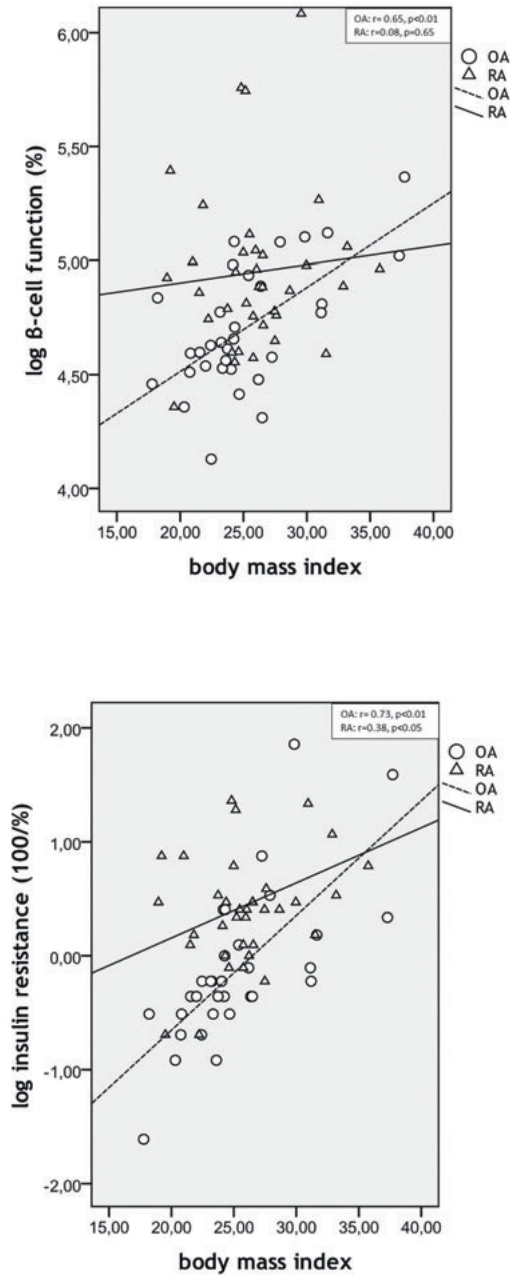
Figure 4. Change in insulin resistance and pancreatic beta cell function in RA patients after 6 months anti-TNF treatment categorized in tertiles for delta inflammatory parameters.
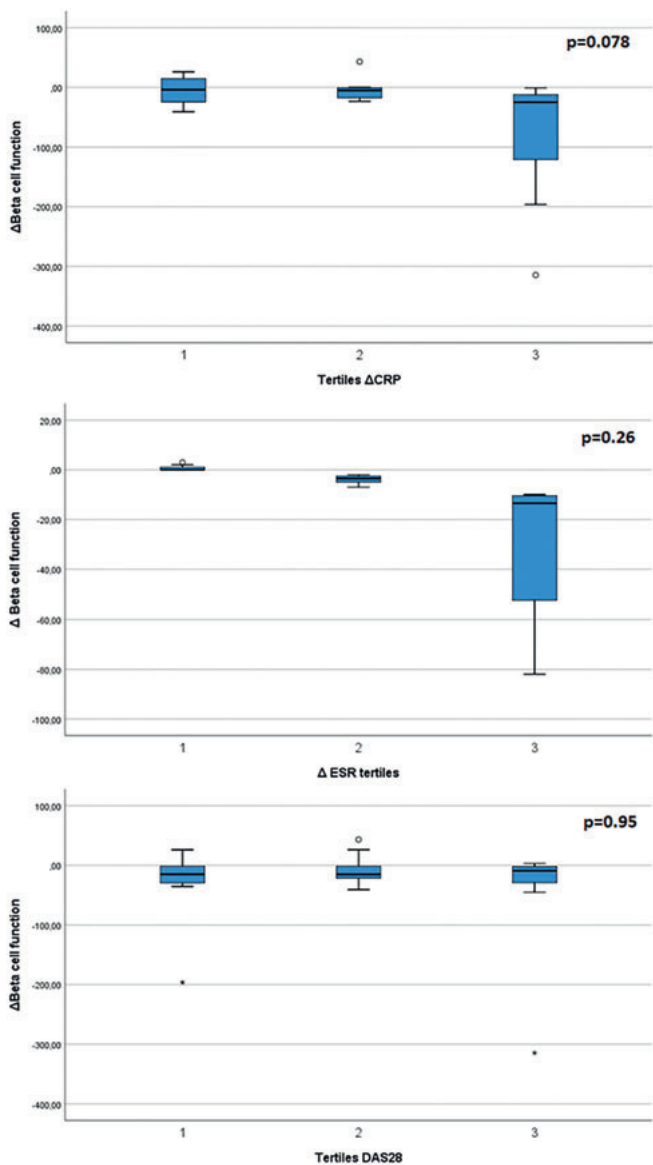
Tertiles ΔCRP: 1=9 - 0, 2= 0 - -3, 3=-4 - -161; tertiles ΔESR: 1=3 - 0, 2=-7 - -2, 3= -10 -- -82; tertiles ΔDAS28: 1= 0.3 - -0.7, 2= -1.2 - -2.2, 3= -2.2 - -3.5.

Inflammation, insulin resistance and beta cell function
To analyse the association between change in systemic inflammation and change in IR and beta cell function patients were stratified in equal tertiles of delta inflammatory parameters, i.e. ∆CRP, ∆ESR and ∆DAS28. Results are displayed in figure 4.

Correlations between insulin resistance, beta cell function and body composition data per group
In the RA group, except for a correlation between BMI and IR (r=0.38, p<0.05) (see figure 3) no significant correlations were found between IR or beta cell function and body composition (data not shown).

In the OA group IR and beta cell function were correlated (p<0.01) with BMI (r=0.73, r=0.65 respectively, figure 3), whole body fat percentage (r=0.65, r=0.60 respectively), android fat percentage (r=0.72, r=0.56 respectively) and (p<0.05) gynoid fat percentage (r=0.39, r=0.48 respectively). IR but not beta cell function was also significantly correlated with VAT mass (r=-0.66, p<0.01, r=0.31, p=0.14 respectively) and LBM (r=0.41, p=0.04, r=0.11, p=0.58 respectively).

The effect of anti-TNF treatment
The results of the comparisons between OA and RA patients after 6 months anti-TNF treatment are displayed in figure 2 and table 2. Eventually, 5 RA patients and 3 OA patients were excluded from follow up due to lost to follow up, change in anti-inflammatory treatment and change in glucose/cholesterol lowering medication. Both inflammatory markers ESR and CRP decreased significantly in the RA group compared to the OA group. Also DAS28 and HAQ decreased significantly in RA. In contrast to the OA patients, in the RA group beta cell function and gynoid fat percentage decreased significantly (p<0.05 and p=0.01). Total cholesterol, LDL, apolipoprotein A and also HDL increased significantly after 6 months of treatment in the RA group compared to the OA group (p<0.01). However, total cholesterol/HDL ratio did not change at follow up.

Discussion

Insulin resistance (IR) is increased in rheumatoid arthritis (RA) and it is assumed that IR, systemic inflammation and body composition are interrelated. We hypothesized that a decrease of systemic inflammation and change in body composition would favourably affect IR in RA patients. The present study showed: 1) IR and beta cell function were

significantly higher in RA than in OA; 2) no significant correlations were found between IR or beta cell function and body composition in RA patients; 3) pancreatic beta cell function and IR improved after anti-TNF treatment in RA patients with highest decrease of CRP and ESR, albeit that this did not reach statistical significance.

This latter effect might be due to a decrease in hyper-metabolism and resting energy expenditure that comes along with inflammation and active disease[28, 29]. However, there was no clinical relevant alteration of the overall body composition.

Together with the inflammatory markers, IR and beta cell function were significantly higher in RA than in OA. Overall, in the OA group IR and beta cell function were in the normal range, whereas in the RA group IR and beta cell function were both raised. Inflammation is considered crucial in the pathogenesis of IR, Therefore, these observed differences were expected as RA is a high-grade inflammatory disease compared to OA which is a low-grade inflammatory disease [2]. When we investigated the effect of systemic inflammation in more detail by dividing the RA patients in tertiles according to change in CRP, ESR and DAS28 levels, we found that IR and especially beta cell function improved most after anti-TNF treatment in the RA patients with the highest decrease of CRP and ESR. This suggests that reducing inflammation also improves IR and beta cell function, whether or not this is anti-TNF specific or caused by inflammation reduction [30]. As we found beta cell function equally raised compared to IR and also found no differences between RA and OA in impaired glucose tolerance overall, it's unlikely that beta cell function was significantly impaired in our group of RA patients as was found by Ferraz-Amaro et al. [8].

In OA patients there were clear correlations between IR, beta cell function and BMI and especially android fat percentages, as expected, while in RA only BMI was modestly correlated with IR. Total fat percentage and BMI were slightly higher in RA, but except for gynoid fat percentage, which was significantly higher in RA compared to OA, no significant differences were found in android fat percentage and VAT or LBM, which we had expected. This is to some extent in contrast to the existing literature where increases of BMI and body fat after anti-TNF have been described[31]. Generally, increases of BMI and body fat and BMI were observed after more than a year treatment. Therefore, the 6 months anti-TNF treatment in our study might have been be too short to detect changes in body composition particularly as in other studies also no changes of in BMI and/or body composition were observed after 6 months or shorter duration of

anti-TNF treatment[31]. Altogether, these data show that inflammation rather than an altered body composition explains the higher IR and beta cell function in RA, however further research to discover the exact pathophysiologic mechanism is still needed. Theoretically, a direct effect of anti-TNF on the insulin pathway and fat metabolism cannot be ruled out. However, as more studies demonstrated a correlation between systemic inflammation and insulin resistance, it is plausible to assume the impact of anti-TNF is based on the anti-inflammatory effect. This is underscored by several studies where the effect of other anti-inflammatory antirheumatic drugs therapy on the insulin resistance in RA patients was investigated[32, 33]. No significant differences in total fat percentage and VAT mass between RA and OA patients were found. This might be explained by the fact that OA is associated with obesity and physical inactivity leading to an altered body composition in comparison to the general population[34]. Furthermore, OA is a disease which has many similarities with RA, like for instance chronic pain and joint deformity that both could result in reduced physical activity. Our findings suggest that reduced physical activity and inflammation play an important role in the body composition of both groups, but presumably in different ways and gradations.

Strength of this study was that factors that could have influenced the results, i.e. use of corticosteroids, statin use, a history of CVD or metabolic diseases were excluded. Moreover, changes in medication use during the study period were prohibited. With OA patients as controls, the effect of anti-TNF treatment could be better evaluated, as time can also influence results. Our study has its limitations. It may be argued that the study duration was too short to capture the metabolic effects of anti-TNF on the insulin action and body composition. Nonetheless, as several studies did observe similar effects after comparable treatment period[14, 31], this did not hamper the assessment of the relation between systemic inflammation and insulin resistance

In conclusion, this study showed that IR and beta cell function are increased in RA patients compared to OA patients. Anti-TNF treatment improved IR and beta cell function in RA patients with highest decrease of CRP and ESR which was not explained by change in body composition. The data suggest that this is caused by lowering of inflammatory activity in general, however a direct effect by blocking TNF cannot be excluded in this study and needs further investigation. Nevertheless, our data indicate that reducing systemic inflammation and disease activity reduces IR and beta cell function which ultimately might lessen the CV disease burden.

References

1. Khovidhunkit W, Kim MS, Memon RA, Shigenaga JK, Moser AH, Feingold KR, et al. Effects of infection and inflammation on lipid and lipoprotein metabolism: mechanisms and consequences to the host. J Lipid Res. 2004;45:1169-96.

2. Tilg H, Moschen AR. Inflammatory mechanisms in the regulation of insulin resistance. Mol Med. 2008;14(3-4):222-31.

3. Wang Z, Nakayama T. Inflammation, a link between obesity and cardiovascular disease. Mediators Inflamm. 2010;2010:Article ID 535918.

4. Liefmann R. Endocrine imbalance in rheumatoid arthritis and rheumatoid spondylitis; hyperglycemia unresponsiveness, insulin resistance, increased gluconeogenesis and mesenchymal tissue degeneration; preliminary report. Acta Med Scand. 1949;136(3):226-32.

5. Svenson KL, Lundqvist G, Wide L, Hallgren R. Impaired glucose handling in active rheumatoid arthritis: effects of corticosteroids and antirheumatic treatment. Metabolism. 1987;36(10):944-8.

6. Svenson KL, Lundqvist G, Wide L, Hallgren R. Impaired glucose handling in active rheumatoid arthritis: relationship to the secretion of insulin and counter-regulatory hormones. Metabolism. 1987;36(10):940-3.

7. Svenson KL, Pollare T, Lithell H, Hallgren R. Impaired glucose handling in active rheumatoid arthritis: relationship to peripheral insulin resistance. Metabolism. 1988;37(2):125-30.

8. Ferraz-Amaro I, Garcia-Dopico JA, Medina-Vega L, Gonzalez-Gay MA, Diaz-Gonzalez F. Impaired beta cell function is present in nondiabetic rheumatoid arthritis patients. Arthritis Res Ther. 2013;15(1):R17.

9. Tejera-Segura B, Lopez-Mejias R, de Vera-Gonzalez AM, Jimenez-Sosa A, Olmos JM, Hernandez JL, et al. Relationship Between Insulin Sensitivity and beta-Cell Secretion in Nondiabetic Subjects with Rheumatoid Arthritis. The Journal of rheumatology. 2019;46(3):229-36.

10. Roubenoff R, Roubenoff RA, Ward LM, Holland SM, Hellmann DB. Rheumatoid cachexia: depletion of lean body mass in rheumatoid arthritis. Possible association with tumor necrosis factor. The Journal of rheumatology. 1992;19(10):1505-10.

11. Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. Science. 1993;259(5091):87-91.

12. Borst SE. The role of TNF-alpha in insulin resistance. Endocrine. 2004;23(2-3):177-82.

13. Krogh-Madsen R, Plomgaard P, Moller K, Mittendorfer B, Pedersen BK. Influence of TNF-alpha and IL-6 infusions on insulin sensitivity and expression of IL-18 in humans. American journal of physiology Endocrinology and metabolism. 2006;291(1):E108-14.

14.   Burska AN, Sakthiswary R, Sattar N. Effects of Tumour Necrosis Factor Antagonists on Insulin Sensitivity/Resistance in Rheumatoid Arthritis: A Systematic Review and Meta-Analysis. PLoS One. 2015;10(6):e0128889.

15.   Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis and rheumatism. 1988;31(3):315-24.

16.   Furst DE, Keystone EC, Kirkham B, Kavanaugh A, Fleischmann R, Mease P, et al. Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2008. Annals of the rheumatic diseases. 2008;67 Suppl 3:iii2-25.

17.   Altman R, Alarcon G, Appelrouth D, Bloch D, Borenstein D, Brandt K, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hand. Arthritis and rheumatism. 1990;33(11):1601-10.

18.   Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis and rheumatism. 1995;38(1):44-8.

19.   Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis and rheumatism. 1980;23(2):137-45.

20.   Levy JC, Matthews DR, Hermans MP. Correct homeostasis model assessment (HOMA) evaluation uses the computer program. Diabetes Care. 1998;21(12):2191-2.

21.   Otten J, Ahren B, Olsson T. Surrogate measures of insulin sensitivity vs the hyperinsulinaemic-euglycaemic clamp: a meta-analysis. Diabetologia. 2014;57(9):1781-8.

22.   Kim B, Choi HY, Kim W, Ahn C, Lee J, Kim JG, et al. The cut-off values of surrogate measures for insulin resistance in the Korean population according to the Korean Genome and Epidemiology Study (KOGES). PLoS One. 2018;13(11):e0206994.

23.   Tang Q, Li X, Song P, Xu L. Optimal cut-off values for the homeostasis model assessment of insulin resistance (HOMA-IR) and pre-diabetes screening: Developments in research and prospects for the future. Drug Discov Ther. 2015;9(6):380-5.

24.   Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. Diabetes Care. 2004;27(6):1487-95.

25.   Kaul S, Rothney MP, Peters DM, Wacker WK, Davis CE, Shapiro MD, et al. Dual-energy X-ray absorptiometry for quantification of visceral fat. Obesity (Silver Spring). 2012;20(6):1313-8.

26.   Dessein PH, Joffe BI, Stanwix A, Botha AS, Moomal Z. The acute phase response does not fully predict the presence of insulin resistance and dyslipidemia in inflammatory arthritis. The Journal of rheumatology. 2002;29(3):462-6.

27.   Expert Panel on Detection E, Treatment of High Blood Cholesterol in A. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA. 2001;285(19):2486-97.

28. Masuko K. Rheumatoid cachexia revisited: a metabolic co-morbidity in rheumatoid arthritis. Frontiers in nutrition. 2014;1:20.

29. Straub RH. Insulin resistance, selfish brain, and selfish immune system: an evolutionarily positively selected program used in chronic inflammatory diseases. Arthritis Res Ther. 2014;16 Suppl 2:S4.

30. Chen DY, Chen YM, Hsieh TY, Hsieh CW, Lin CC, Lan JL. Significant effects of biologic therapy on lipid profiles and insulin resistance in patients with rheumatoid arthritis. Arthritis Res Ther. 2015;17:52.

31. Peluso I, Palmery M. The relationship between body weight and inflammation: Lesson from anti-TNF-alpha antibody therapy. Hum Immunol. 2016;77(1):47-53.

32. Bissell LA, Hensor EM, Kozera L, Mackie SL, Burska AN, Nam JL, et al. Improvement in insulin resistance is greater when infliximab is added to methotrexate during intensive treatment of early rheumatoid arthritis-results from the IDEA study. Rheumatology (Oxford). 2016;55(12):2181-90.

33. Ursini F, Russo E, Ruscitti P, Giacomelli R, De Sarro G. The effect of non-TNF-targeted biologics and small molecules on insulin resistance in inflammatory arthritis. Autoimmun Rev. 2018;17(4):399-404.

34. Fernandes GS, Valdes AM. Cardiovascular disease and osteoarthritis: common pathways and patient outcomes. Eur J Clin Invest. 2015;45(4):405-14.

9

Summary, general discussion
and future perspectives

Chapter

10

Summary and general discussion

This thesis describes the role of systemic inflammation resulting from inflammatory joint disease for the development of cardiovascular disease (CVD), particularly cardiac disease, and describes potential therapeutic and preventive strategies for cardiovascular disease risk management in inflammatory joint disease (IJD) patients.

Part I

In **chapter 2** we describe the prevalence of CVD and the overlapping mechanisms of inflammation in the development of CVD in two forms of IJD, i.e. rheumatoid arthritis (RA) and gout. Rheumatoid arthritis and gout are associated with a 50–70% increased risk of cardiovascular disease compared with the general population. These patients do not only have inflammation of the joints but also experience systemic effects, including cardiovascular and thrombotic manifestations. Different underlying pathophysiological mechanisms, such as systemic inflammation, elevated oxidative stress, endothelial dysfunction, and changes in lipid profiles, might contribute to a substantially higher cardiovascular risk in these patients. The increased cardiovascular risk not only includes a higher rate of ischemic cardiovascular disease but also clinical heart failure (70%) and subclinical heart failure which in RA seems far more prevalent than previously thought. Therapeutic intervention with current antirheumatic treatment in rheumatoid arthritis resulted in favourable effects on CVD risk, reducing the risk for CVD with approximately 30%. Unfortunately, in gout, evidence that urate-lowering therapy has consistent beneficial effects on cardiovascular outcomes is still scarce.

In **chapter 3** we investigated the effect of biologic disease modifying anti-rheumatic drugs (DMARD's) on cardiac function and the incidence and prevalence of congestive heart failure in RA patients in a systematic review. Literature focusing on imaging studies mostly showed improvement of cardiac function assessed either with echocardiography or cardiac magnetic resonance imaging (cMRI) in RA patients treated with anti-tumor necrosis factor (TNF), anti-interleukin (IL)-6 and anti-IL-1 drugs. However, most studies were of low (methodological) quality. Large prevalence and incidence studies demonstrated that RA patients treated with anti-TNF biological DMARD's had a lower risk for congestive heart failure (CHF)compared to RA patients treated with non-biological DMARD's (i.e. conventional synthetic (cs)DMARD's). In addition, studies assessing the effect of anti-TNF on plasma NT-proBNP levels showed a significant and clinically relevant decrease of this cardiac wall stress biomarker

indicating improvement of Left ventricular (LV) filling pressures because of ameliorated cardiac function. Therefore, based on the literature, we concluded that biologic DMARD's have an ameliorating effect on cardiac function. However, this research area was hampered by a lack of uniform study design, correct definition of CHF or cardiac dysfunction, improper use of cardiac function assessment tools and absence of well-defined study populations.

Against the background of the previous chapter, **chapter 4** consists of an observational study on the effect of anti-TNF therapy on diastolic and systolic function in RA patient using comprehensive echocardiography and biomarker assessments. We observed a 23% decrease in NT-proBNP after anti-TNF treatment, suggesting some improvement of cardiac function. However, echocardiography showed no improvement nor deterioration of the cardiac function in RA patients as a result of anti-TNF treatment. These unexpected results can be explained by the following causes. First, this could have been due to the low prevalence of cardiac dysfunction at baseline as only three (7%) patients had diastolic dysfunction. Therefore, the study may have been underpowered to detect improvement of the cardiac function after anti-TNF therapy. Second, this population had a relatively short disease duration and a relatively low disease activity compared to other studies where an increased prevalence of cardiac dysfunction in RA patients compared to healthy subjects were found. Third, in addition, our population was relatively cardiac healthy as patients were relatively young and had low prevalence of cardiovascular comorbidities, and were thus less prone to the development of cardiac dysfunction.

In chapter **5**, a case report of a female systemic lupus erythematosus (SLE) patient with heart failure with preserved ejection fraction (HFpEF) is discussed. We assumed that HFpEF was mediated by systemic inflammation secondary to SLE. Therefore, anti-inflammatory therapy with belimumab was added (a biological agent against soluble B-lymphocyte stimulator protein). After 16-weeks of treatment, the patient reported an improved condition. Also, cardiopulmonary exercise test and echocardiography results improved, indicating normalization of the left ventricular (LV) diastolic function. Altogether, this case suggests that targeting inflammation might have therapeutic potential in a subset of HFpEF-patients.

Part II
The prevalence of cardiac diseases associated with ankylosing spondylitis (AS) was investigated in elderly AS patients aged 50-75 years, compared to matched osteoarthritis

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(OA) controls as reported in **Chapter 6**. This study revealed that AS-patients had a five times increased risk of aortic valve regurgitation (AVR) compared to OA controls. Disease activity, disease duration and use of anti-TNF were not associated with AVR. Although AVR was mostly mild, it is important to realize that any stage of AVR is considered to be pathological as trace/mild regurgitation may progress to severe regurgitation which compromises LV function. However, if timely recognized it can be monitored adequately and in severe cases treated with aortic valve or aortic root replacement thereby preventing the development of CHF. Therefore, our findings indicate that echocardiographic screening of elderly AS patients (50-75 years) should be considered. Furthermore, unexpectedly, conduction disorders and diastolic LV dysfunction, based on the 2016 criteria of the ASE/EACVI, were rare in both AS-patients and controls, and the prevalence was comparable for both groups.

In **chapter 7** the association between human leukocyte antigen (HLA)-B27 genotype and aortic root diameter in AS patients was investigated. HLA-B27+ AS patients had a significantly increased aortic root index compared to HLA-B27- AS patients. This association was not explained by difference in age, sex nor cardiovascular risk factors. The prevalence of AVR was, however, similar in both groups. Furthermore, aortic dilatation was more often seen in HLA-B27+ AS patients, although it failed to reach statistical significance. Finally, our data suggest a sex and HLA-B27 genotype linked difference in aortic root index as male HLA-B27+ patients had an increased aortic root index compared to the HLA-B27- male patients and the overall female AS patients.

Part III

In **chapter 8** we performed a cross-sectional study in AS patients and healthy controls to assess the difference in retinal vasculature and to assess the value of retinal screening for cardiovascular disease. This study showed several retinal microvascular changes in AS patients, compared to healthy controls, of which some have been associated with cardiovascular risk. The most prominent changes in AS patients consisted of straighter arterioles and a higher vessel density. In addition, male AS patients showed a decreased arteriovenular ratio compared to male controls, whereas no specific changes were found in women with AS. In AS, high disease activity and previous CVD were associated with wider venules, whereas treatment with biologicals was related to wider arterioles. This proof of concept study indicates that retinal imaging techniques might be useful for the detection of microvascular changes in AS patients. If confirmed in further longitudinal follow up, these techniques might be useful for the early recognition of CVD in AS.

In **chapter 9** we performed a prospective observational cohort study to assess the effect of anti-inflammatory treatment with anti-TNF on the insulin resistance (IR) and body composition in RA patients. This study showed that IR and beta cell function are increased in RA patients compared to OA patients. Anti-TNF treatment improved beta cell function with 19% and IR and beta cell function particularly improved in RA patients with highest decrease of CRP and ESR which was both not explained by change in body composition. The data suggest that this is caused by lowering of inflammatory activity in general. Altogether, our data indicate that reducing systemic inflammation and disease activity reduces IR and beta cell function. This could ultimately lead to a reduction in CVD burden.

Table 1. Answers to the research questions

Chapter 1	General introduction
	Part I
Chapter 2	Different underlying pathophysiological mechanisms, such as systemic inflammation, elevated oxidative stress, endothelial dysfunction, and changes in lipid profiles, might contribute to a substantially higher cardiovascular risk in inflammatory joint disease patients.
Chapter 3	Literature shows an ameliorating effect of bDMARD's on the cardiac function and the prevalence and incidence of CHF in RA patients.
Chapter 4	NT-pro-BNP decreased with 23% after anti-TNF treatment suggesting an (moderate) improvement of cardiac function. However, we found no effect of anti-TNF on the diastolic and systolic function assessed with echocardiography.
Chapter 5	Anti-inflammatory treatment with belimumab showed improvement of SLE induced HFpEF.
	Part II
Chapter 6	Elderly (50-75 years) AS patients have an up to five-time increased risk for aortic valve regurgitation compared to OA controls. Therefore, our findings indicate that echocardiographic screening of elderly AS patients (50-75 years) should be considered. Conduction disorders and diastolic dysfunction were rare in both populations.
Chapter 7	HLA-B27+ AS patients had a significantly increased aortic root index compared to HLA-B27- AS patients. The prevalence of AVR was however similar in both groups.
	Part III
Chapter 8	AS patients have several retinal microvascular changes of which some have been associated with cardiovascular risk.
Chapter 9	Anti-TNF treatment improved IR and beta cell function in RA patients with high CRP and ESR. This improvement was not explained by change in body composition.
Chapter 10	Summary, general discussion and future perspectives

Future research

Multiple studies showed a direct relation between systemic inflammation and CVD in the past decennia. In RA, the increased risk for CVD has led to the development of CV risk management guidelines, e.g. the European Alliance of Associations for Rheumatology (EULAR). However, CVD risk management guidelines are still lacking for other systemic inflammatory disease and therefore need to be developed. In addition, there are still mechanisms and clinical manifestations in these patients which need to be further investigated.

Aortic valve regurgitation in AS

More specific guidelines for CVD risk management in AS patients should be developed. Follow up studies in AS patients with AVR are required to assess the clinical course of AVR. This is necessary to assess the cost-effectiveness of echocardiographic screening in AS patients. If aortic valve regurgitation, in a significant amount of AS patients, evolves to severe and symptomatic AVR requiring aortic valve/root replacement, the need for mandatory and repetitive echocardiographic screening of the AS population will be established. Perhaps, a specific age limit can be determined from which onwards echocardiographic screening should be done. Prospective cohort studies such as the CARDAS study offer a great opportunity to perform such a follow up. Obviously, cost-effectiveness of echocardiographic screening in AS patients should also be considered. Furthermore, future studies should aim to assess the possible sex differences in respect to the development of cardiac disease including AVR.

Anti-inflammatory therapy and cardiac dysfunction in IJD

The effect of anti-inflammatory therapy on cardiac dysfunction should be further assessed. There is accumulating evidence that systemic inflammation may lead to cardiac dysfunction, particularly diastolic dysfunction in patients with chronic inflammatory diseases. This process starts with inflammation-induced microvascular dysfunction, leading to deposition of collagen with subsequent stiffness and hypertrophy of cardiomyocytes and a decreased ability of the myocardium to contract and relax, which might evolve into heart failure with preserved ejection fraction. Until now no large cohort studies could give a concluding answer to this research question. This is mainly due to the fact that in most studies the subjects did not have baseline LV diastolic dysfunction at rest. They probably required exercise echocardiography to unveil baseline diastolic LV dysfunction which could then be demonstrated to be potentially amenable to treatment with anti-TNF.

Our case report in chapter 5 describes the favorable effect of anti-inflammatory therapy in a SLE associated HFpEF and this could be indicative for a larger future study. We found a possible causal relation between systemic inflammation and HFpEF. However, this relation has not been studied in adequately powered studies. We further investigated this (potential) effect in the CHARM study (chapter 4). However, unexpectedly we found a (very) low prevalence of diastolic dysfunction in the RA population and could therefore only demonstrate indirectly (decline of NT-proBNP levels) favorable effects on cardiac (dys)function. Future studies therefore should investigate the effect of anti-inflammatory therapy in IJD patients with evidence of diastolic dysfunction at rest or during exercise. If diastolic dysfunction shows improvement at follow up in a large cohort this can further elucidate the link between systemic inflammation and cardiac dysfunction paving the road for preventive therapeutic strategies. To recruit a sufficient amount of IJD patients with diastolic dysfunction, future studies could aim to screen HFpEF patients for a medical history of IJD in which the effect of more strong/effective anti-inflammatory therapy can then be assessed.

Inflammatory pathways and CVD
The role of specific inflammatory pathways in the development of CVD, i.e. oxidative stress and cytokines, in IJD has not yet been fully elucidated.

As new anti-inflammatory therapies with e.g. bDMARDs or tsDMARDs (i.e. anti-IL-17, anti-IL-12 and JAK-inhibitors) target more specific inflammatory pathways, the underlying mechanisms for CVD could also be revealed. It will then also become clear if and to what extent anti-inflammatory therapies differ between each other with respect to CVD risk reducing effects. Future studies should therefore assess these specific pathways and also the effect of specific bDMARDs on the risk of CVD. In reverse, these studies should also assess if the CVD risk increases when drugs are tapered. The latter treatment strategy is used more often in clinical practice.

Nederlandse samenvatting

Samenvatting en discussie

Dit proefschrift beschrijft de rol van systemische ontsteking als gevolg van inflammatoire gewrichtsziekten bij de ontwikkeling van hart- en vaatziekten (HVZ), in het bijzonder hartziekten, en beschrijft mogelijke therapeutische en preventieve strategieën voor risicomanagement van hart- en vaatziekten bij patiënten met inflammatoire gewrichtsziekten.

Deel I

In **hoofdstuk 2** beschrijven we de prevalentie van HVZ en de overlappende ontstekingsmechanismen bij de ontwikkeling van HVZ bij reumatoïde artritis (RA) en jicht. RA en jicht zijn geassocieerd met een 50-70% verhoogd risico op HVZ in vergelijking met de algemene bevolking. Deze patiënten hebben niet alleen ontsteking van de gewrichten, maar ondervinden ook systemische effecten, waaronder manifestaties in het hart en de vaten. Verschillende onderliggende pathofysiologische mechanismen, zoals systemische ontsteking, verhoogde oxidatieve stress, endotheeldysfunctie en veranderingen in het lipidenprofiel, kunnen bijdragen aan een verhoogd risico op HVZ bij deze groep patiënten. Het verhoogde risico op HVZ omvat niet alleen een hoger percentage ischemische HVZ, maar ook subklinisch hartfalen, wat vaker lijkt voor te komen dan eerder werd gedacht. Vroegtijdige behandeling met ontstekingsverlagende medicijnen bij reumatoïde artritis resulteerde in een verminderd risico op HVZ.

Bij jicht is het bewijs dat uraatverlagende medicijnen een gunstig effect hebben op HVZ helaas nog schaars.

In **hoofdstuk 3** onderzochten we in een systematische review het effect van biologic disease modifying anti-rheumatic drugs (bDMARD's) op de hartfunctie en het effect van bDMARD's op de incidentie en prevalentie van hartfalen bij RA patiënten. Literatuur die zich richtte op beeldvormend onderzoek toonde meestal verbetering van de hartfunctie aan bij RA patiënten die werden behandeld met anti-tumor necrose factor (anti-TNF), anti-interleukine (anti-IL)-6 en anti-IL-1 geneesmiddelen. Deze beeldvormende onderzoeken werden verricht met echocardiografie of cardiale magnetische resonantie (cMRI) beeldvorming. De meeste studies waren echter van lage (methodologische) kwaliteit. Grote prevalentie- en incidentiestudies toonden aan dat RA-patiënten behandeld met anti-TNF een lager risico op hartfalen (HF) hadden in vergelijking

met RA-patiënten die werden behandeld met niet-bDMARD's (d.w.z. conventionele synthetische (cs)DMARD's). Bovendien toonden studies naar het effect van anti-TNF op de plasma NT-proBNP een daling van deze biomarker aan. Dit wijst op een verbetering van de linker ventriculaire (LV) vullingsdruk als gevolg van een verbeterde hartfunctie. Daarom concludeerden wij dat bDMARD therapie bij RA patiënten een gunstig effect heeft op de hartfunctie. Een eenduidig antwoord op de onderzoeksvraag was echter moeilijk te geven vanwege het gebruik van verschillende onderzoeksopzetten, het gebruik van verschillende beeldvormende onderzoeksmethoden en niet goed gedefinieerde studiepopulaties.

Tegen de achtergrond van het vorige hoofdstuk, beschrijft **hoofdstuk 4** een observationele studie naar het effect van anti-TNF therapie op de diastolische en systolische hartfunctie in RA patiënten onderzocht middels echocardiografie en biomarker onderzoek. We zagen een daling van 23% in het NT-proBNP plasmaspiegel na anti-TNF therapie, wat wijst op een enige verbetering van de hartfunctie. Echocardiografisch onderzoek toonde echter geen effect van anti-TNF therapie op de hartfunctie bij RA patiënten. Een beperking van deze studie was dat hartfunctiestoornissen weinig voorkwamen in de geobserveerde patiëntenpopulatie, waardoor bij slechts een beperkt aantal patiënten het effect van anti-TNF therapie op de hartfunctie onderzocht kon worden.

In **hoofdstuk 5** wordt een casus besproken van een patiënte met systemisch lupus erythematosus (SLE) en hartfalen met behouden ejectiefractie (heart failure with preserved ejection fraction (HFpEF)). Onze hypothese was dat HFpEF werd gemedieerd door systemische ontsteking secundair aan SLE. Derhalve werd ontstekingsremmende therapie middels belimumab (een biologisch middel tegen B-lymfocyten stimulator eiwit) aanvullend gestart. Na 16 weken behandeling meldde de patiënte een verbetering van de conditie. Ook de resultaten van de cardiopulmonale inspanningstest en het echocardiografisch onderzoek toonden verbetering van de hartfunctie, wat wijst op normalisering van de LV diastolische functie. Al met al. suggereert deze casus dat ontstekingsremmende therapie de hartfunctie kan verbeteren in een specifieke subgroep HFpEF patiënten.

Deel II

In **hoofdstuk 6** wordt de prevalentie van hartziekten die zijn geassocieerd met ankyloserende spondylitis (AS) onderzocht bij oudere AS patiënten in de leeftijd van 50-75 jaar, en vergeleken met gematchte osteoartritis (OA) controle patiënten. Deze

studie toonde aan dat AS patiënten een vijf maal verhoogd risico hebben op aortaklep insufficiëntie (AoI) in vergelijking met OA controles. Ziekteactiviteit, ziekteduur en gebruik van anti-TNF waren niet geassocieerd met AoI. Hoewel de AoI meestal mild was, is het belangrijk in acht te nemen dat elk stadium van AoI als pathologisch wordt beschouwd, aangezien een milde AoI zich kan ontwikkelen tot een ernstige AoI. Indien tijdig herkend, kan dit echter adequaat worden behandeld met een aortaklep- of aortawortelvervanging. Daarom geven onze bevindingen aan dat echocardiografische screening van oudere AS patiënten (50-75 jaar) moet worden overwogen.

Tegen de verwachting in kwamen geleidingstoornissen en LV diastolische dysfunctie (o.b.v. de 2016 ASE/EACVI criteria) weinig en vergelijkbaar voor in beide groepen.

In **hoofdstuk 7** wordt de associatie tussen humaan leukocyten antigen (HLA)-B27 genotype en de aortawarteldiameter bij AS patiënten onderzocht. HLA-B27+ AS patiënten hadden een significant verhoogde aortawortel index vergeleken met HLA-B27- AS patiënten. Deze associatie werd niet verklaard door verschil in leeftijd, geslacht of cardiovasculaire risicofactoren. De prevalentie van AoI was echter vergelijkbaar in beide groepen. Bovendien werd aortadilatatie vaker gezien bij HLA-B27+ AS patiënten, hoewel dit geen statistische significantie bereikte. Tenslotte suggereren onze gegevens een geslachts- en HLA-B27 genotype-gerelateerd verschil in de aortawortelindex, aangezien mannelijke HLA-B27+ patiënten een verhoogde aortawortelindex hebben in vergelijking met de HLA-B27- mannelijke patiënten en de vrouwelijke AS patiënten in het algemeen.

Deel III

In **hoofdstuk 8** hebben we een cross-sectionele studie uitgevoerd bij AS patiënten en gezonde controles om het verschil in retinale vasculatuur te beoordelen en om de waarde van retinale screening op hart- en vaatziekten te evalueren. Deze studie toonde verschillende retinale microvasculaire veranderingen bij AS patiënten vergeleken met gezonde controles, waarvan sommige geassocieerd zijn met cardiovasculaire risico's. De meest opvallende veranderingen bij AS patiënten bestonden uit rechtere arteriolen en een hogere vaatdichtheid. Bovendien vertoonden mannelijke AS-patiënten een verminderde arteriovenulaire ratio in vergelijking met mannelijke controles, terwijl er geen specifieke veranderingen werden gevonden bij vrouwen met AS. Bij AS waren een hoge ziekteactiviteit en een voorgeschiedenis met HVZ geassocieerd met wijdere venulen, terwijl behandeling met bDMARD's gerelateerd was aan wijdere arteriolen. Deze proof of concept studie geeft aan dat beeldvormende onderzoek van het netvlies

nuttig kan zijn voor de detectie van microvasculaire veranderingen bij AS patiënten. Indien bevestigd in longitudinale follow-up studies, zouden deze technieken nuttig kunnen zijn voor de vroegtijdige herkenning van HVZ in AS.

In **hoofdstuk 9** hebben we een prospectieve observationele cohort studie uitgevoerd om het effect van ontstekingsremmende therapie met anti-TNF te onderzoeken op de insuline resistentie (IR) en lichaamssamenstelling in RA patiënten. Deze studie toonde aan dat IR en bètacel functie verhoogd zijn bij RA patiënten in vergelijking met OA controle patiënten. Anti-TNF therapie verbeterde de IR en bètacel functie bij RA patiënten met de hoogste daling van C-reactief proteïne (CRP) en bezinking (BSE). Dit effect werd niet verklaard door verandering in de lichaamssamenstelling. De gegevens suggereren dat dit wordt veroorzaakt door verlaging van de algehele ontstekingsactiviteit. Al met al. wijzen onze gegevens erop dat het verminderen van systemische ontsteking en ziekteactiviteit de IR en bètacelfunctie vermindert. Dit zou uiteindelijk kunnen leiden tot een verminderd risico op HVZ.

Toekomstig onderzoek

Meerdere studies hebben in de afgelopen decennia een direct verband aangetoond tussen systemische ontsteking en HVZ. Bij RA heeft het verhoogde risico op HVZ geleid tot de ontwikkeling van risicomanagement richtlijnen voor HVZ (EULAR). Richtlijnen voor risicomanagement voor HVZ ontbreken echter nog voor andere systemische ontstekingsziekten en moeten daarom nog worden ontwikkeld. Bovendien zijn er nog steeds mechanismen en klinische verschijnselen bij deze patiënten die verder moeten worden onderzocht.

Aortaklepinsufficiëntie in AS

Het is aanbevolen dat een specifiek risicomanagement richtlijn voor HVZ bij AS-patiënten wordt ontwikkeld. Follow-up studies bij AS-patiënten met AoI zijn nodig om het klinische beloop van AoI te beoordelen. Dit is nodig om de kosteneffectiviteit van echocardiografische screening bij AS-patiënten te beoordelen. Als AoI bij een aanzienlijk aantal AS-patiënten evolueert tot ernstige en symptomatische AoI waarvoor aortaklep-/wortelvervanging nodig is, impliceert dit dat verplichte en herhaalde echocardiografische screening van de AS-populatie nodig is. Door aanvullend onderzoek moet aangetoond worden of een leeftijdsgrens zinvol is vanaf welke echocardiografische screening moet worden uitgevoerd. Prospectieve cohortstudies zoals de CARDAS-studie bieden een uitgelezen kans om daarop volgend een dergelijk follow-up onderzoek uit te voeren.

Uiteraard moet hierbij ook rekening worden gehouden met de kosteneffectiviteit van echocardiografische screening bij AS-patiënten. Daarnaast moeten toekomstige studies zich richten op het beoordelen van de mogelijke geslachtsverschillen met betrekking tot de ontwikkeling van hartziekten, waaronder AoI.

Ontstekingsremmende therapie en hartfunctiestoornissen bij IGZ

Het effect van ontstekingsremmende therapie op de hartfunctie moet verder worden onderzocht. Er zijn steeds meer aanwijzingen dat systemische ontsteking kan leiden tot hartfunctiestoornissen, vooral diastolische dysfunctie bij patiënten met inflammatoire gewrichtsziekten. Dit proces begint met ontstekingsgemedieerde microvasculaire dysfunctie, die leidt tot afzetting van collageen met daaropvolgende stijfheid en hypertrofie van cardiomyocyten en een verminderd vermogen van het myocard om samen te trekken en te ontspannen, wat kan uitmonden in HFpEF. Tot dusver konden grote cohortstudies echter geen sluitend antwoord geven op deze onderzoeksvraag. Dit is vooral te wijten aan het feit dat in de meeste studies de proefpersonen op baseline geen diastolische dysfunctie hadden in rust. Waarschijnlijk had inspannings-echocardiografie uitgevoerd moeten worden om de aanwezige LV diastolische dysfunctie aan het licht te brengen. Vervolgens kan onderzocht worden of anti-TNF therapie de hartfunctie in deze patiënten verbeterd.

De casus in hoofdstuk 5 beschrijft het gunstige effect van ontstekingesremmende therapie op de hartfunctie in een patiënte met SLE geassocieerde HFpEF. Wij vonden een mogelijk causaal verband tussen systemische ontsteking en HFpEF. Dit verband is echter nog niet onderzocht in studieverband. We hebben dit (potentiële) effect verder onderzocht in de CHARM studie (hoofdstuk 4). Echter, tegen onze verwachting in vonden we een (zeer) lage prevalentie van diastolische dysfunctie in de RA populatie en konden derhalve alleen een indirect (daling van NT-proBNP niveaus) gunstig effect op de hartfunctie aantonen. Toekomstige studies zouden daarom het effect van ontstekingsremmende therapie moeten onderzoeken bij inflammatoire gewrichtsziekten-patiënten met aanwijzingen voor diastolische dysfunctie in rust of tijdens inspanning. Indien de diastolische dysfunctie verbetert bij follow up in een grote cohort studie kan dit het verband tussen systemische ontsteking en cardiale dysfunctie verder ontrafelen en de weg vrijmaken voor preventieve therapeutische strategieën. Om voldoende inflammatoire gewrichtsziekten patiënten met diastolische dysfunctie te rekruteren, is het aanbevolen dat toekomstige studies zich richten op het screenen van

HFpEF-patiënten met inflammatoire gewrichtsziekten waarbij het effect van sterkere/ effectievere ontstekingsremmende therapie op de hartfunctie kan worden beoordeeld.

Ontstekingsmechanismen en HVZ

De rol van specifieke ontstekingsmechanismen in de ontwikkeling van HVZ, o.a. oxidatieve stress en cytokines, bij inflammatoire gewrichtsziekte is nog niet volledig opgehelderd.

Echter bieden nieuw ontwikkelde anti-inflammatoire therapieën (o.a. bDMARD's) die aangrijpen op specifieke ontstekingsmechanismen (bv. anti-IL-17, anti-IL12 en JAK-remmers) de mogelijkheid onderzoeken op te zetten om de onderliggende rol van specifieke ontstekingsmechanismen in de ontwikkeling van HVZ te ontrafelen. Middels deze onderzoeken kan duidelijk worden of het onderdrukken van specifieke ontstekingsmechanismen het risico op HVZ kan verminderen en in welke mate het kan worden verminderd. Daarnaast zou in deze toekomstige onderzoeken ook gekeken moeten worden wat het effect is van het afbouwen van deze anti-inflammatoire therapieën op het risico op HVZ. Aangezien deze behandelstrategie steeds vaker in de praktijk toegepast wordt.

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Appendices

List of publications
Curriculum Vitae
Dankwoord

List of publications

1. Baniaamam M, Vedder D, Hansildaar R, Tausche AK, Gerritsen M, Nurmohamed MT. Cardiovascular risk in inflammatory arthritis: rheumatoid arthritis and gout. Lancet Rheumatol. 2021 Jan;3(1):e58-e70.
2. Baniaamam M, Paulus WJ, Blanken AB, Nurmohamed MT. The effect of biological DMARDs on the risk of congestive heart failure in rheumatoid arthritis: a systematic review. Expert Opin Biol Ther. 2018 May;18(5):585-594.
3. Baniaamam M, Handoko ML, Agca R, Heslinga SC, Konings TC, van Halm VP, Nurmohamed MT. The Effect of Anti-TNF Therapy on Cardiac Function in Rheumatoid Arthritis: An Observational Study. J Clin Med. 2020 Sep 29;9(10):3145.
4. Baniaamam M, Voskuyl AE, Nurmohamed MT, Handoko ML. Clinical improvement of cardiac function in a patient with systemic lupus erythematosus and heart failure with preserved ejection fraction treated with belimumab. BMJ Case Rep. 2021 Jan 15;14(1):e237549.
5. van Bentum RE, Baniaamam M, Kinaci-Tas B, van de Kreeke JA, Kocyigit M, Tomassen J, den Braber A, Visser PJ, Ter Wee MM, Serné EH, Verbraak FD, Nurmohamed MT, van der Horst-Bruinsma IE. Microvascular changes of the retina in ankylosing spondylitis, and the association with cardiovascular disease - the eye for a heart study. Semin Arthritis Rheum. 2020 Dec;50(6):1535-1541.
6. van den Oever IAM, Baniaamam M, Simsek S, Raterman HG, van Denderen JC, van Eijk IC, Peters MJL, van der Horst-Bruinsma IE, Smulders YM, Nurmohamed MT. The effect of anti-TNF treatment on body composition and insulin resistance in patients with rheumatoid arthritis. Rheumatol Int. 2021 Feb;41(2):319-328.

Submitted:

1. Unexpected high aortic valve regurgitation prevalence in a contemporary large cohort Dutch ankylosing spondylitis patients - the CARDAS study. *Submitted*.
2. Aortic root diameter is associated with HLA-B27: identifying the patient with ankylosing spondylitis at risk for aortic valve regurgitation. *Submitted*.
3. The effect of anti-TNF treatment on body composition and insulin resistance in patients with ankylosing spondylitis. *Submitted*.

Curriculum vitae

Milad Baniaamam was born on the 5th of February in 1989 in Teheran, Iran. Due to political unrest and safety reasons after the Iran-Iraq war, Milad and his family fled to the Netherlands in 1992. He grew up in Amsterdam and finished high school at the Bredero College in 2007. Milad started medical school at the Vrije Universiteit in 2009. During his master he followed his surgery internship at the Sint Maarten Medical Centre in Sint Maarten and he did and extra-curricular internship in Tanzania, at the Kilimatinde Hospital and the Manyoni hospital in the Manyoni district. His interest in research was stimulated by his research internship at the Cardiology department at the Amsterdam UMC location VU medical center. After he obtained his medical degree in December 2015, he started working as physician at the cardiology department in the Spaarne Gasthuis in Hoofddorp. Following his ambitions to pursue a PhD, he applied for a full-time clinical research position on cardiac diseases in inflammatory joint disease patients. In October 2016 he started as PhD candidate at Reade and Amsterdam UMC location VU medical center under supervision of Michael T. Nurmohamed and co-guidance of Irene E. van der Horst-Bruinsma, M. Louis Handoko and Walter J. Paulus. Milad initiated a clinical research project on the effect of anti-inflammatory therapy on diastolic dysfunction in RA patients (REVERSE study), and he successfully finished two ongoing clinical research projects in which he maintained close contact with the echocardiography department of the VUmc. In 2017 he received a research grant from Pfizer for the REVERSE study. In addition, Milad worked as physician at the Rheumatology department in Reade. In 2021, Milad started his training to become an occupational physician. In his spare time he loves to play sports, travelling and especially spend time with his family and friends. Milad is happily married with Marielle van Aalst and they have two lovely children, Florence (2019) and Parsa (2021).

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chocolaatje. Zonder jouw inbreng was het ons niet gelukt om deze studies tot een succesvol einde te brengen, veel dank hiervoor!

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altijd stand te houden. Ik heb die periode als turbulent ervaren maar het is jouw liefde en geborgenheid geweest en door de normen en waarden die je mij hebt geleerd dat ik mij heb kunnen focussen op mijn toekomst en idealen. Mijn eeuwige dank en liefde hiervoor mijn liefste moeder.

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Liefste Mariëlle, mijn vrouw, mijn maatje, wat was jij een ongelofelijke steun tijdens mijn promotietraject zoals met zoveel dingen in mijn leven. Toen ik aan mijn promotietraject begon was jij al aan het einde van jouw promotietraject waardoor jij mij op sleeptouw nam en tips gaf. Waarschijnlijk werd je soms gek van me als ik weer eens over mijn onderzoeken met je wilde sparren of mijn frustraties met je wilde delen, desondanks was je er altijd voor mij. De gezegde luidt "Achter elke sterke man staat een sterkere vrouw", daar is écht geen woord van gelogen. Inmiddels heeft onze relatie sinds twee jaar een nieuwe dimensie gekregen en mijn leven meer betekenis gekregen door onze kleine wondertjes Florence en Parsa. Dank je wel voor alles mijn liefste!!

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