

Increased Prevalence of Diastolic Heart Failure in Patients with Rheumatoid Arthritis Correlates with Active Disease, but Not with Treatment Type

Thomas Schau, Michael Gottwald, Olga Arbach, Martin Seifert, Maren Schöpp, Michael Neuß, Christian Butter, and Michael Zänker

ABSTRACT. Objective. Although heart failure (HF) is a major cause of premature mortality, there is little information regarding its prevalence and associated risk factors in patients with rheumatoid arthritis (RA). In this study, we evaluated the prevalence of HF in a community-based RA cohort. Further, we investigated the effect of RA activity and present treatment on HF rate and cardiac structure.

Methods. A diagnostic workup for HF according to the European Society of Cardiology recommendations was performed in 157 patients with RA fulfilling the American College of Rheumatology/European League Against Rheumatism criteria (68% women, age 61 ± 13 yrs) from our outpatient clinic and in 77 age- and sex-matched controls.

Results. The prevalence of HF in patients with RA (24%) was unexpectedly high and differed significantly from the control sample (6%, $p = 0.001$). Diastolic HF was the dominant type (23% vs 6%), and clinical symptoms alone were of low diagnostic value. Active RA (28-joint Disease Activity Score ≥ 2.6 : OR 3.4, 95% CI 1.3–9.8) was an independent risk factor of HF, as well as systemic inflammation (erythrocyte sedimentation rate > 16 mm/h: OR 5.4, 95% CI 2.1–16; C-reactive protein > 10 mg/l: OR 2.6, 95% CI 0.8–8.0) and RA duration > 10 years (OR 2.6, 95% CI 1.2–5.8). HF in RA was associated with concentric hypertrophy (48% vs 17%, $p < 0.001$) and reduced longitudinal strain (-17.2% vs -19.7% , $p < 0.001$). However, the prevalence of HF was equivalent between the treatment groups [conventional synthetic disease-modifying antirheumatic drugs (DMARD) 25%, tumor necrosis factor inhibitors 22%, other biological DMARD 27%].

Conclusion. Recognition of all diastolic HF in RA requires a complex diagnostic approach. Active rather than inactive RA places patients at a higher risk for HF, whereas influence of RA treatment on HF risk needs to be elucidated in further studies. (J Rheumatol First Release September 15 2015; doi:10.3899/jrheum.141647)

Keyword Indexing Terms:

DIASTOLIC HEART FAILURE RHEUMATOID ARTHRITIS CARDIOVASCULAR RISK
DISEASE ACTIVITY GLOBAL LONGITUDINAL STRAIN CONCENTRIC HYPERTROPHY

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Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease with a prevalence between 0.8–1%^{1,2}. RA leads to mutilating joint destruction and associated disabilities. It also contributes to the reduction in life expectancy of 8–15 years, which is mainly attributed to the increased prevalence of coronary artery disease (CAD)^{3,4} and heart failure (HF)^{5,6,7}. A positive correlation has been described between persistent systemic inflammation, endothelial dysfunction, and accelerated atherosclerosis^{6,8}. Whereas classical cardiovascular (CV) risk factors are known to be overrepresented in patients with RA^{9,10,11,12}, chronic inflammatory disease activity with increased cytokine levels itself may additionally contribute to atherosclerosis as well as to structural cardiac changes as seen with left ventricular (LV) hypertrophy, atrial dilatation, and pulmonary hypertension (HTN) in RA^{13,14,15}.

Most of the previously reported increased prevalence rates of HF in RA (3.9–11.6%) are based on the analysis of databases from addressed, clinically manifested congestive HF or HF requiring hospital admission^{5,9,10,11,12}. This reflects

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a major part of HF, but not necessarily early forms of diastolic HF.

In contrast, our previous observations revealed that no less than 50% of our patients with RA confirmed dyspnea on exertion or edema when asked by standardized questionnaire. Interestingly, the rate of symptoms correlated with higher disease activity in RA.

Clinical symptoms and even clinical exercise tests may be confounded by underlying arthritis and impaired function¹⁶, and are thus of limited use in patients with RA.

Nevertheless, echocardiographic and magnetic resonance imaging (MRI) data in patients with RA have also indicated predominant diastolic dysfunction^{17,18,19,20} with a higher prevalence, ranging from 26% up to 66%^{21,22}. These findings suggest that diastolic HF, which is a result of diastolic dysfunction, may have been underestimated in previous studies as well as in daily practice. This becomes more important because the associated mortality is only slightly reduced compared with mortality associated with systolic HF, which is still 4 times higher than in individuals without any HF^{23,24,25}.

At present, there is no single diagnostic test for HF, in part because it is a complex syndrome requiring a careful history and physical examination for proper diagnosis. Cardinal manifestations include dyspnea, fatigue, and fluid retention; however, some patients present without any symptoms and/or signs of fluid overload.

Whereas the clinical Framingham criteria may underscore functional impairment of ventricular filling, the current European Society of Cardiology (ESC) guidelines for diagnosis of HF^{26,27} combine clinical symptoms with laboratory findings [N-terminal pro B-type natriuretic peptide (NT-proBNP)], and echocardiographic results.

To explain the high rate of symptomatic patients with RA and to avoid further underestimation of HF risk, our study systematically evaluated the prevalence of clinically overt as well as subclinical systolic and diastolic HF for the first time in an unselected community-based RA cohort using the current ESC recommendations.

Further, our study investigated the influence of persistently active RA and present treatment type on HF risk and its underlying functional and structural myocardial changes.

MATERIALS AND METHODS

Study design. After approval by the Ethics Committee of the Medical Association Brandenburg, all 162 patients with RA treated in our outpatient clinic and fulfilling both the 1987 American College of Rheumatology (ACR) and the 2010 ACR/European League Against Rheumatism classification criteria²⁸ were consecutively screened for our study from April to June 2010. One patient refused consent and 4 patients had incomplete echocardiographic data. Finally, 157 patients were enrolled.

An age- and sex-matched control group (n = 77) was recruited from a neighboring district office and among former hospital staff. CV status of these subjects was unknown; however, subjects with rheumatic diseases were excluded.

Clinical assessment. Patients and controls gave written informed consent

according to the Declaration of Helsinki (2008), and were assessed for CV risk factors and comorbidity using standardized questionnaires, clinical examination of signs and symptoms of HF, serology [including NT-proBNP (Roche), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), median CRP of previous 24 mos, total cholesterol/high-density lipoprotein ratio], electrocardiography, and transthoracic echocardiography. Diagnosis of arterial HTN required increased blood pressure values (> 140/90 mmHg) at rest on 2 different days or had a current prescription of antihypertensive drugs.

RA activity was assessed by the 28-joint Disease Activity Score (DAS28) based on ESR. DAS28 definition of remission DAS28 < 2.6^{28,29} was used. Patients with DAS28 ≥ 2.6 were considered as patients with persistent disease activity. Functional state was measured using the Health Assessment Questionnaire (HAQ)³⁰. Additionally, chest radiograph, thoracic ultrasonography, spirometry, arterial blood gas, and urine analysis were performed. Actual treatment of RA was assessed. Typical clinical symptoms and signs of HF were carefully investigated based on clinical Framingham criteria: dyspnea on ordinary exertion [graded equivalent to New York Heart Association (NYHA) classes], nocturnal cough, nocturia, edema, cardiomegaly, third heart sound rales, pleural effusion, pulmonary vein congestion, and tachycardia.

Echocardiographic analysis. Data were obtained from examination and offline analysis by different experienced cardiologists blinded to clinical characteristics (Vivid-q-ultrasound system and EchoPAC v6.1 workstation, GE Vingmed Ultrasound AS). LV size, geometry, ejection fraction (EF; Simpson method), and diastolic function were assessed according to the American Society of Echocardiography recommendations, and LV mass index (LVMI) > 95 g/m² for women and > 115 g/m² for men defined LV hypertrophy^{31,32}. Speckle tracking was performed in apical 4-chamber and long-axis views. Average peak longitudinal systolic strain values from all LV segments yielded LV global longitudinal systolic strain (GLS).

According to the ESC criteria valid in 2010, systolic HF was defined by reduced EF (LVEF < 50%) and increased NT-proBNP. Diagnosis of diastolic HF was based on clinical symptoms in the presence of elevated NT-proBNP, a preserved EF (LVEF > 50%) in a nondilated left ventricle (LV end diastolic volume < 97 ml/m²) and of abnormalities in LV diastolic function/filling^{26,33}. In detail, diastolic HF was diagnosed in cases fulfilling the following criteria: (1) symptoms/signs and (2) E/e' ratio > 15 or NT-proBNP > 220 pg/ml with (3) E/e' ratio > 8 or atrial fibrillation³³.

Statistical analysis. Echocardiographic data of 4 patients with RA were incomplete and all data of these subjects were omitted for statistical analysis. Remaining 157 datasets were complete without missing variables.

Groups were compared using Wilcoxon signed-rank test for independent samples and continuous variables, and chi-square test or Fisher's exact test (sample size < 5) for categorical variables. Differences were considered statistically significant at p < 0.05.

Multiple logistic regression models were used to determine significant risk factors for HF. Separate multiple logistic regression models were calculated. In each of these models, adjustments for age, sex, and HTN factors were significantly associated with the risk of developing HF. Multicollinearity between the different covariables could be excluded. Variance inflation factors were < 5 for all covariables. Interactions between remaining covariables were tested and found not to be significant (data not shown). We used the open source software "R" v2.12.1 (R-Foundation for Statistical Computing).

RESULTS

Demographic and disease variables. Patients with RA and the control group were comparable in age and sex distribution. CV risk factors were not significantly different except for a higher prevalence of obesity (body mass index > 30 kg/m² in 38% vs 13%, p < 0.001) and HTN (56% vs 40%, p = 0.026) in the RA cohort (Table 1).

Table 1. Demographic, cardiovascular, and echocardiographic variables of control group compared with patients with RA, including subanalysis of patients with and without HF. Values are n (%) unless otherwise specified.

Variables	Control Group, RA Group, n = 157		p	Subanalysis RA Group		p
	n = 77			HF, n = 38 (24%)	No HF, n = 119 (76%)	
HF	5 (6)	38 (24)	0.001	38 (100)	0	
HFNEF	5 (6)	36 (23)	0.002	36 (95)	0	
HFREF	0	2 (1)		2 (5)	0	
Age, yrs, mean ± SD	59 ± 12	61 ± 13	0.307	72 ± 10	57 ± 12	< 0.001
Female	53 (69)	107 (68)	0.882	33 (87)	74 (62)	0.008
BMI > 30 kg/m ²	10 (13)	59 (38)	< 0.001	17 (45)	42 (35)	0.338
Hypertension	31 (40)	88 (56)	0.026	32 (84)	56 (47)	< 0.001
Present smoker	20 (26)	55 (36)	0.182	7 (18)	48 (40)	0.018
Pack-yrs, median (IQR)	10 (2–16)	15 (6–26)	0.023	9 (4–14)	15 (6–26)	0.201
Diabetes mellitus	6 (8)	21 (13)	0.280	7 (18)	14 (12)	0.287
Hypercholesterolemia	27(35)	38 (24)	0.089	9 (24)	29 (24)	1.000
CKD/eGFR < 60 ml/min	5 (6)	24 (15)	0.060	12 (32)	12 (10)	0.003
CAD	2 (3)	12 (8)	0.237	6 (16)	6 (5)	0.072
Stroke/TIA	2 (3)	3 (2)	0.665	1 (3)	2 (2)	0.567
PAD	2 (3)	15 (10)	0.062	6 (16)	9 (8)	0.200
CV risk score, median (range)	2 (0–3)	2 (0–4)	0.590	3 (2–5)	1 (0.5–4)	< 0.001
Hemoglobin, mmol/l, mean ± SD	8.6 ± 0.7	8.1 ± 0.8	< 0.001	7.7 ± 0.8	8.3 ± 0.7	< 0.001
Actual CRP, mg/l, median (IQR)	1.5 (0.7–3.4)	1.8 (0.9–5.0)	0.125	2.8 (1.4–6.5)	1.6 (0.9–4.4)	0.038
Dyspnea						
NYHA class 0–1	63 (81)	90 (57)	< 0.001	7 (18)	83 (70)	< 0.001
Class 2	11 (15)	28 (18)	0.577	9 (24)	19 (16)	0.331
Class 3	2 (3)	37 (24)	< 0.001	20 (53)	17 (14)	< 0.001
Class 4	1 (1)	2 (1)	1.000	2 (5)	0	0.057
Nocturia	14 (18)	48 (31)	0.058	24 (65)	24 (20)	< 0.001
Rales	0	9 (6)	0.061	4 (11)	5 (4)	0.216
Third heart sound	3 (4)	10 (7)	0.720	5 (14)	5 (4)	0.247
Edema	3 (4)	62 (39)	< 0.001	24 (65)	38 (32)	0.001
Framingham HF criteria–positive	0	43 (27)	< 0.001	23 (62)	20 (17)	< 0.001
Clinical symptoms			< 0.001			< 0.001
Suggesting HF	24 (31)	98 (62)		38 (100)	60 (50)	
Thereof confirming HF	5 (21)	38 (39)		38 (100)	0 (0)	
NT-proBNP, pg/ml, median (IQR)	83 (43–142)	110 (58–280)	0.004	543 (327–941)	85 (46–125)	< 0.001
NT-proBNP > 220 pg/ml	9 (12)	49 (31)	0.001	38 (100)	11 (10)	< 0.001
Thereof confirming HF	5 (56)	38 (78)	0.636	38 (100)	0 (0)	
Echocardiography						
LVEF, %, mean ± SD	67 ± 6	67 ± 8	0.168	65 ± 9	69 ± 14	0.252
Proportion < 50%	0	4 (3)	0.175	2 (5)	2 (2)	0.247
LVEDVi, ml, mean ± SD	41 ± 12	40 ± 11	0.615	37 ± 11	40 ± 11	0.042
LVMI, women, mean ± SD	83 ± 24	95 ± 25	0.002	107 ± 34	90 ± 18	0.012
Proportion > 95 g/m ²	15 of 53 (28)	44 of 107 (42)	0.118	19 of 33 (59)	25 of 74 (34)	0.005
LVMI, men, mean ± SD	97 ± 25	97 ± 20	0.813	122 ± 19	95 ± 19	0.009
Proportion > 115 g/m ²	5 of 24 (21)	9 of 50 (18)	0.761	3 of 5 (60)	6 of 45 (13)	0.035
LV geometry						
Normal	34 (44)	48 (32)	0.040*	7 (17)	41 (34)	0.175*
Remodeling	23 (30)	55 (34)	0.523*	10 (27)	45 (39)	0.242*
Concentric hypertrophy	12 (16)	38 (24)	0.174*	18 (48)	20 (17)	< 0.001*
Eccentric hypertrophy	8 (10)	16 (10)	1.000*	3 (8)	13 (10)	0.763*
Diastolic dysfunction	30 (39)	92 (59)	0.003	33 (87)	59 (50)	< 0.001
Grade 1	28 (36)	34 (22)	0.019*	12 (32)	22 (18)	0.113*
Grade 2	2 (3)	52 (33)	< 0.001*	17 (46)	35 (29)	0.112*
Grade 3	0	6 (4)	0.194*	4 (11)	2 (2)	0.031*
GLS, %, median	–20.4	–19.5	0.018	–17.2	–19.7	< 0.001
IQR	–21.6 to –19.1	–21.2 to –17.8		–19.7 to –16.1	–21.3 to –18.3	

* Fisher's exact test. RA: rheumatoid arthritis; HF: heart failure; HFNEF: HF with normal ejection fraction; HFREF: HF with reduced ejection fraction; BMI: body mass index; IQR: interquartile range; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; CAD: coronary artery disease; TIA: transient ischemic attack; PAD: peripheral artery disease; CV: cardiovascular; CRP: C-reactive protein; NYHA: New York Heart Association; NT-proBNP: N-terminal pro B-type natriuretic peptide; LV: left ventricular; LVEF: LV ejection fraction; LVEDVi: LV end-diastolic volume index; LVMI: LV mass index; GLS: global longitudinal strain.

Prevalence of HF, diagnostic investigations, and differential diagnosis. Rate of HF was significantly higher in patients compared to controls (24% vs 6%, $p = 0.001$) and diastolic HF (23% vs 6%, $p = 0.002$) was the predominant type. In contrast, only 2 patients (1%) had systolic HF (Table 1).

Any clinical signs of HF were present in 62% of the RA group (vs 31% controls, $p < 0.001$), but HF was diagnosed in only 40% of these clinically symptomatic patients (21% of symptomatic controls), while in 60%, HF could not be confirmed because of normal NT-proBNP and echocardiography, suggesting low positive predictive value (PPV) of clinical HF symptoms in patients with RA (PPV 39%) as well as in controls (PPV 21%; Supplementary Figure 1 available online at jrheum.org). In the patients with RA, detection of a third heart sound (PPV 50%), nocturia (PPV 48%), and dyspnea NYHA > 1 (PPV 42%) were of higher predictive value than edema (PPV 39%) and rales (PPV 38%). In the control subjects, edema (PPV 67%) was of higher value than third heart sound (PPV 33%), dyspnea NYHA > 1 (PPV 29%), and nocturia (PPV 14%). Other causes of dyspnea in patients with RA were chronic lung diseases (31%), acute respiratory tract infection (15%), pulmonary arterial HTN (15%), obesity (23%), and high RA activity with fatigue (8%).

Elevated NT-proBNP > 220 pg/ml was also more present in patients than controls (31% vs 12%, $p = 0.001$) and highly indicative for HF in RA (PPV 78%).

Diastolic dysfunction could be diagnosed in as many as

92 patients (59%) versus 30 controls (39%, $p = 0.003$), but PPV were only 39% and 17%.

Traditional risk factors for HF in RA. A significantly higher proportion of patients with HF were women (87% vs 62%, OR 2.8, 95% CI 1.2–71, $p = 0.008$), had HTN (84% vs 47%, OR 4.7, 95% CI 2.2–10.9, $p < 0.001$), had chronic kidney disease (estimated glomerular filtration rate < 60 ml/min, 32% vs 10%, $p = 0.003$), had higher CV risk scores (median 3% vs 1% predicted relative risk of fatal CV disease according to the ESC guideline for the management of dyslipidemias, $p < 0.001$), or were older (mean 72 yrs vs 57 yrs, OR for age > 70 yrs: 7.8, 95% CI 3.8–16.3, $p < 0.001$).

As expected, HF prevalence increased with age (Figure 1), yet HF started 10 years earlier in patients with RA (HF rate 2.9% in 5th and 4.3% in sixth decade) and remained always 2- to 3-fold higher in patients with RA compared with controls (34.5% vs 18.2% in the 7th decade, 48.7% vs 11.1%, $p = 0.009$ in the 8th, and 70% vs 33.3% in the 9th decade).

Inflammatory risk factors for HF in patients with RA. Comparing patients with RA with and without HF, patients with HF presented a markedly more severe course of their underlying disease as evidenced by significantly higher disease activity index and inflammatory markers (Table 2). At a cutoff median CRP value of 10 mg/l over 24 months (median CRP over 2 yrs > 10 mg/l), frequency of HF was almost doubled from 22% to 43% (Supplementary Figure 2B available online at jrheum.org).

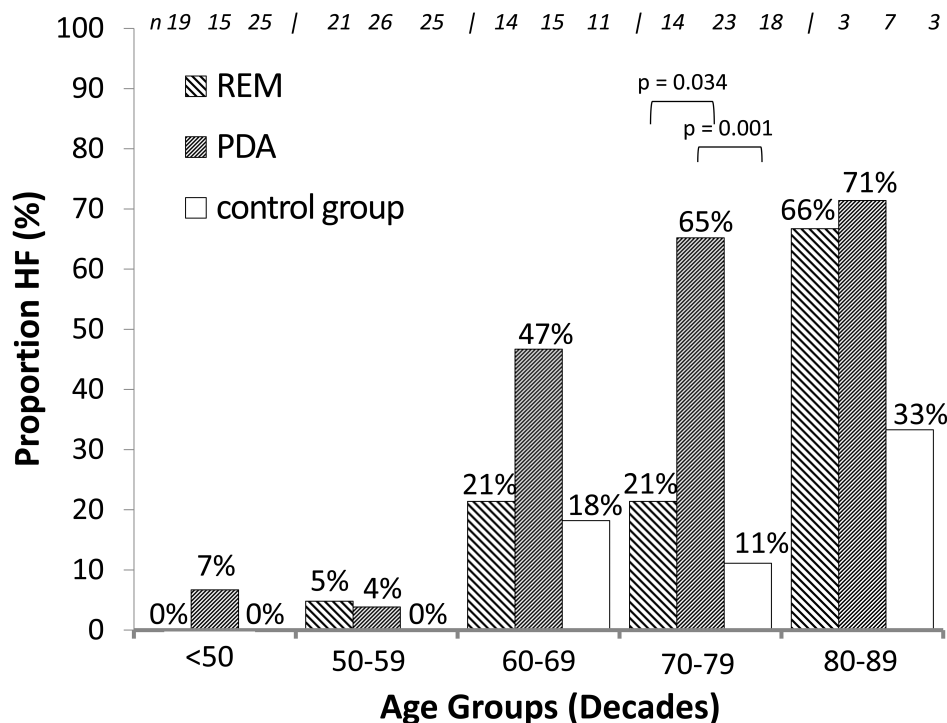


Figure 1. Age-related distribution of the proportion of HF (in percent) in patients with RA with REM (DAS28 < 2.6, $n = 71$) and PDA (DAS28 ≥ 2.6 , $n = 86$) compared with the control group ($n = 77$). HF: heart failure; RA: rheumatoid arthritis; REM: remission; DAS28: 28-joint disease activity score; PDA: persistent disease activity.

Table 2. Disease variables of patients with RA including subanalysis of patients with and without HF. Values are n (%) unless otherwise specified.

Disease Variables	RA Group, n = 157	HF, n = 38 (24%)	Subanalysis RA No HF, n = 119 (76%)	p
Duration of RA, yrs, mean ± SD	12 ± 11	16 ± 13	11 ± 10	0.128
RF-positive	123 (78)	29 (76)	94 (79)	0.902
ACPA-positive	109 (69)	25 (66)	84 (71)	0.721
Median CRP over 2 yrs, median (IQR)	2.3 (1.2–5.0)	2.4 (1.3–5.7)	2.2 (1.1–4.7)	0.374
ESR in mm/h, mean ± SD	16 ± 14	23 ± 15	13 ± 13	< 0.001
DAS28, median (IQR)	2.7 (2.0–3.4)	3.1 (2.6–3.8)	2.5 (1.8–3.2)	0.001
DAS28 < 2.6, remission	71 (45)	9 (24)	62 (52)	0.003*
DAS28 2.6–3.2	40 (25)	12 (32)	28 (24)	0.392*
DAS28 > 3.2	46 (30)	17 (45)	29 (24)	0.024*
HAQ, median (IQR)	1.1 (0.8–2.0)	1.4 (1.0–2.5)	1.1 (0.5–1.8)	0.014
HAQ > 1	86 (55)	25 (66)	61 (51)	0.137
Treatment groups				
csDMARD only	67 (43)	17 (45)	50 (42)	0.851*
TNFi	64 (40)	14 (37)	50 (42)	0.707*
Other bDMARD	26 (17)	7 (18)	19 (16)	0.917*
Corticosteroid use	91 (58)	24 (63)	67 (56)	0.700
Dose, mg/d, mean ± SD	3.2 ± 3.3	4.0 ± 3.3	2.8 ± 3.1	0.060
NSAID use	42 (27)	7 (18)	35 (29)	0.300

* Fisher's exact test. RA: rheumatoid arthritis; HF: heart failure; RF: rheumatoid factor; ACPA: anticitrullinated protein antibodies; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; DAS28: 28-joint Disease Activity Score; HAQ: Health Assessment Questionnaire; DMARD: disease-modifying antirheumatic drugs; csDMARD: conventional synthetic DMARD; TNFi: tumor necrosis factor inhibitors; bDMARD: biological DMARD; NSAID: nonsteroidal antiinflammatory drugs.

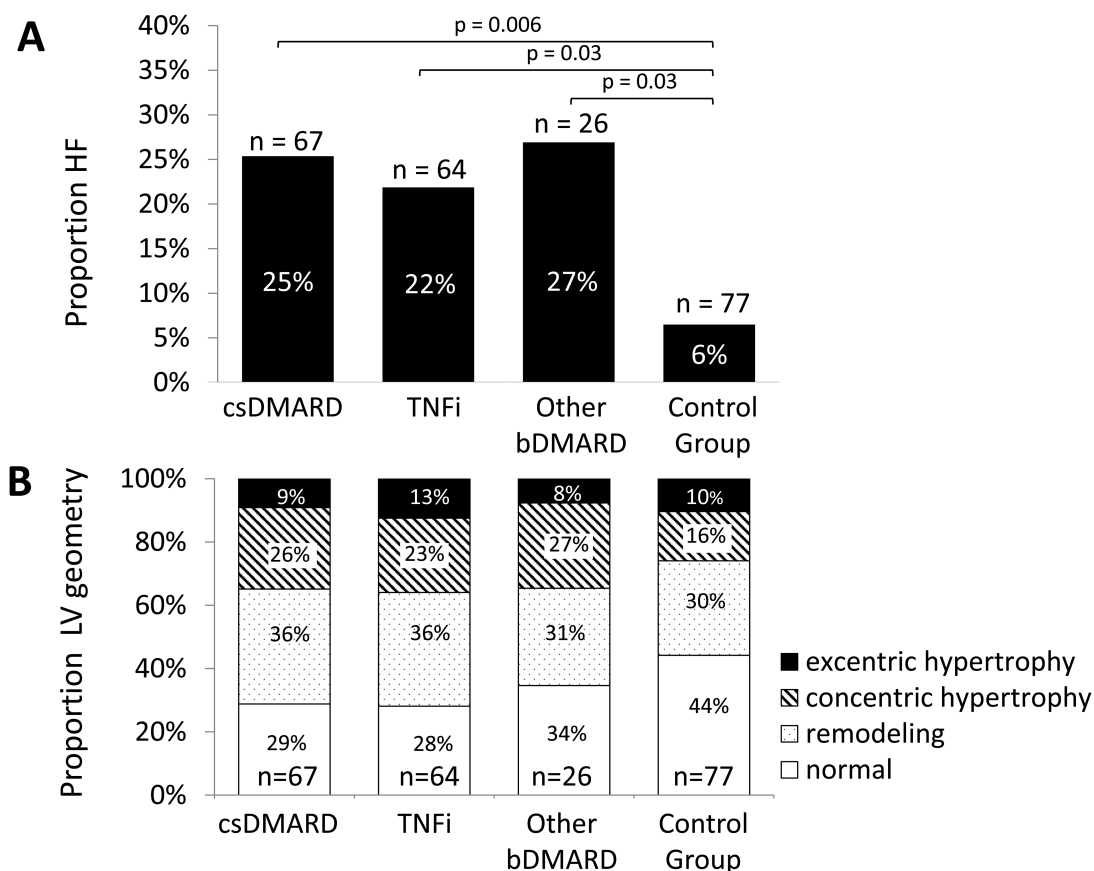


Figure 2. Proportion of HF (A) and different LV geometry (B) depending on different therapies (csDMARD, TNFi, and other bDMARD) compared with control group. HF: heart failure; LV: left ventricular; DMARD: disease-modifying antirheumatic drugs; csDMARD: conventional synthetic DMARD; TNFi: tumor necrosis factor inhibitors; bDMARD: biological DMARD.

Persistently active disease despite therapy (DAS28 \geq 2.6) was significantly more frequent in patients with HF (Table 2). Accordingly, the proportion of HF rose from 13% in remission to 30% in patients with low disease activity (DAS 2.6–3.2) and as high as 37% in patients with DAS $>$ 3.2 (Supplementary Figure 2A available online at jrheum.org).

In line with higher inflammatory activity, functional status was significantly worse in patients with RA with HF (Table 2). With increasing HAQ value, the HF proportion went up from 18% (HAQ \leq 1) to 40% (HAQ $>$ 3, $p = 0.012$; Supplementary Figure 2D available online at jrheum.org).

Finally, longstanding RA with duration $>$ 15 years was associated with higher HF prevalence compared with shorter disease history (40% vs 17%, $p = 0.003$; Supplementary Figure 2C available online at jrheum.org).

Adjusting for age, sex, and HTN, DAS \geq 2.6, RA duration $>$ 10 years, median CRP $>$ 10 mg/l, ESR $>$ 16 mm/h, and HAQ $>$ 2 remained risk factors significantly associated with the presence of HF in RA (Table 3).

HF prevalence and RA treatment. Proportions of patients with HF were comparable for patients treated with conventional synthetic disease-modifying antirheumatic drugs (csDMARD; 25%), tumor necrosis factor inhibitors (TNFi; 22%), and other biological DMARD (bDMARD; 27%), but were significantly increased compared with the control group (Figure 2). Also, additional use of nonsteroidal antiinflammatory drugs (NSAID) and steroids was comparable between patients with and without HF, despite a nonsignificant trend to a higher mean steroid dose in the HF group (Table 2).

Echocardiographic findings, LV geometry, and speckle tracking strain imaging. In a subanalysis, patients with HF had a significantly higher mean LVMI with a higher proportion of concentric hypertrophy (48% vs 17%, $p < 0.001$) compared with the non-HF subgroup, in which the majority had concentric remodeling (Table 1). Distribution of the various LV geometries was equivalent again between the different treatment groups (csDMARD, TNFi, bDMARD; Figure 2).

Interestingly, median GLS (Supplementary Figure 3,

available online at jrheum.org) was markedly impaired in patients with RA versus controls (-19.5% vs -20.4% , respectively, $p = 0.018$; Table 1). In line with our clinical findings, median GLS was significantly more impaired in patients with RA with HF compared with patients without HF (-17.2% vs -19.7% , $p < 0.001$). Using the cutoff value of -18% (determined in receiver-operator characteristic analysis), GLS was significantly associated with HF in patients with RA in univariate (OR 6.5, 95% CI 2.9–15, $p < 0.001$) and multiple logistic regression after adjustment for age, sex, and HTN (OR 4.9, 95% CI 2.0–12, $p < 0.001$; Table 3).

DISCUSSION

In our cross-sectional study, we found a surprisingly high overall prevalence of HF in patients with RA compared with controls (24% vs 6%, $p = 0.004$) mainly because of diastolic HF (23%) while HF with reduced EF was rare (1%). This is important because even diastolic HF increases mortality risk 4-fold²³ and HF in general is a major contributor to reduced lifespan in patients with RA^{3,7,10,34,35,36}.

Several previous studies have reported HF in 3.9–11.6% of patients with RA. However, these reports were based solely on clinical databases, retrospective analyses, or different diagnostic criteria for HF, mostly addressing clinically manifested congestive HF^{5,9,10,11,12} and did not use the ESC guidelines for diagnosing HF, which combine clinical or echocardiographic HF signs with NT-proBNP testing.

However, studies that have evaluated myocardial structure and function in patients with RA have found diffuse myocardial abnormalities in up to 21%³⁷ and LV diastolic dysfunction in 26–66% of patients with RA^{21,22}. Our data confirm diastolic dysfunction in 59% of patients with RA and 39% of controls.

In our cohort, clinical symptoms usually attributed to HF while part of the Framingham criteria were present in still higher rates (62% vs 31% in controls, $p < 0.001$), and dyspnea on ordinary exertion appeared as a frequent problem in our RA population (43% vs 19% in controls, $p < 0.001$). Interestingly, by using NT-proBNP, echocardiography, and

Table 3. Multiple logistic regression analysis of patients with RA with HF (n = 38) versus without HF (n = 119) for different disease variables in univariate analysis and adjusted for age, sex, and HTN in multivariate analysis.

Variables	Univariate analysis		Multiple Logistic Regression, OR Adjusted for Age, Sex, HTN*	
	OR (95% CI)	p	OR (95% CI)	p
DAS28 \geq 2.6	3.5 (1.6–8.4)	0.003	3.4 (1.3–9.8)	0.018
RA disease duration $>$ 10 yrs	3.5 (1.7–6.9)	$<$ 0.001	2.6 (1.2–5.8)	0.021
HAQ $>$ 2	2.9 (1.3–6.4)	0.001	1.3 (0.4–3.5)	0.653
CRP median $>$ 10 mg/l	2.6 (0.8–8.0)	0.097	4.8 (1.1–21)	0.037
ESR $>$ 16 mm/h	6.0 (2.8–13)	$<$ 0.001	5.4 (2.1–16)	$<$ 0.001
GLS $>$ -18%	6.5 (2.9–15)	$<$ 0.001	4.9 (2.0–12)	$<$ 0.001

* Results of separate logistic regression models. RA: rheumatoid arthritis; HF: heart failure; HTN: hypertension; DAS28: 28-joint Disease Activity Score; HAQ: Health Assessment Questionnaire; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; GLS: global longitudinal strain.

spirometry, HF could be ruled out in 61% of these patients and further diagnostic workup attributed the clinical symptoms to concomitant lung disease, anemia, and RA-related fatigue. Accordingly, a low PPV of dyspnea (37%) reflects the pitfall of a sole symptom-based HF diagnosis. Finally, in patients with RA, none of the clinical symptoms or signs of HF had a high PPV, and a third heart sound (PPV 50%) was still the best. In contrast, NT-proBNP was a useful tool, with high PPV (78%) for diagnosing HF despite its precondition for the ESC HF diagnosis and previous discussion about a possibly reduced specificity in patients with RA²². Of the 49 patients with NT-proBNP > 220 pg/ml, only 4 had neither HF symptoms nor diastolic dysfunction; 6 patients were additionally symptomatic for HF, but were lacking echocardiographic abnormalities; and 1 patient had additional diastolic dysfunction, but was clinically asymptomatic. The PPV of NT-proBNP in control subjects (56%) was worse than in patients with RA.

While some of the traditional risk factors were comparable with controls (i.e., hypercholesterolemia, diabetes, smoking), others such as rate of obesity and pack-years of smoking were significantly overexpressed in patients with RA. HTN, which is one of the major contributors to diastolic HF, was considerably frequent in our RA cohort (59% vs 40% in controls) and again significantly increased in the subgroup of patients with HF (84%). However, these data are comparable with reported prevalence rates of HTN in RA^{20,38,39,40}.

Nearly half of our patients with HF (48%) had increased LVMI, with concentric hypertrophy as an often-seen consequence of HTN. In patients without HF, the proportion with concentric hypertrophy was similar to controls (17% vs 16%) and concentric remodeling without hypertrophy was predominant (39% vs 30%), confirming the findings by others^{41,42}. Nevertheless, reports of ventricular geometry are heterogeneous and include predominant LV hypertrophy^{38,43}, as well as findings of reduced LVMI and concentric remodeling in patients with RA¹⁹. Variations of imaging techniques (echocardiography, MRI) may contribute to these different results.

In 2-dimensional, speckle-tracking echocardiography, we found significantly impaired GLS in patients with diastolic HF. Because of the helical structure of the cardiac ventricular anatomy, this finding reflects abnormal myocardial function at the subendocardial level, which is most susceptible to the deleterious effects of interstitial fibrosis, and is suggested as a putative cause of diastolic dysfunction in RA. Such predominantly subendocardial LV interstitial fibrosis with impaired GLS and diastolic dysfunction has been formerly demonstrated in CAD, HTN, diabetes, and obesity⁴⁴, and was related to metabolic, inflammatory, and hormonal changes resulting in perivascular fibrosis and increased collagen deposition⁴⁵. The pathogenesis of LV interstitial fibrosis in patients with HTN has been associated with microvascular abnormalities, hypertrophy, and altered renin-angiotensin-aldosterone system⁴⁶.

In this respect, impaired subendocardial function found in our patients might be a result of both increased prevalence of obesity and HTN, as well as chronic inflammatory processes.

Systemic inflammatory activity itself is an additional proven independent CV risk factor because it (1) is involved in the different stages of atherogenesis⁴⁷, (2) aggravates traditional CV risk factors⁸, and (3) is found to be associated with distinct myocardial abnormalities, e.g., LV hypertrophy^{37,43}. In our study, active RA and increased inflammatory markers were shown to be significant independent risk factors of HF (DAS28 \geq 2.6: OR 3.4, ESR > 16 mm/h: OR 5.4, CRP > 10 mg/dl: OR 4.8), which supports the validity of our results.

Our findings demonstrate that, compared with controls, HF prevalence in patients with RA was doubled in remission, yet increased 4- to 6-fold in active disease. Therefore, targeted treatment of inflammation and RA activity until reaching remission (as well as additionally addressing traditional CV risk factors) appears to be highly important in avoiding the development of HF in patients with RA, possibly irrespective of the chosen therapy regimen.

The influence of bDMARD or csDMARD on HF in RA is still under investigation^{39,48,49}. TNFi may reduce CV events in patients with RA⁵⁰, and a study found that TNFi was not associated with an increased risk of hospital admissions for incident HF compared with csDMARD³⁹. We found no suggestion that TNFi increased the prevalence of HF in our patients with RA. In addition, concomitant use of steroids and NSAID was not significantly different in patients with and without HF.

In this context, further evaluation is required as to whether HF, particularly diastolic HF, itself may contribute to the ongoing inflammation by increased TNF- α expression.

One strength of our study is that it presents data on an unselected community-based RA cohort of 157 patients from a single center. Based on extensive differential diagnostics, our results provide interesting and clinically relevant insights into the echocardiographic structure and prevalence of HF in patients with RA. A followup study in this cohort is warranted and under way.

Limitations of our study include recruitment of control persons. Although they were recruited per random and only known rheumatic diseases were excluded, they were all present or former white-collar employees, whereas patients with RA also included blue-collar workers, which might result in yet higher CV risk. It would have been interesting to compare our findings with a large epidemiologic control cohort. However, this was limited by the intense diagnostic workup of our study participants and the used diagnostic guidelines.

An important consideration in our study is its cross-sectional design, which collects data at a specific timepoint rather than in a longitudinal manner, and could thus influence the categorization of whether patients have persistently active or inactive RA. However, as we follow targeted

treatment regimens in all patients with RA, we achieve early remission in many cases. Patients, who persisted in low or moderate disease activity, usually did so for longer periods, despite different therapies and close followup, giving the DAS28 of study entry more than temporary account. In addition, we found comparable effects of single CRP values at study entry and the median of CRP values of the previous 24 months on HF prevalence. Finally, HF prevalence correlated with increasing HAQ that can be seen as a product of high disease activity over a long period of time.

HF classified as NYHA > 2 is still a contraindication for most of the TNFi. We therefore have to consider bias of indication when comparing HF rates in different treatment groups. Yet, we did not exclude any outpatients with dyspnea on exertion (NYHA 2–3) from prescription of TNFi, since we found no worsening in our previous pilot study. Individuals with HF at NYHA stage 4 usually require hospital admission and would have missed study recruitment for both RA and control cohort.

Combining clinical diagnostics with echocardiography and NT-proBNP measurement according to the ESC guidelines revealed that an unexpected one-fourth of all patients with RA had diastolic HF, predominantly associated with concentric hypertrophy and reduced longitudinal strain. Increased disease activity (DAS28) and elevated inflammatory markers (CRP, ESR) were independent risk factors for HF, and the prevalence of HF was doubled in remission, yet increased 4- to 6-fold in active RA, irrespective of treatment type. Therefore, targeted treatment of inflammation and RA activity until reaching remission (as well as additionally addressing traditional CV risk factors) appears to be highly important in avoiding the development of diastolic HF and the related increased mortality in patients with RA.

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ONLINE SUPPLEMENT

Supplementary data for this article are available online at jrheum.org

REFERENCES

- Symmons DP. Epidemiology of rheumatoid arthritis: determinants of onset, persistence and outcome. *Best Pract Res Clin Rheumatol* 2002;16:707-22.
- Huscher D, Merkesdal S, Thiele K, Zeidler H, Schneider M, Zink A; German Collaborative Arthritis Centres. Cost of illness in rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and systemic lupus erythematosus in Germany. *Ann Rheum Dis* 2006;65:1175-83.
- Solomon DH, Karlson EW, Rimm EB, Cannuscio CC, Mandl LA, Manson JE, et al. Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis. *Circulation* 2003;107:1303-7.
- Solomon DH, Goodson NJ, Katz JN, Weinblatt ME, Avorn J, Setoguchi S, et al. Patterns of cardiovascular risk in rheumatoid arthritis. *Ann Rheum Dis* 2006;65:1608-12.
- Wolfe F, Michaud K. Heart failure in rheumatoid arthritis: rates, predictors, and the effect of anti-tumor necrosis factor therapy. *Am J Med* 2004;116:305-11.
- Crowson CS, Nicola PJ, Kremers HM, O'Fallon WM, Therneau TM, Jacobsen SJ, et al. How much of the increased incidence of heart failure in rheumatoid arthritis is attributable to traditional cardiovascular risk factors and ischemic heart disease? *Arthritis Rheum* 2005;52:3039-44.
- Nicola PJ, Crowson CS, Maradit-Kremers H, Ballman KV, Roger VL, Jacobsen SJ, et al. Contribution of congestive heart failure and ischemic heart disease to excess mortality in rheumatoid arthritis. *Arthritis Rheum* 2006;54:60-7.
- Peters MJ, Symmons DP, McCarey D, Dijkmans BA, Nicola P, Kvien TK, et al. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. *Ann Rheum Dis* 2010;69:325-31.
- Mutru O, Laakso M, Isomäki H, Koota K. Cardiovascular mortality in patients with rheumatoid arthritis. *Cardiology* 1989;76:71-7.
- Wolfe F, Freundlich B, Straus WL. Increase in cardiovascular and cerebrovascular disease prevalence in rheumatoid arthritis. *J Rheumatol* 2003;30:36-40.
- Nicola PJ, Maradit-Kremers H, Roger VL, Jacobsen SJ, Crowson CS, Ballman KV, et al. The risk of congestive heart failure in rheumatoid arthritis: A population-based study over 46 years. *Arthritis Rheum* 2005;52:412-20.
- Giles JT, Fernandes V, Lima JA, Bathon JM. Myocardial dysfunction in rheumatoid arthritis: epidemiology and pathogenesis. *Arthritis Res Ther* 2005;7:195-207.
- Dawson JK, Goodson NG, Graham DR, Lynch MP. Raised pulmonary artery pressures measured with Doppler echocardiography in rheumatoid arthritis patients. *Rheumatology* 2000;39:1320-5.
- Voskuyl AE. The heart and cardiovascular manifestations in rheumatoid arthritis. *Rheumatology* 2006;45 Suppl 4:iv4-7.
- Davis JM 3rd, Roger VL, Crowson CS, Kremers HM, Therneau TM, Gabriel SE. The presentation and outcome of heart failure in patients with rheumatoid arthritis differs from that in the general population. *Arthritis Rheum* 2008;58:2603-11.
- Giles JT, Malayeri AA, Fernandes V, Post W, Blumenthal RS, Bluemke D, et al. Left ventricular structure and function in patients with rheumatoid arthritis, as assessed by cardiac magnetic resonance imaging. *Arthritis Rheum* 2010;62:940-51.
- Mustonen J, Laakso M, Hirvonen T, Mutru O, Pirnes M, Vainio P, et al. Abnormalities in left ventricular diastolic function in male patients with rheumatoid arthritis without clinically evident cardiovascular disease. *Eur J Clin Invest* 1993;23:246-53.
- Corrao S, Salli L, Arnone S, Scaglione R, Pinto A, Licata G. Echo-Doppler left ventricular filling abnormalities in patients with rheumatoid arthritis without clinically evident cardiovascular disease. *Eur J Clin Invest* 1996;26:293-7.
- Myasoedova E, Davis JM 3rd, Crowson CS, Roger VL, Karon BL, Borgeson DD, et al. Brief report: rheumatoid arthritis is associated with left ventricular concentric remodeling: results of a population-based cross-sectional study. *Arthritis Rheum* 2013;65:1713-8.
- Aslam F, Bandali SJ, Khan NA, Alam M. Diastolic dysfunction in rheumatoid arthritis: a meta-analysis and systematic review. *Arthritis Care Res* 2013;65:534-43.
- Crowson CS, Myasoedova E, Davis JM 3rd, Roger VL, Karon BL, Borgeson D, et al. Use of B-type natriuretic peptide as a screening tool for left ventricular diastolic dysfunction in rheumatoid arthritis

- patients without clinical cardiovascular disease. *Arthritis Care Res* 2011;63:729-34.
22. Gonzalez-Juanatey C, Testa A, Garcia-Castelo A, Garcia-Porrúa C, Llorca J, Ollier WE, et al. Echocardiographic and Doppler findings in long-term treated rheumatoid arthritis patients without clinically evident cardiovascular disease. *Semin Arthritis Rheum* 2004;33:231-8.
 23. Vasan RS, Larson MG, Benjamin EJ, Evans JC, Reiss CK, Levy D. Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction: Prevalence and mortality in a population-based cohort. *J Am Coll Cardiol* 1999;33:1948-55.
 24. Roger VL, Weston SA, Redfield MM, Hellermann-Homan JP, Killian J, Yawn BP, et al. Trends in heart failure incidence and survival in a community-based population. *JAMA* 2004;292:344-50.
 25. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med* 2006;355:251-9.
 26. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, et al; ESC Committee for Practice Guidelines (CPG). ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur Heart J* 2008;29:2388-442.
 27. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, et al; ESC Committee for Practice Guidelines. 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;14:803-69.
 28. Wells G, Becker JC, Teng J, Dougados M, Schiff M, Smolen J, et al. Validation of the 28-joint Disease Activity Score (DAS28) and European League Against Rheumatism response criteria based on C-reactive protein against disease progression in patients with rheumatoid arthritis, and comparison with the DAS28 based on erythrocyte sedimentation rate. *Ann Rheum Dis* 2008;68:954-60.
 29. Felson DT, Smolen JS, Wells G, Zhang B, van Tuyl LH, Funovits J, et al. American College of Rheumatology/European League against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. *Arthritis Rheum* 2011;63:573-86.
 30. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. *Arthritis Rheum* 1980;23:137-45.
 31. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al; Chamber Quantification Writing Group; American Society of Echocardiography's Guidelines and Standards Committee; European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005;18:1440-63.
 32. 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;10:165-93.
 33. Paulus WJ, Tschöpe C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE, et al. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. *Eur Heart J* 2007;28:2539-50.
 34. Goodson N, Symmons D. Rheumatoid arthritis in women: still associated with an increased mortality. *Ann Rheum Dis* 2002;61:955-6.
 35. Maradit-Kremers H, Nicola PJ, Crowson CS, Ballman KV, Gabriel SE. Cardiovascular death in rheumatoid arthritis: a population-based study. *Arthritis Rheum* 2005;52:722-32.
 36. Kitas GD, Gabriel SE. Cardiovascular disease in rheumatoid arthritis: state of the art and future perspectives. *Ann Rheum Dis* 2011;70:8-14.
 37. Koivuniemi R, Paimela L, Suomalainen R, Leirisalo-Repo M. Cardiovascular diseases in patients with rheumatoid arthritis. *Scand J Rheumatol* 2013;42:131-5.
 38. Rudominer RL, Roman MJ, Devereux RB, Paget SA, Schwartz JE, Lockshin MD, et al. Rheumatoid arthritis is independently associated with increased left ventricular mass but not reduced ejection fraction. *Arthritis Rheum* 2009;60:22-9.
 39. Solomon DH, Rassen JA, Kuriya B, Chen L, Harrold LR, Graham DJ, et al. Heart failure risk among patients with rheumatoid arthritis starting a TNF antagonist. *Ann Rheum Dis* 2013;72:1813-8.
 40. Garza-García C, Rocío SS, Orea-Tejeda A, Castillo-Martínez L, Eduardo C, López-Campos JL, et al. Risk factors for asymptomatic ventricular dysfunction in rheumatoid arthritis patients. *ISRN Cardiol* 2013;2013:635439.
 41. Meune C, Wahbi K, Assous N, Weber S, Kahan A, Allanore Y. Myocardial dysfunction in rheumatoid arthritis: a controlled tissue-Doppler echocardiography study. *J Rheumatol* 2007; 34:2005-9.
 42. Guler H, Seyfeli E, Sahin G, Duru M, Akgul F, Saglam H, et al. P wave dispersion in patients with rheumatoid arthritis: its relation with clinical and echocardiographic parameters. *Rheumatol Int* 2007;27:813-8.
 43. Mavrogeni S, Karabela G, Stavropoulos E, Gialafos E, Sfendouraki E, Kyrou L, et al. Imaging patterns of heart failure in rheumatoid arthritis evaluated by cardiovascular magnetic resonance. *Int J Cardiol* 2013;168:4333-5.
 44. Geyer H, Caracciolo G, Abe H, Wilansky S, Carej S, Gentile F, et al. Assessment of myocardial mechanics using speckle tracking echocardiography: fundamentals and clinical applications. *J Am Soc Echocardiogr* 2010;23:351-69.
 45. Horwich TB, Fonarow GC. Glucose, obesity, metabolic syndrome, and diabetes relevance to incidence of heart failure. *J Am Coll Cardiol* 2010;55:283-93.
 46. Zhong J, Basu R, Guo D, Chow FL, Byrns S, Schuster M, et al. Angiotensin-converting enzyme 2 suppresses pathological hypertrophy, myocardial fibrosis, and cardiac dysfunction. *Circulation* 2010;122:717-28.
 47. Sattar N, McCarey DW, Capell H, McInnes IB. Explaining how "high-grade" systemic inflammation accelerates vascular risk in rheumatoid arthritis. *Circulation* 2003;10:2957-63.
 48. Anker SD, Coats AJ. How to RECOVER from RENAISSANCE? The significance of the results of RECOVER, RENAISSANCE, RENEWAL and ATTACH. *Int J Cardiol* 2002;86:123-30.
 49. Listing J, Strangfeld A, Kekow J, Schneider M, Kapelle A, Wassenberg S, et al. Does tumor necrosis factor alpha inhibition promote or prevent heart failure in patients with rheumatoid arthritis? *Arthritis Rheum* 2008;58:667-77.
 50. Jacobsson LT, Turesson C, Gülfe A, Kapetanovic MC, Petersson IF, Saxne T, et al. Treatment with tumor necrosis factor blockers is associated with a lower incidence of first cardiovascular events in patients with rheumatoid arthritis. *J Rheumatol* 2005;32:1213-8.