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Original Article

Preclinical cardiac organ damage during statin treatment in patients with inflammatory joint diseases: the RORA-AS statin intervention study

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Abstract

Objective. Statin treatment has been associated with reduction in blood pressure and arterial stiffness in patients with inflammatory joint diseases (IJD). We tested whether statin treatment also was associated with regression of preclinical cardiac organ damage in IJD patients.

Methods. Echocardiography was performed in 84 IJD patients (52 RA, 20 ankylosing spondylitis, 12 psoriatric arthritis, mean age 61 (9) years, 63% women) without known cardiovascular disease before and after 18 months of rosuvastatin treatment. Preclinical cardiac organ damage was identified by echocardiography as presence of left ventricular (LV) hypertrophy, LV concentric geometry, increased LV chamber size and/or dilated left atrium.

Results. At baseline, hypertension was present in 63%, and 36% used biologic DMARDs (bDMARDs). Preclinical cardiac organ damage was not influenced by rosuvastatin treatment (44% at baseline *vs* 50% at follow-up, $P = 0.42$). In uni- and multivariable logistic regression analyses, risk of preclinical cardiac organ damage at follow-up was increased by higher baseline body mass index [odds ratio (OR) 1.3, 95% CI: 1.1, 1.5, $P = 0.01$] and presence of preclinical cardiac organ damage at baseline (OR 6.4, 95% CI: 2.2, 18.5, $P = 0.001$) and reduced by use of bDMARDs at follow-up (OR 0.3, 95% CI: 0.1, 0.9, $P = 0.03$).

Conclusion. Rosuvastatin treatment was not associated with a reduction in preclinical cardiac organ damage in IJD patients after 18 months of treatment. However, use of bDMARDS at follow-up was associated with lower risk of preclinical cardiac organ damage at study end, pointing to a possible protective cardiac effect of bDMARDs in IJD patients.

ClinicalTrials.gov: https://clinicaltrials.gov/NCT01389388

Key words: inflammatory joint diseases, rosuvastatin, preclinical cardiac organ damage, echocardiography

CLINICAL SCIENCE

Rheumatology key messages

- Preclinical cardiac organ damage at baseline was associated with higher risk of preclinical cardiac organ damage at follow-up.
- Statin treatment did not reduce risk of preclinical cardiac organ damage.
- Use of biologic DMARDs was associated with a lesser risk of developing preclinical cardiac organ damage.

Introduction

Patients with inflammatory joint diseases (IJD) have a higher risk of developing cardiovascular disease (CVD) compared with the general population [1], which is related to a combination of an increased burden of traditional CVD risk factors and inflammation [2, 3]. Clinical CVD is preceded by structural cardiac abnormalities referred to as preclinical cardiac organ damage [4]. Presence of preclinical cardiac organ damage is associated with high risk of subsequent clinical CVD including coronary artery disease, heart failure and atrial

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fibrillation, but is potentially reversible [4, 5]. Having IJD is an independent risk factor for development of preclinical cardiac organ damage [6–8], but little is known about the reversibility of cardiac organ damage in this population. However, recent studies in obese patients have suggested that low-grade inflammation is associated with lack of regression of preclinical cardiac organ damage [9, 10]. Statin treatment has anti-inflammatory properties, but inconsistent effects of statin treatment on preclinical cardiac organ damage has been reported in different studies [11–14]. We have previously demonstrated in the ROsuvastatin in RA, Ankylosing Spondylitis and other inflammatory joint diseases (RORA-AS) study that long-term statin treatment was associated with reduction in carotid atherosclerosis, arterial stiffness, blood pressure and improved endothelial function measured by flow-mediated dilatation in patients with IJD [15–17]. Both higher blood pressure and arterial stiffness predispose to the development of preclinical cardiac organ damage [5, 18], but it is not known whether statin treatment is associated with a favourable reduction in preclinical cardiac organ damage in IJD patients. Thus, the aim of the present study was to assess whether rosuvastatin treatment was associated with regression of preclinical cardiac organ damage in IJD patients after 18 months of treatment.

Methods

Patient population and study design

This prospectively planned sub-study of the RORA-AS study was performed at the Preventive Cardio-Rheuma Clinic at the Department of Rheumatology, Diakonhjemmet Hospital in Oslo, Norway from January 2010 to August 2013. Details of the study design have been published previously [15, 16]. In short, statin-naïve patients aged 35–80 years referred to the Preventive Cardio-Rheuma Clinic at Diakonhjemmet Hospital were invited to participate in the RORA-AS study if they had asymptomatic carotid artery plaque(s) and no contraindication to statin therapy. Rosuvastatin treatment was initiated with a 20 mg dose and titrated to a maximum of 40 mg once daily if the treatment goal for low-density lipoprotein (LDL) cholesterol $\leq$1.8 mmol/l was not obtained [16]. In total 96 patients completed follow-up and 62% reached the LDL cholesterol goal [16]. For the present sub-study participants were excluded if they had established CVD ($n = 9$) defined as previous myocardial infarction, percutaneous coronary intervention procedure, cardiac surgery, stroke, or transient ischaemic attack, or missing echocardiograms at baseline or follow-up ($n = 3$). Thus, the present sub-study consisted of 84 (88%) patients.

All participants signed an informed consent according to the Declaration of Helsinki, and the research protocol was approved by the Regional Committee for Medical and Health Research Ethics (Region South East) and performed according to good clinical practice. The ClinicalTrials.gov identifier is NCT01389388.

Cardiovascular risk factors

CVD risk factors including smoking status, diabetes, medication history and presence of established CVD was recorded using a standardized questionnaire. The biochemical laboratory at Diakonhjemmet Hospital (European Standard accredited 2009) measured levels of total cholesterol and CRP by routine procedures using a Cobas 600 analyser [16]. LDL cholesterol was calculated as described by Friedewald *et al.* [19]. The ESR was analysed using the Westergren method. Blood pressure was measured following the European Society of Hypertension guidelines [4], using OMRON M7 apparatus (Kyoto, Japan). Hypertension was defined as history of hypertension, use of antihypertensive medication or elevated blood pressure $\geq$140/90 mmHg at the baseline clinic visit. Antihypertensive treatment was initiated as indicated by clinical practice during the study period. Body mass index was calculated as body weight in kg divided by the square of height in meters. Overweight was defined as a body mass index of 25.0–29.9 kg/m^2. Obesity was defined as a body mass index $\geq$30 kg/m^2. Disease activity was measured by the DAS in 28 joints [20].

Echocardiography

All transthoracic echocardiograms were performed following a standardized protocol on a Vivid 7 scanner (GE Vingmed Ultrasound, Horten, Norway). Images were stored digitally on compact discs and forwarded for expert interpretation at the Bergen Echocardiography Core Laboratory at the University of Bergen, Bergen, Norway. Offline digital workstations equipped with Image Arena software version 4.6 (Tom Tec Imaging Systems GmbH, Unterschleissheim, Germany) were used. All examinations were read by one investigator (H.M.) and intraobserver variability was assessed in 20 randomly selected patients by repeated analysis on the same cine loop. Quantitative echocardiography was performed following the joint European Association of Echocardiography and American Society of Echocardiography guidelines [21]. Left ventricular (LV) mass was indexed for height$^{2.7}$ and LV hypertrophy was defined by sex-specific cut-offs as LV mass index $>$47 g/m$^{2.7}$ in women and $>$50 g/m$^{2.7}$ in men [4, 22]. Concentric LV geometry was considered present if the relative wall thickness (LV wall thickness/LV chamber diameter ratio) was $\geq$0.43 [4, 5]. Left atrial (LA) dilatation was defined as LA end-systolic volume indexed for height^2 $>$16.5 ml/m^2 in women and $>$18.5 ml/m^2 in men [4, 23]. LV chamber size was considered increased if the LV end-diastolic diameter/height exceeded 3.4 (cm/m) in men and $>$3.3 (cm/m) in women [4]. Preclinical cardiac organ damage was defined as any presence of LV hypertrophy, LV concentric geometry, increased LV chamber size and/or dilated LA in accordance with current

guidelines from the European Society of Cardiology/ European Society of Hypertension [4].

Statistics

The statistical analyses were performed using IBM SPSS Statistics version 24.0 (IBM Corp., Armonk, NY, USA). Continuous variables are expressed as mean (S.D.). Categorical variables are presented as numbers and percentages. Non-normally distributed variables (CRP) were reported as median and interquartile range, and log transformed before comparisons in uni- and multivariable analyses. Diagnostic groups were compared using one-way analysis of variance (ANOVA). Student's paired-sample *t*-test or McNemar's test was used when comparing continuous or categorical variables at baseline and follow-up, as appropriate. Predictors and covariables of cardiac organ damage were identified in multivariable logistic regression analyses and results are reported as odds ratios (OR) with 95% CIs. Reproducibility of echocardiographic measurements was tested by the intraclass correlation coefficient of LV mass. A two-tailed *P*-value of <0.05 was considered statistically significant in all analyses.

Results

Clinical characteristics at baseline and follow-up

The majority of the patients had RA (62%), while 24% had ankylosing spondylitis (AS) and 14% had psoriatic arthritis (PsA). Mean age in the total study population was 61 (9) years and 63% were women. Except for the expected sex difference between the individual IJD groups ($P = 0.01$) and a borderline significant difference in the prevalence of obesity ($P = 0.05$), prevalence of CVD risk factors or IJD disease duration did not differ between the groups at baseline (Table 1). The prevalence of hypertension was 63% at baseline in the total study population, and neither the prevalence of hypertension nor the prevalence of antihypertensive treatment differed between groups (Tables 1 and 2).

At baseline 64% of the patients used synthetic DMARDs (sDMARDs) and 36% used biologic DMARDs (bDMARDs) (Table 2). Use of sDMARDs was more common among RA and PsA patients ($P = 0.001$), while use of bDMARDs did not differ between groups (Table 1). A similar proportion of patients used NSAIDs, while more of the RA patients used prednisolone compared with the other patient groups ($P = 0.04$) (Table 1). The proportion of patients using prednisolone was similar between patients with increased *vs* those with normal body mass index (25% *vs* 31%, $P = 0.53$).

At follow-up, blood pressure and total cholesterol had decreased significantly ($P < 0.001$), while body mass index had increased slightly ($P = 0.02$) (Table 2). The proportion of patients on antihypertensive treatment had increased by 19% ($P < 0.001$) (Table 2).

Preclinical cardiac organ damage at baseline and follow-up

In the total study population, preclinical cardiac organ damage was revealed in 44% of the patients at baseline and in 50% of the patients at follow-up ($P = 0.42$) (Table 2 and Fig. 1). When comparing baseline and follow-up values in the total study population, a small increase in LA volume during follow-up was seen ($P = 0.01$, Table 2). However, there was no significant change in the combined or individual prevalences of LV hypertrophy, LV concentric geometry or dilatation of the LA or LV chamber (Table 2). The prevalence of preclinical cardiac organ damage did not differ between disease groups at follow-up (Fig. 2). The reproducibility of echocardiographic measurements was assessed for LV mass and was excellent (intraclass correlation coefficient 0.91; 95% CI: 0.75, 0.97).

Uni- and multivariable covariables of preclinical cardiac organ damage

In univariable analysis, increased risk of preclinical cardiac organ damage at follow-up was associated with higher baseline body mass index and presence of preclinical cardiac organ damage at baseline ($P < 0.01$, Table 3), while no association with sex, age, hypertension or antirheumatic treatment at baseline was found (Table 3). Higher baseline body mass index (OR 1.3, 95% CI: 1.1, 1.5, $P = 0.01$) and presence of preclinical cardiac organ damage at baseline (OR 6.4, 95% CI: 2.2, 18.5, $P = 0.001$) remained significantly associated with risk of preclinical cardiac organ damage at follow-up also in multivariable logistic regression analyses (Table 3). Use of bDMARDs at follow-up was associated with lower risk of preclinical cardiac organ damage both in uni- and in multivariable analyses at study end (OR 0.3, 95% CI: 0.1, 0.9, $P = 0.03$), Table 3). Adjusting for additional CDV risk factors, including hypertension, smoking, diabetes and serum total cholesterol at baseline, in the multivariable models did not change these results (data not shown). No significant association was found between change in antihypertensive therapy or LDL cholesterol at follow-up for the risk of preclinical cardiac organ damage at study end (Table 3).

Discussion

This is the first study to test the effect of statin treatment on the prevalence of preclinical cardiac organ damage in IJD patients. Despite the previously reported beneficial effect of rosuvastatin treatment on blood pressure, arterial stiffness and carotid plaque height in the RORA-AS study, the present sub-study revealed no effect of rosuvastatin treatment on the prevalence of preclinical cardiac organ damage after 18 months of rosuvastatin treatment. Although statin treatment is important in CVD prevention through reduction of atherosclerosis, the role of statin treatment for prevention of preclinical cardiac organ damage is less established.

Table 1 Baseline characteristics of the study population by diagnosis group

	RA (n = 52)	AS (n = 20)	PsA (n = 12)	P
Demographics				
Age, mean (S.D.), years	62 (8)	58 (9)	59 (8)	0.12
Women, n (%)	39 (75)	8 (40)	6 (50)	0.01
Disease duration, mean (S.D.), years	17 (11)	23 (11)	15 (14)	0.12
DAS28, mean (S.D.)	4.9 (4.9)	—	5.1 (4.7)	0.13
Cardiovascular risk factors				
Smoking, n (%)	9 (17)	3 (15)	3 (25)	0.76
Systolic blood pressure, mean (S.D.), mmHg	142 (21)	145 (15)	147 (24)	0.74
Diastolic blood pressure, mean (S.D.), mmHg	83 (9)	85 (9)	87 (11)	0.31
Hypertension, n (%)	31 (60)	15 (75)	7 (58)	0.45
Body mass index, mean (S.D.), kg/m^2	25.0 (3.2)	24.7 (2.4)	26.3 (3.5)	0.36
Obesity, n (%)	4 (8)	0 (0)	3 (25)	0.05
Overweight, n (%)	19 (37)	7 (35)	3 (25)	0.75
Total cholesterol, mean (S.D.), mmol/l	6.5 (1.2)	6.0 (0.8)	6.5 (1.1)	0.32
Diabetes, n (%)	4 (8)	2 (10)	1 (8)	0.95
Medication				
Anti-hypertensive treatment, n (%)	14 (27)	4 (20)	2 (17)	0.68
Prednisolone, n (%)	20 (39)	2 (10)	2 (17)	0.04
NSAIDs, n (%)	20 (39)	10 (50)	5 (42)	0.67
sDMARDs, n (%)	35 (73)	5 (28)	10 (83)	0.001
bDMARDs, n (%)	17 (35)	8 (44)	5 (42)	0.77
Inflammatory markers				
ESR, mean (S.D.), mm/hour	16 (10)	14 (10)	16 (9)	0.73
CRP, median (IQR), mg/l	3 (1, 4)	1 (1, 6)	4 (2, 6)	0.36

AS: ankylosing spondylitis; DAS28: DAS in 28 joints; bDMARD: biologic DMARD; IQR: interquartile range; PsA: psoriatic arthritis; RA: rheumatoid arthritis; sDMARD: synthetic DMARD.

Divergent results have been reported from studies assessing the impact of statin treatment on cardiac structure by echocardiography in groups of patients without IJD. In elderly hypertensive patients, pitavastatin treatment had a beneficial effect on LV diastolic function and LA structure and function [11]. Also in patients with non-ischaemic heart failure, atorvastatin treatment was associated with improvement in LV ejection fraction and LV chamber size [12], while another study in patients with hypertrophic cardiomyopathy demonstrated no effect of atorvastatin on reduction of LV mass [13]. Over 10 years of follow-up in 2389 participants free of established CVD from the Multi-Ethnic study of Atherosclerosis, a very modest association between statin use and less increase in LV mass assessed by cardiac magnetic resonance imaging was found [14].

The prevalence of preclinical cardiac organ damage was 44% at baseline in the study. This is in line with a previous study of 200 RA patients in which abnormal LV geometry was found in 58% [24]. Cardiac remodelling in patients with IJDs has also been studied in a population-based prospective cohort of 160 RA patients during 5 years of follow-up [25]. In that study, LV mass decreased among RA patients, and LA dilatation increased. In accordance with these previous results, we also found a modest increase in LA size during follow-up, although no decrease in LV mass was seen in the present IJD cohort after long term statin treatment. Of note, our IJD cohort included RA, AS and PsA patients. We have previously reported differences in LV remodelling between IJD patient groups. In particular, RA patients had more concentric LV remodelling, and AS patients more LV hypertrophy compared with controls [8, 26]. However, a reduction in preclinical cardiac organ damage was not observed in any of the individual disease groups in the present study.

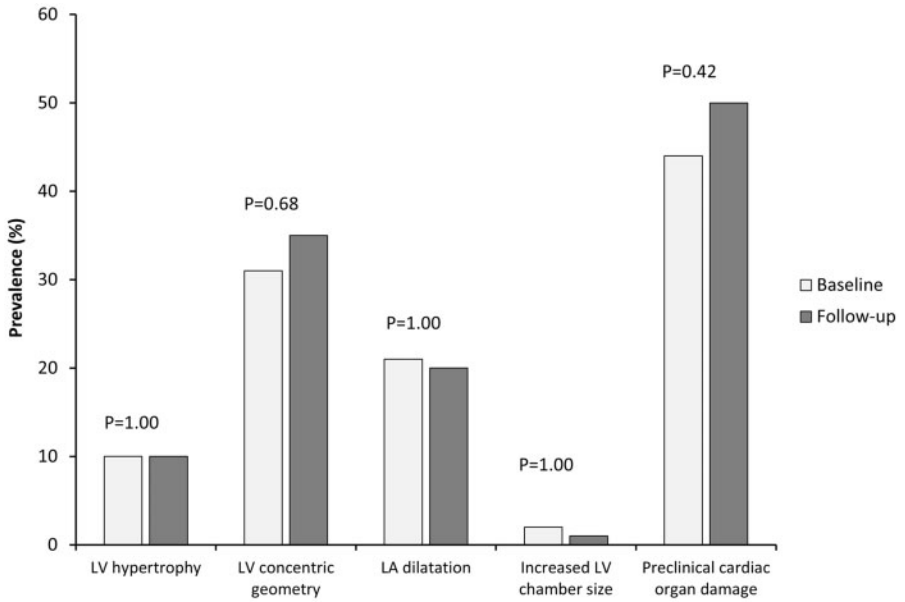
An interesting finding was that the use of bDMARDs at study end was associated with lower risk of preclinical cardiac organ damage at follow-up. This is in line with a previous report by Daïen *et al.*, demonstrating that 6 months of treatment with the TNFα inhibitor etanercept significantly reduced LV mass index in RA patients [27]. TNFα has been shown to promote LV hypertrophy in mouse models, and in TNFα knock-out mice LV hypertrophy development was attenuated [28]. TNFα inhibition has also been shown to reduce arterial stiffness and presence of atherosclerosis in IJD patients [29], factors that are both associated with unfavourable LV remodelling [30, 31]. In patients with established CVD, inhibition of IL-1β with 150 mg canakinumab led to a 15% reduction in new CVD events in the Canakinumab Antiinflammatory Thrombosis Outcome Study (CANTOS) trial [32]. There is also evidence that statin treatment in itself has anti-inflammatory effects [33]. In a small PET study in AS patients, both carotid arterial wall inflammation and CRP was reduced by statin treatment [34]. Also other studies of statin treatment in IJD patients have reported beneficial reduction in disease activity, aortic

Table 2 Changes from baseline to follow-up for the total study population

	Baseline (n = 84)	Follow-up (n = 84)	Change	P
Cardiovascular risk factors				
Smoking, *n* (%)	15 (18)	13 (16)	2 (2)	0.63
Systolic blood pressure, mean (S.D.), mmHg	144 (20)	135 (17)	−8 (19)	<0.001
Diastolic blood pressure, mean (S.D.), mmHg	84 (9)	79 (8)	−5 (10)	<0.001
Hypertension, *n* (%)	53 (63)	49 (58)	−4 (5)	0.45
Body mass index, mean (S.D.), kg/m^2	25.1 (3.1)	25.5 (3.4)	0.3 (1.3)	0.02
Total cholesterol, mean (S.D.), mmol/l	6.4 (1.1)	4.0 (0.6)	−2.4 (1.0)	<0.001
LDL cholesterol, mean (S.D.), mmol/l	4.0 (1.0)	1.7 (0.4)	−2.3(0.9)	<0.001
Diabetes, *n* (%)	7 (8)	7 (8)	0 (0)	1.00
DAS28, mean (S.D.)	4.6 (4.1)	2.8 (1.2)	−1.8 (4.0)	0.001
Medication				
Anti-hypertensive treatment, *n* (%)	20 (24)	36 (43)	16 (19)	<0.001
Prednisolone, *n* (%)	24 (29)	25 (30)	1 (1)	1.00
NSAIDs, *n* (%)	35 (42)	32 (38)	−3 (4)	0.66
sDMARDs, *n* (%)[a]	50 (64)	50 (60)	0 (0)	1.00
bDMARDs, *n* (%)[a]	30 (36)	35 (42)	5 (6)	0.27
Preclinical cardiac organ damage				
LV mass index, mean (S.D.), g/m$^{2.7}$	37.0 (10.7)	37.3 (10.0)	0.3 (7.1)	0.71
LV hypertrophy, *n* (%)	8 (10)	8 (10)	0 (0)	1.00
RWT, mean (S.D.)	0.39 (0.09)	0.40 (0.09)	0.01 (0.09)	0.58
LV concentric geometry (%)	26 (31)	29 (35)	3 (4)	0.68
Abnormal LV geometry (%)	29 (35)	34 (41)	5 (6)	0.42
LA volume index, mean (S.D.), ml/m^2 [b]	13.1 (5.4)	14.5 (5.8)	1.4 (4.7)	0.01
Dilated LA (%)[b]	17 (21)	16 (20)	−1 (−0.4)	1.00
LV end-diastolic diameter/height, mean (S.D.), (cm/m)	2.7 (0.3)	2.7 (0.3)	0.0 (0.3)	0.80
Increased LV chamber size (%)	2 (2)	1 (1)	−1 (1)	1.00
Any preclinical cardiac organ damage (%)	37 (44)	42 (50)	5 (6)	0.42

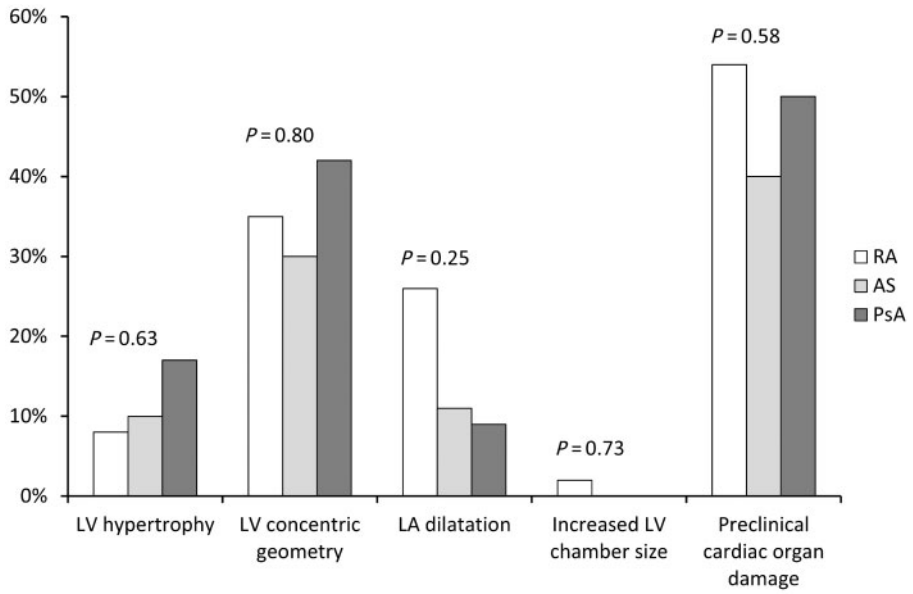
[a]Missing data in six patients at baseline. [b]Missing data in two patients at baseline and five at follow-up. DAS: DAS in 28 joints; bDMARD: biologic DMARD; LA: left atrium; LDL: low density lipoprotein; LV: left ventricle; RWT: relative wall thickness; sDMARD: synthetic DMARD.

Fig. 1 Preclinical cardiac organ damage at baseline and follow-up in total study population



LA: left atrial; LV: left ventricular.

FIG. 2 Prevalence of different types of preclinical cardiac organ damage at follow-up in individual groups of IJD



AS: ankylosing spondylitis; IJD: inflammatory joint disease; LA: left atrial; LV: left ventricular; PsA: psoriatic arthritis.

TABLE 3 Associations of preclinical cardiac organ damage at follow-up in uni- and multivariable analyses

	Unadjusted analysis		Age- and sex adjusted		Multivariable model[a]	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Baseline						
Preclinical cardiac organ damage	5.8 (2.2, 14.9)	<0.001	6.0 (2.3, 15.7)	<0.001	6.4 (2.2, 18.5)	0.001
Body mass index, kg/m^2	1.3 (1.1, 1.5)	0.002	1.3 (1.1, 1.6)	0.002	1.3 (1.1, 1.5)	0.01
Age, years	1.0 (0.9, 1.0)	0.66	1.0 (0.9, 1.0)[b]	0.65		
Male sex	0.9 (0.4, 2.2)	0.82	0.9 (0.4, 2.2)[c]	0.79		
Systolic blood pressure, mmHg	1.0 (1.0, 1.0)	0.27	1.0 (1.0, 1.0)	0.32		
Hypertension	1.1 (0.5, 2.7)	0.82	1.2 (0.5, 3.1)	0.68		
Total cholesterol, mmol/l	1.3 (0.9, 1.9)	0.20	1.3 (0.9, 1.9)	0.21		
Diabetes	0.7 (0.2, 3.5)	0.69	0.8 (0.2, 3.6)	0.72		
DAS28	1.0 (0.9, 1.1)	0.46	1.0 (0.9, 1.1)	0.49		
bDMARDs	0.5 (0.2, 1.2)	0.14	0.5 (0.2, 1.2)	0.12		
sDMARDs	2.1 (0.8, 5.5)	0.12	2.1 (0.8, 5.5)	0.13		
Prednisolone	1.6 (0.6, 4.2)	0.10	1.8 (0.6, 4.9)	0.27		
NSAIDs	0.6 (0.3, 1.5)	0.27	0.6 (0.2, 1.4)	0.25		
Antihypertensive medication	2.2 (0.8, 6.4)	0.13	2.4 (0.8, 6.8)	0.11		
Follow-up						
bDMARDs	0.3 (0.1, 0.8)	0.02	0.3 (0.1, 0.8)	0.02	0.3 (0.1, 0.9)	0.03
Antihypertensive medication	1.0 (0.4, 2.5)	0.92	1.1 (0.4, 2.7)	0.82		
Change in antihypertensive medication	0.6 (0.2, 1.7)	0.32	0.6 (0.2, 1.8)	0.35		
LDL cholesterol, mmol/l	1.6 (0.5, 5.1)	0.38	1.6 (0.5, 5.3)	0.40		

[a]Adjusted for presence of preclinical cardiac organ damage at baseline, BMI at baseline and use of bDMARDs at follow-up. [b]Adjusted for sex. [c]Adjusted for age. bDMARD: biologic DMARD; LDL: low density lipoprotein; sDMARD: synthetic DMARD; OR: odds ratio.

stiffening and improvement in endothelial function [35–37]. Likewise, in the current study disease activity improved during follow-up. We have previously shown that higher disease activity was associated with unfavourable cardiac remodelling in RA patients [8]; however, in the present study disease activity was not associated with preclinical cardiac organ damage, possibly because of a limited sample size. Taken together

these results underline the importance of inflammation for development of preclinical and clinical CVD. However, the pleiotropic anti-inflammatory effects of statin treatment are much smaller than those of bDMARDs, and we did not observe any benefit of rosuvastatin treatment on preclinical cardiac organ damage in our study.

Finally, although the prevalence of obesity was low in our IJD cohort, also higher body mass index at baseline was associated with higher risk of preclinical cardiac organ damage at follow-up. We observed a small increase in body mass index during the study, and this could have contributed to the lack of regression of preclinical cardiac organ damage during the follow-up period. These findings are consistent with recent publications showing that excess body weight is a main driver of unfavourable LV remodelling in hypertensive patients [9, 10]. In patients with IJDs, overweight and obesity are established risk factors for development of the joint disease, but also increase the severity of the disease. In addition high body weight may also be a consequence of having IJD, due to reduced physical activity [38]. Thus, maintaining normal body weight is a key factor in the management of IJD patients, and the current results underline the cardiac benefits of retaining healthy body weight in IJD patients.

There are some limitations to our study. This echocardiographic study was a prospectively planned sub-study of the RORA-AS study aiming to assess the effect of rosuvastatin treatment on carotid atherosclerosis in IJD patients [16]. The RORA-AS study was conducted without a control group receiving placebo, because it was considered unethical to deviate from guideline-recommended statin treatment of patients with established atherosclerosis in the carotid arteries. Another limitation of this study is that we compiled the three different diagnoses, RA, PsA and AS, into one single IJD group. We have previously shown that RA and AS have different LV remodelling patterns. However, the present analysis targeted preclinical cardiac organ damage as a composite of the different cardiac abnormalities previously reported in these patient groups. This approach is recommended by current European guidelines [4], and was also necessary to obtain sufficient statistical power to describe our end point. However it resulted in a wider CI for the risk of preclinical cardiac organ damage at follow-up. Furthermore, the mechanism of the CVD inflammation is comparable across the three different patient groups, which supports our approach. The low prevalence of obesity in the study limits the generalizability of the study results to populations with higher prevalence of obesity. The strengths of this study include the prospective and longitudinal design, as well as the use of an echocardiographic core laboratory as recommended in echocardiographic studies to ensure sufficient quality and reproducibility of echocardiographic measurements [39].

In conclusion, rosuvastatin treatment over 18 months did not reduce the risk of preclinical cardiac organ damage in IJD patients. In contrast, use of bDMARDs at study end was associated with lower risk of preclinical cardiac organ damage at follow-up implicating a need for future research exploring the possible cardioprotective effect of bDMARDs in patients with IJD.

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References

1 Schieir O, Tosevski C, Glazier RH, Hogg-Johnson S, Badley EM. Incident myocardial infarction associated with major types of arthritis in the general population: a systematic review and meta-analysis. Ann Rheum Dis 2017;76:1396–404.

2 Solomon DH, Reed GW, Kremer JM *et al*. Disease activity in rheumatoid arthritis and the risk of cardiovascular events. Arthritis Rheumatol 2015;67:1449–55.

3 Nikiphorou E, de Lusignan S, Mallen C *et al*. Prognostic value of comorbidity indices and lung diseases in early rheumatoid arthritis: a UK population-based study. Rheumatology (Oxford) 2020;59:1296–305.

4 Williams B, Mancia G, Spiering W *et al*. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J 2018;39:3021–104.

5 Gerdts E, Cramariuc D, de Simone G *et al*. Impact of left ventricular geometry on prognosis in hypertensive patients with left ventricular hypertrophy (the LIFE study). Eur J Echocardiogr 2008;9:809–15.

6 Midtbø H, Semb AG, Matre K *et al*. Left ventricular systolic myocardial function in ankylosing spondylitis. Arthritis Care Res (Hoboken) 2019;71:1276–83.

7 Midtbø H, Semb AG, Matre K, Kvien TK, Gerdts E. Disease activity is associated with reduced left ventricular systolic myocardial function in patients with rheumatoid arthritis. Ann Rheum Dis 2017;76:371–6.

8 Midtbø H, Gerdts E, Kvien TK *et al*. Disease activity and left ventricular structure in patients with rheumatoid arthritis. Rheumatology (Oxford) 2015;54:511–9.

9 de Simone G, Devereux RB, Izzo R *et al*. Lack of reduction of left ventricular mass in treated hypertension:

the strong heart study. J Am Heart Assoc 2013;2: e000144.

10 Lønnebakken MT, Izzo R, Mancusi C *et al*. Left ventricular hypertrophy regression during antihypertensive treatment in an outpatient clinic (the Campania Salute Network). J Am Heart Assoc 2017;6: e004152.

11 Warita S, Kawasaki M, Tanaka R *et al*. Effects of pitavastatin on cardiac structure and function and on prevention of atrial fibrillation in elderly hypertensive patients: a prospective study of 2-years' follow-up. Circ J 2012;76:2755–62.

12 Sola S, Mir MQ, Lerakis S, Tandon N, Khan BV. Atorvastatin improves left ventricular systolic function and serum markers of inflammation in nonischemic heart failure. J Am Coll Cardiol 2006;47:332–7.

13 Bauersachs J, Stork S, Kung M *et al*. HMG CoA reductase inhibition and left ventricular mass in hypertrophic cardiomyopathy: a randomized placebo-controlled pilot study. Eur J Clin Invest 2007;37:852–9.

14 Strand LN, Young RL, Bertoni AG *et al*. New statin use and left ventricular structure: estimating long-term associations in the Multi-Ethnic Study of Atherosclerosis (MESA). Pharmacoepidemiol Drug Saf 2018;27:570–80.

15 Ikdahl E, Rollefstad S, Hisdal J *et al*. Sustained improvement of arterial stiffness and blood pressure after long-term rosuvastatin treatment in patients with inflammatory joint diseases: results from the RORA-AS Study. PLoS One 2016;11:e0153440.

16 Rollefstad S, Ikdahl E, Hisdal J *et al*. Rosuvastatin-induced carotid plaque regression in patients with inflammatory joint diseases: the rosuvastatin in rheumatoid arthritis, ankylosing spondylitis and other inflammatory joint diseases study. Arthritis Rheumatol 2015;67:1718–28.

17 Ikdahl E, Hisdal J, Rollefstad S *et al*. Rosuvastatin improves endothelial function in patients with inflammatory joint diseases, longitudinal associations with atherosclerosis and arteriosclerosis: results from the RORA-AS statin intervention study. Arthritis Res Ther 2015;17:279.

18 Schillaci G, Mannarino MR, Pucci G *et al*. Age-specific relationship of aortic pulse wave velocity with left ventricular geometry and function in hypertension. Hypertension 2007;49:317–21.

19 Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972;18:499–502.

20 Klarenbeek NB, Koevoets R, van der Heijde DM *et al*. Association with joint damage and physical functioning of nine composite indices and the 2011 ACR/EULAR remission criteria in rheumatoid arthritis. Ann Rheum Dis 2011;70:1815–21.

21 Lang RM, Badano LP, Mor-Avi V *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;16:233–70.

22 Gerdts E, Izzo R, Mancusi C *et al*. Left ventricular hypertrophy offsets the sex difference in cardiovascular risk (the Campania Salute Network). Int J Cardiol 2018; 258:257–61.

23 Kuznetsova T, Haddad F, Tikhonoff V *et al*. Impact and pitfalls of scaling of left ventricular and atrial structure in population-based studies. J Hypertens 2016;34: 1186–94.

24 Myasoedova E, Davis JM 3rd, Crowson CS *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.

25 Davis JM 3rd, Lin G, Oh JK *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.

26 Midtbø H, Gerdts E, Berg IJ *et al*. Ankylosing spondylitis is associated with increased prevalence of left ventricular hypertrophy. J Rheumatol 2018;45:1249–55.

27 Daïen CI, Fesler P, du Cailar G *et al*. Etanercept normalises left ventricular mass in patients with rheumatoid arthritis. Ann Rheum Dis 2013;72:881–7.

28 Sun M, Chen M, Dawood F *et al*. Tumor necrosis factor-alpha mediates cardiac remodeling and ventricular dysfunction after pressure overload state. Circulation 2007; 115:1398–407.

29 Angel K, Provan SA, Fagerhol MK *et al*. Effect of 1-year anti-TNF-alpha therapy on aortic stiffness, carotid atherosclerosis, and calprotectin in inflammatory arthropathies: a controlled study. Am J Hypertens 2012;25: 644–50.

30 Eskerud I, Gerdts E, Larsen TH, Lønnebakken MT. Left ventricular hypertrophy contributes to Myocardial Ischemia in Non-obstructive Coronary Artery Disease (the MicroCAD study). Int J Cardiol 2019;286:1–6.

31 Lønnebakken MT, Eskerud I, Larsen TH *et al*. Impact of aortic stiffness on myocardial ischaemia in non-obstructive coronary artery disease. Open Heart 2019;6: e000981.

32 Ridker PM, Everett BM, Thuren T *et al*. Antiinflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med 2017;377:1119–31.

33 Albert MA, Danielson E, Rifai N, Ridker PM, Investigators P. Effect of statin therapy on C-reactive protein levels: the pravastatin inflammation/CRP evaluation (PRINCE): a randomized trial and cohort study. JAMA 2001;286: 64–70.

34 van der Valk FM, Bernelot Moens SJ, Verweij SL *et al*. Increased arterial wall inflammation in patients with ankylosing spondylitis is reduced by statin therapy. Ann Rheum Dis 2016;75:1848–51.

35 Maki-Petaja KM, Booth AD, Hall FC *et al*. Ezetimibe and simvastatin reduce inflammation, disease activity, and aortic stiffness and improve endothelial function in rheumatoid arthritis. J Am Coll Cardiol 2007;50:852–8.

36 Li GM, Zhao J, Li B *et al*. The anti-inflammatory effects of statins on patients with rheumatoid arthritis: a systemic review and meta-analysis of 15 randomized controlled trials. Autoimmun Rev 2018;17:215–25.

37 Wallace SM, Maki-Petaja KM, Cheriyan J *et al*. Simvastatin prevents inflammation-induced aortic stiffening and endothelial dysfunction. Br J Clin Pharmacol 2010;70:799–806.

38 McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med 2011;365:2205–19.

39 Galderisi M, Henein MY, D'hooge J *et al*. Recommendations of the European Association of Echocardiography: how to use echo-Doppler in clinical trials: different modalities for different purposes. Eur J Echocardiogr 2011;12:339–53.