Disease Activity in Ankylosing Spondylitis and Associations to Markers of Vascular Pathology and Traditional Cardiovascular Disease Risk Factors: A Cross-sectional Study

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ABSTRACT. ***Objective.*** To compare the risk of cardiovascular disease (CVD) in ankylosing spondylitis (AS) and population controls, and to examine the associations between disease activity and CVD risk.

Methods. A cross-sectional study was done of patients with AS grouped according to Ankylosing Spondylitis Disease Activity Score (ASDAS) into ASDAS-high and ASDAS-low. Markers of vascular pathology, impaired endothelial function [asymmetric dimethylarginine (ADMA)], and arterial stiffness [augmentation index (AIx) and pulse wave velocity (PWV)], and traditional CVD risk factors [blood pressure, lipids, body mass index (BMI), CVD risk scores] were compared between AS and controls as well as across ASDAS-high versus ASDAS-low versus controls using ANCOVA analyses.

Results. Altogether, 151 patients with AS and 134 controls participated. Patients had elevated ADMA (μmol/l) and AIx (%) compared to controls: mean difference (95% CI): 0.05 (0.03, 0.07), $p < 0.001$ and 2.6 (0.8, 4.3), $p = 0.01$, respectively. AIx increased with higher ASDAS level, p(trend) < 0.04. There were no significant group differences of PWV. BMI was higher in ASDAS-high compared to ASDAS-low ($p = 0.02$). Total cholesterol was lower in AS compared to controls, and lower with higher ASDAS, p(trend) = 0.02. CVD risk scores were similar across groups except for Reynolds Risk Score, where the ASDAS-high group had a significantly higher score, compared to both ASDAS-low and controls.

Conclusion. Elevated ADMA and AIx in AS support a higher CVD risk in AS. Elevated AIx and BMI in AS with high ASDAS indicate an association between disease activity and CVD risk. Lower total cholesterol in AS may contribute to underestimation of CVD risk. (First Release Feb 1 2015; J Rheumatol 2015;42:645–53; doi:10.3899/jrheum.141018)

Key Indexing Terms:
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Patients with ankylosing spondylitis (AS) have an increased risk of premature mortality, with a relative risk of about 1.5–1.8 compared to the general population, and cardiovascular disease (CVD) contributes to the increased risk[1,2,3]. Valvular disease and conduction disturbances may occur, but they accounted for only about 35% of the excess CVD mortality in a study by Lehtinen[1]. Population studies have shown that patients with AS have an increased risk of atherosclerotic CVD[4,5]. However, the importance of different mediators of the increased risk of CVD is not fully understood. In rheumatoid arthritis (RA), the development of atherosclerosis is related to both traditional CVD risk factors and RA disease manifestations[6].

Vascular pathology such as endothelial dysfunction and arterial stiffness are markers of CVD risk, but few studies have evaluated vascular pathology in AS. Asymmetric dimethylarginine (ADMA) impairs endothelium dependent vasodilation and thus endothelial function[7]. Arterial stiffness can be measured noninvasively as augmentation index (AIx) and pulse wave velocity (PWV)[8]. Both ADMA and arterial stiffness have been found to be increased in

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patients with AS compared to controls[9,10], indicating an increased CVD risk. Traditional CVD risk factors have been explored in patients with AS in several studies. Lower atherogenic lipids among patients with AS compared to controls have been reported[11]. There are conflicting results regarding the distribution of other traditional CVD risk factors such as blood pressure (BP) and body mass index (BMI), but in a metaanalysis these factors were not elevated in patients with AS[11].

Inflammation can enhance endothelial dysfunction and arterial stiffness[12,13,14,15], and in RA, disease activity has been shown to be associated with endothelial dysfunction and arterial stiffness[16,17]. Little is known about the associations between disease activity and CVD risk in AS.

The aim of our study was to compare CVD risk in AS and controls. A second aim was to assess associations between AS disease activity score (ASDAS) and CVD risk by comparing the distribution of markers of vascular pathology (impaired endothelial function and arterial stiffness) and traditional CVD risk factors between patients with high and low ASDAS and population controls.

MATERIALS AND METHODS

Design. This cross-sectional study was carried out between 2008 and 2010. The study was approved by the Regional Committee of Ethics and performed according to the Helsinki Declaration. All participants gave their written consent.

Patients and controls. All individuals in a hospital cohort of patients with AS (identified through medical records) from the Oslo area, diagnosed according to the modified New York criteria[18], were asked to participate in the study. The control group was randomly selected by Statistics Norway based on the following stratification criteria: age, sex, and residential area of the participating patients. The only exclusion criterion was a history of inflammatory rheumatic disease. The control group underwent the same examinations as the patients with AS.

Demographics and health status. Information about demographics, comorbidities (hypertension, diabetes, and CVD) and medication was initially self-reported in a questionnaire. CVD was defined as CVD with an atherosclerotic pathogenesis (angina pectoris, myocardial infarction, transitory ischemic attack, cerebrovascular infarction, or intermittent claudication). All information was later confirmed during the consultation by a cardiologist (AGS).

Disease characteristics. Symptom duration was defined from symptom onset. ASDAS and Bath AS Disease Activity Index (BASDAI) were calculated on the basis of self-reported disease activity variables and C-reactive protein (CRP) levels (ASDAS only)[19,20]. Information on HLA-B27 was obtained from the medical records.

Laboratory measurements. Blood samples were drawn after at least 4 h of fasting and the following were analyzed: erythrocyte sedimentation rate (ESR, mm/h, Westergren method), CRP (mg/l), total cholesterol (TC, mmol/l), and high-density lipoprotein cholesterol (HDL-C, mmol/l; COBAS 6000, Roche Diagnostics). Low-density lipoprotein cholesterol (LDL-C, mmol/l) was calculated using the Friedewald equation[21]. Plasma were frozen at –80°C and later analyzed for ADMA and L-arginine using high-performance liquid chromatography and precolumn derivatization with o-phthaldialdehyde (Sigma Chemicals Co.) as described in detail elsewhere[22]. The interassay coefficients of variation were < 5% for both.

Arterial stiffness. Arterial stiffness was assessed using a Sphygmocor device (AtCor), and was measured as AIx and PWV[8]. We recorded pulse waves at the radial artery, and the central pulse waves were estimated through a validated transfer factor[23], standardized to a heart rate of 75 bpm. AIx was calculated as the percentage of the pulse pressure that is augmented by wave reflection. PWV is a measure of the speed of the pulse wave through the central arteries. We recorded the time for the pulse to travel to the femoral and carotid artery with a simultaneously recorded echocardiogram and measured the distance between these sites. The PWV was calculated as distance/time (m/s). The participants fasted for at least 4 h and rested in a supine position at least 5 min before the examination. Repeated recordings were made for each patient until obtaining measurements of high quality, and the mean value of these was calculated.

Traditional CVD risk factors. Weight and height were measured and BMI was calculated (kg/m^2). Brachial BP was measured after at least 5 min of supine rest using the OMRON M7. Several measurements were performed until 2 differed by ≤ 5 mm Hg in both systolic and diastolic pressure, and the average of these 2 measurements was calculated.

The European Heart Score, the Framingham Risk Score, and the Reynolds Risk Score were calculated[24,25,26,27]. The European Heart Score predicts risk of fatal atherosclerotic CVD in the subsequent 10 years on the basis of age, sex, systolic BP, TC, HDL-C, and smoking habits. The cardiovascular score for high-risk countries was used[24]. The European Heart Score is designed for patients aged between 40 and 65 years[24], and individuals outside this age range were excluded. The Framingham Risk Score was calculated by the general cardiovascular disease 10-year risk score for having a CVD event on the basis of age, sex, TC, HDL-C, diabetes, smoking habits, and systolic BP (treated/untreated)[25]. The Reynolds Risk Score predicts risk of having a future heart attack, stroke, or other major heart disease in the next 10 years on the basis of age, sex, systolic BP, TC, HDL-C, CRP, and family history of premature heart attack[26,27]. Participants with established CVD and diabetes were excluded from analyses concerning CVD risk scores.

Statistical analyses. Statistical analyses were performed using SPSS version 21.0. The patients with AS were divided into subgroups (ASDAS-high/ASDAS-low) according to levels of disease activity using an established cutoff value[28]: high/very high disease activity (ASDAS score ≥ 2.1) versus inactive/moderate disease activity (ASDAS score < 2.1). Descriptive data of patients with AS, subgroups of patients with AS, and controls were compared by bivariate analyses using Student t test, Mann-Whitney U test, and chi-square test/Fisher's exact test (when the expected number of cases in 1 cell was < 5), as appropriate.

The level of markers of vascular pathology (ADMA, ratio L-arginine/ADMA, AIx, PWV) and traditional CV risk factors were compared across groups. We compared all patients with AS versus controls, as well as ASDAS-high versus ASDAS-low versus controls by ANCOVA, with markers of vascular pathology and traditional CVD risk factors as dependent variables. We calculated overall p values, p values for trend, and p values between the groups. The CVD risk scores (European Heart Score, Framingham Risk Score, and Reynolds Risk Score) had a non-normal distribution and were log-transformed. All analyses were adjusted for age and sex. Except for risk scores, analyses were also adjusted for variables considered as confounders, which were BMI (except the analyses where BMI was a dependent variable) and smoking habits. In addition, analyses were adjusted for factors with major influence on the outcome: ADMA and ratio L-arginine/ADMA were adjusted for creatinine, AIx for central mean arterial pressure (CMAP) and height, PWV for CMAP, lipids for use of statins, BP for use of antihypertensive. Residual plots were examined for all analyses. The patients with AS were also grouped according to disease activity measured by BASDAI (cutoff at 4) and CRP (cutoff at 3 mg/l), and similar analyses were performed.

RESULTS

Out of 257 patients with AS who were asked, 159 agreed to participate (respondent rate 62%). To find controls, 329 persons were asked to participate and 134 agreed (respon-

dent rate 41%). Because the maximum age of the controls was 70 years, we excluded 8 patients with AS aged > 70 years. The ASDAS score was calculated for 142 out of the 151 patients with AS because of missing BASDAI/Patient Global scores in 9 patients. ASDAS was < 2.1 in 69 patients and ≥ 2.1 in 73 patients.

Descriptive data. The demographic data, comorbidities, medications, and disease characteristics are presented in Table 1. The patients with AS were younger and used nonsteroidal antiinflammatory drugs (NSAID) and prednisolone more frequently compared to controls. As expected, the patients with AS had higher ESR and CRP. There were some differences between the AS subgroups: patients with AS with high ASDAS were older, were more often female, had longer symptom duration, and as expected, had higher levels of BASDAI, ESR, and CRP. The use of prednisolone was more frequent in the ASDAS-high group, compared to both ASDAS-low and controls. Regarding comorbidities, it is noteworthy that more patients in the ASDAS-high group had a history of CVD compared to controls [9 (12.3%) versus 7 (5.2%); p value = 0.07] as well as compared to patients in ASDAS-low group [9 (12.3%) versus 3 (3.4%); p value = 0.09], but the numbers were low and not statistically significant. The ASDAS-low and controls were similar except for younger age and more frequent use of NSAID in ASDAS-low, but unlike ASDAS-high, there were no significant differences in ESR and CRP.

Vascular pathology and traditional CVD risk factors. Table 2 shows the adjusted analyses of markers of vascular pathology and traditional CVD risk factors between AS and controls, and Figures 1 and 2 show the analyses of the ASDAS-high and ASDAS-low subgroups as well as controls (Supplementary Table S1, available online at jrheum.org). ADMA was significantly higher and the L-arginine/ADMA ratio was significantly lower in patients with AS compared to controls (Table 2), in both the high and low ASDAS patient groups (Figure 1). AIx was higher in AS than controls (Table 2), and there was a significant trend between AIx and disease activity, with significantly higher AIx for the ASDAS-high subgroup compared to controls (Figure 1). There were no differences in PWV between the groups, and additional adjustments for loss of height did not alter results.

The atherogenic lipids, TC and LDL-C, were significantly lower in patients with AS compared to controls (Table 2) with a trend toward lower lipids with higher ASDAS (Figure 2). BMI was significantly higher in ASDAS-high compared to ASDAS-low (Figure 2). There

Table 1. Characteristics of patients with ankylosing spondylitis (AS) and controls.

Characteristics	AS, n = 151			Controls, n = 134
	AS, all	AS, ASDAS ≥ 2.1, n = 73	AS, ASDAS < 2.1, n = 69	
Demographic data				
Age, years, mean (SD)	49.2 (11.1)[a]	51.4 (10.4)[d]	46.8 (11.2)[c]	52.7 (11.4)
Sex, male, n (%)	92 (60.9)	38 (52.1)[d]	49 (71.0)	78 (58.2)
Smoking, current, n (%)	30 (19.9)	17 (23.3)	10 (14.5)	30 (22.6)
Presence of comorbidities, n (%)				
Hypertension	30 (19.9)	14 (19.2)	13 (18.8)	30 (22.6)
Diabetes	8 (5.3)	5 (6.8)	2 (2.9)	4 (3.0)
CVD	12 (7.9)	9 (12.3)	3 (4.3)	7 (5.2)
Current use of medication, n (%)				
Antihypertensive	34 (22.5)	18 (24.7)	13 (18.8)	28 (20.9)
Statins	18 (11.9)	11 (15.1)	7 (10.1)	16 (11.9)
NSAID	99 (65.6)[a]	47 (64.4)[b]	46 (66.7)[c]	17 (12.8)
DMARD	24 (16.0)	12 (16.4)	10 (14.5)	NA
TNF-α inhibitors	29 (19.3)	11 (15.1)	18 (26.1)	NA
Prednisolone	12 (7.9)[a]	10 (13.7)[b,d]	1 (1.4)	3 (3.2)
Disease characteristics				
Symptom duration, yrs, mean (SD)	23.1 (10.5)	25.4 (9.9)[d]	20.3 (9.8)	NA
ASDAS, mean (SD)	2.3 (1.0)	3.0 (0.6)	1.5 (0.5)	NA
BASDAI, mean (SD)	3.7 (1.9)	4.8 (1.6)[d]	2.6 (1.3)	NA
HLA-B27–positive, n (%)	120 (95.2)	59 (96.7)	55 (94.8)	NA
ESR, mm/h, median (IQR)	17 (7–28)[a]	23 (14–33)[b,d]	11 (5–19)	8 (4–14)
CRP, mg/l, median (IQR)	3 (1–10)[a]	8 (4–18)[b,d]	2 (1–3)	1 (1–2)

Comparisons using bivariate tests as appropriate; Student t test for normally distributed data, Mann-Whitney U test for not normally distributed data, and chi-square test/Fisher's test [when expected number was < 5 for at least 1 cell in ASDAS subgroups (diabetes and prednisolone)] for counts. [a] p value < 0.05, AS, all versus controls. [b] p value < 0.05, AS, ASDAS ≥ 2.1 versus controls. [c] p value < 0.05, AS, ASDAS < 2.1 versus controls. [d] p value < 0.05, AS, ASDAS ≥ 2.1 versus AS, ASDAS < 2.1. ASDAS: AS Disease Activity Score; BASDAI: Bath AS Disease Activity Index; CRP: C-reactive protein; CVD: cardiovascular disease; DMARD: disease-modifying antirheumatic drugs; ESR: erythrocyte sedimentation rate; NSAID: nonsteroidal antiinflammatory drugs; TNF-α: tumor necrosis factor-α; IQR: interquartile range.

Table 2. Markers of vascular pathology and traditional cardiovascular risk factors in patients with ankylosing spondylitis (AS) and controls.

	AS EMM (SE)	Controls EMM (SE)	Mean Difference (95% CI)	p
Markers of vascular pathology				
ADMA, μmol/l[a]	0.54 (0.01)	0.49 (0.01)	0.05 (0.03, 0.07)	< 0.001
Ratio L-arginine/ADMA[a]	107 (2)	117 (3)	–10 (–16, –4)	0.001
AIx, %[b]	19.4 (0.7)	16.9 (0.7)	2.6 (0.8, 4.3)	0.01
PWV, m/s[c]	7.49 (0.12)	7.55 (0.12)	–0.06 (–0.35, 0.24)	0.71
Traditional CVD risk factors				
TC, mmol/l[d]	5.07 (0.11)	5.31 (0.12)	–0.24 (–0.48, –0.01)	0.04
LDL-C, mmol/l[d]	2.85 (0.10)	3.11 (0.11)	–0.26 (–0.47, –0.05)	0.02
HDL-C, mmol/l[d]	1.53 (0.05)	1.56 (0.05)	–0.03 (–0.13, 0.07)	0.54
Ratio TC/HDL-C[d]	3.59 (0.14)	3.65 (0.14)	–0.06 (–0.35, 0.23)	0.68
BMI, kg/m^2 [e]	25.2 (0.3)	25.5 (0.3)	–0.3 (–1.2, 0.6)	0.48
Brachial SBP, mmHg[f]	126 (2)	127 (2)	–1 (–5, 3)	0.68
CVD risk scores				
InEuropean Heart Score (+0.5)[g]	0.63 (0.05)	0.60 (0.05)	0.03 (–0.11, 0.17)	0.68
InFramingham Risk Score (+0.5)[h]	1.88 (0.04)	1.89 (0.04)	–0.01 (–0.13, 0.10)	0.81
InReynolds Risk Score (+0.5)[h]	1.01 (0.05)	0.96 (0.04)	0.05 (–0.07, 0.18)	0.42

Linear regression models presented with estimated marginal mean (EMM; SE) and estimated difference (95% CI). [a]Adjusted for age, sex, BMI, current smoking, creatinine. [b]Adjusted for age, sex, BMI, current smoking, CMAP, height. [c]Adjusted for age, sex, BMI, current smoking, CMAP. [d]Adjusted for age, sex, BMI, current smoking, use of statins. [e]Adjusted for age, sex, current smoking. [f]Adjusted for age, sex, BMI, current smoking, use of antihypertensive. [g]Adjusted for age, sex, and presented with geometric mean; patients with CVD, diabetes, or outside the age range 40–65 years were excluded. [h]Adjusted for age, sex, and presented with geometric mean; patients with CVD or diabetes were excluded. ADMA: asymmetric dimethylarginine; AIx: augmentation index; BMI: body mass index; CMAP: central mean arterial pressure; CVD: cardiovascular disease; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; PWV: pulse wave velocity; SBP: systolic blood pressure; TC: total cholesterol.

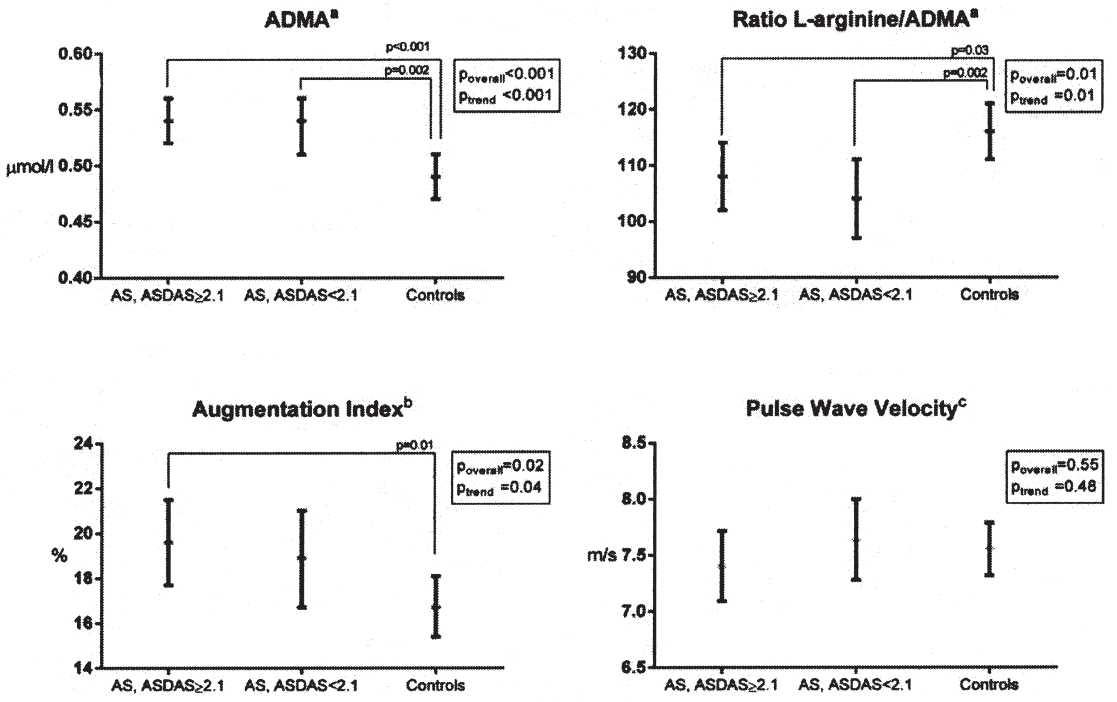

Figure 1. Markers of vascular pathology in patients with ankylosing spondylitis (AS) who have high and low ASDAS, and controls. Linear regression models presented with estimated marginal means and 95% CI. [a]Adjusted for age, sex, BMI, current smoking, and creatinine. [b]Adjusted for age, sex, BMI, current smoking, CMAP, and height. [c]Adjusted for age, sex, BMI, current smoking, and CMAP. ASDAS: AS Disease Activity Score; ADMA: asymmetric dimethylarginine; BMI: body mass index; CMAP: central mean arterial pressure.

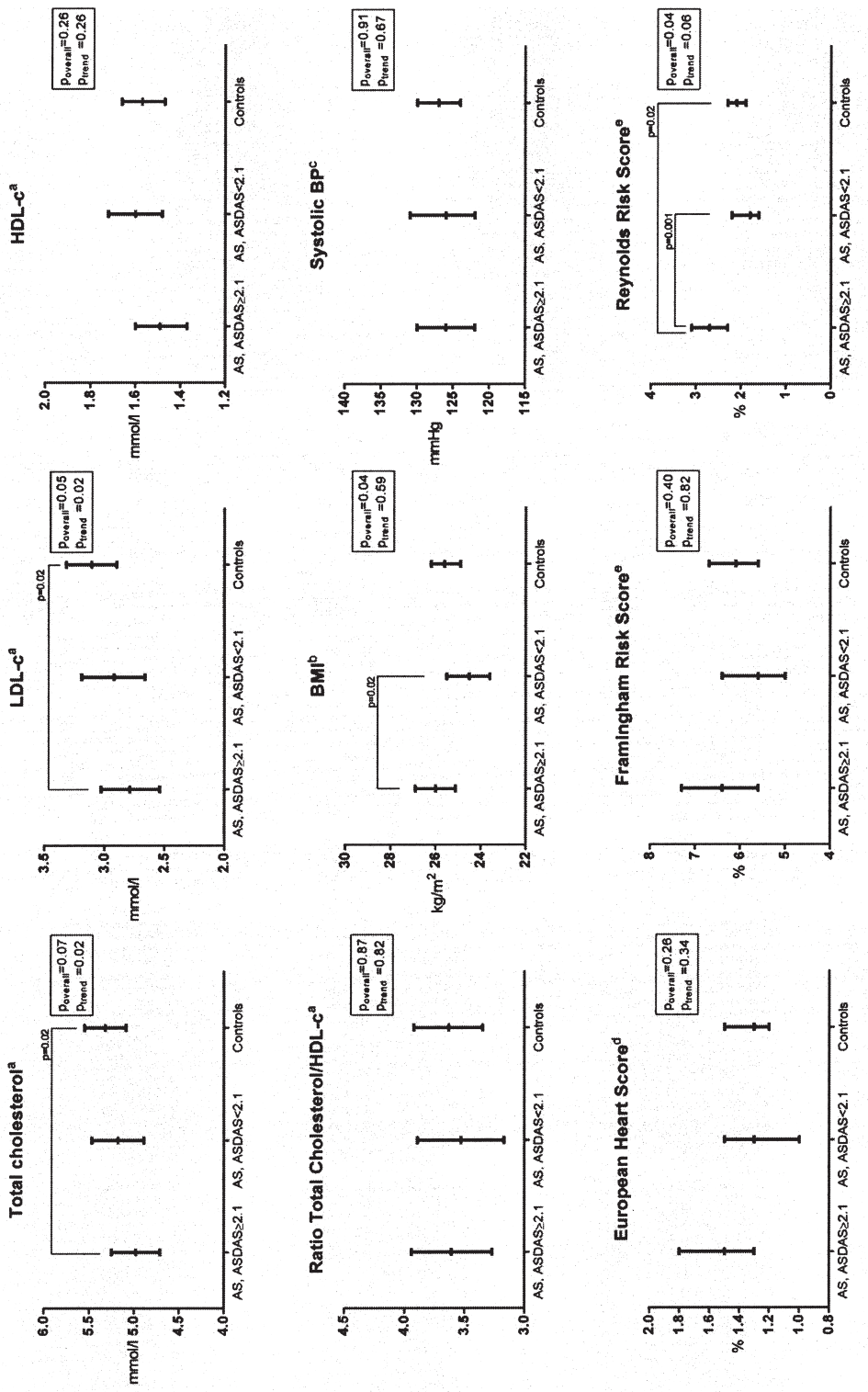

Figure 2. Traditional cardiovascular risk factors in patients with ankylosing spondylitis (AS) who have high and low ASDAS, and controls. Linear regression models presented with estimated marginal means and 95% CI. [a]Adjusted for age, sex, BMI, current smoking, and use of statins. [b]Adjusted for age, sex, current smoking. [c]Adjusted for age, sex, BMI, current smoking, and use of antihypertensive. [d]Adjusted for age and sex, and presented with geometric mean; patients with CVD, diabetes, or outside the age range 40–65 years were excluded. [e]Adjusted for age and sex, and presented with geometric mean; patients with CVD or diabetes were excluded. ASDAS: AS Disease Activity Score; BMI: body mass index; BP: blood pressure; CVD: cardiovascular disease; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol.

were no group differences in the European Heart Score and the Framingham Risk Score. The Reynolds Risk Score was significantly higher in the ASDAS-high subgroup compared to both controls and ASDAS-low (Figure 2).

The analyses with patients with AS grouped according to level of BASDAI and CRP are presented in Supplementary Tables S2 and S3 (available online at jrheum.org). The group differences were mainly the same as for the ASDAS analyses, except for the analyses of TC, LDL-C, and Reynolds Risk Score, which were similar in BASDAI-high versus low (BASDAI cutoff = 4; Supplementary Table S2).

DISCUSSION

The main findings in this cross-sectional study were that patients with AS displayed signs of vascular pathology. Patients with AS had impaired endothelial function, as assessed by ADMA, compared to controls. Arterial stiffness, measured by AIx, was higher in AS than controls, and AIx was also shown to be associated with AS disease activity, as measured by ASDAS. Traditional CVD risk factor levels in patients with AS were comparable to those of population controls but there was a trend toward lower TC and LDL-C with higher disease activity. Patients with high ASDAS had significantly higher Reynolds Risk Scores than controls and patients with low ASDAS.

ADMA impairs endothelium-dependent vasodilation and has been proposed as a risk factor of endothelial dysfunction[7], and circulating ADMA levels have been shown to predict myocardial infarction in the general population[29]. Endothelial vasoreactivity is regulated by nitric oxide (NO), which is produced from L-arginine by the enzyme NO synthetase (NOS). ADMA inhibits NO production by competing with L-arginine as a substrate for NOS[30], and the ratio of L-arginine/ADMA is suggested to be important in regulating NOS, where a high level is favorable[31]. There is evidence that ADMA is elevated in several inflammatory diseases with accelerated atherosclerosis[32]. We found increased ADMA and decreased L-arginine/ADMA ratio in patients with AS, a finding in accordance with results of previous studies[9,33,34], but we found no associations with disease activity. Elevated ADMA and L-arginine/ADMA ratio in our cohort indicate an increased CVD risk in patients with AS.

AIx and PWV are both measures of central arterial stiffness and are validated markers of CVD risk and predictors of CVD mortality[8,35]. AIx is an estimate of the augmentation of the central arterial pressure that is caused by the reflected pulse wave, and is a surrogate measure of arterial stiffness. PWV is a measure of the speed of the pulse wave through the central arteries, and a higher speed indicates stiffer arteries. We found higher AIx in AS compared to controls and a trend of increasing AIx with increasing disease activity, but no such trend was found for PWV. There are few studies examining arterial stiffness in patients with AS, all with a lower number of patients than the present study. Similar to ours, these studies have found higher arterial stiffness in AS compared to controls. Two studies found numerically but nonsignificantly higher AIx in AS[34,36]; 2 other studies found significantly higher PWV[10,37]. The latter study also evaluated correlations between disease activity and arterial stiffness, with findings of no correlation to BASDAI, ESR, or CRP. However, correlation to ASDAS was not examined[37]. We did not find any significant differences in PWV between the ASDAS groups. In patients with AS, PWV measurements may be confounded by thoracic kyphosis, a disease manifestation, which will contribute to an underestimation of the PWV[38]. In RA, there are several studies finding increased arterial stiffness compared to controls[39], and also evidence that disease activity and CRP predicts increased arterial stiffness[40]. Our finding of an association between AIx and disease activity indicates that patients with high disease activity are at highest risk of CVD, similar to findings in RA.

The lipid profile was favorable in the patients with AS compared to controls. Paradoxically, patients with AS had lower TC and LDL-C than the controls. Lower TC in AS has also been reported in a metaanalysis[11]. We found an inverse association between ASDAS and TC and LDL-C, which is in line with a study by Divecha, *et al* reporting lower TC and HDL-C in patients with AS compared to matched controls. In the Divecha, *et al* study, there were inverse correlations between TC and interleukin 6 (IL-6) as well as CRP, supporting our results[41]. In our supplementary analyses, where patients with AS were grouped according to BASDAI and CRP, there were no significant differences in TC and LDL-C between the groups in the BASDAI analyses (Supplementary Table S2, available online at jrheum.org), indicating that CRP is related to the inverse association. Two intervention studies [treatment with tumor necrosis-α (TNF-α) inhibitors] found inverse associations between disease activity and lipid levels[42,43], suggesting that the reduction of lipids was driven by the inflammatory processes. The latter study also demonstrated changes in the HDL-C composition that made HDL-C less atheroprotective in patients with elevated CRP, indicating that altered lipid function is relevant for CVD risk in patients with inflammation[43]. The predictive value of lower TC on future CVD has not been studied in AS. However, in patients with RA, Semb, *et al* found that TC did not predict CVD as strongly as in non-RA patients[44]. Despite patients with RA having lower TC than the non-RA group, their rate of CVD was higher. A similar relationship may also be true for AS, and lower TC can potentially be related to increased CVD risk.

In line with other studies[11], there were no differences in BMI between patients and controls, but in subgroup analyses, BMI was significantly higher in the ASDAS-high group compared to the ASDAS-low group, although the

differences were numerically small. An association between BMI and ASDAS in patients with AS has not been shown previously. Physical activity is an important part of the treatment for AS, and less physical activity could also be a common factor behind increased disease activity and increased BMI. Adipose tissue is an endocrine organ secreting proinflammatory adipokines, which may play relevant roles in the pathophysiology of both inflammatory diseases and CVD[45]. Adipose tissue also produces IL-6, which in turn stimulates CRP production, a component of the ASDAS score, and a known CVD risk factor[46,47]. Accordingly, there is a theoretical link between BMI, AS disease activity, and CVD risk.

We have not identified previous studies on CVD risk scores in AS. The patients with AS in this study had lower atherogenic lipids, but similar BP and smoking habits compared to the controls, indicating that factors other than the traditional CVD risk factors explain the increased risk of CVD in AS. In agreement, we found no differences in European Heart Score and Framingham Risk Score between the groups. However, the Reynolds Risk Score, which includes CRP, a measure of inflammation, was significantly higher in the ASDAS-high subgroup. In RA, Gonzalez, *et al* found that traditional CVD risk factors have a weaker association with CVD outcome than matched non-RA controls[48], and Arts, *et al* showed that established risk models generally underestimate CVD risk in RA[49]. Reynolds Risk Score may give a better estimate of the CVD risk in patients with AS, possibly because CRP is part of this calculator.

A limitation of our study is the cross-sectional design. The results are associations, and thus cannot indicate causality. We did, however, adjust for several possible confounders. The attendance rate of the control group was lower than in the patient group and a selection bias cannot be ruled out. Information about examination of CVD risk/disease was given in the information and invitation letters and this might have recruited control persons who regarded themselves at risk. This potential bias would, however, contribute to an underestimation of the differences in the markers of vascular pathology and traditional CVD risk factors between the AS group and controls, except for the TC and LDL-C in controls, which would be overestimated. The study was designed to be hypothesis generating rather than hypothesis testing, and according to this exploratory nature, a number of variables were compared without correcting for multiple comparisons, following the guideline by Bender and Lange[50]. However, it should be underscored that for this reason, the results must be interpreted with some caution.

It would also be interesting to study the effect of other factors such as HLA-B27 status, and use of NSAID, TNF-α inhibitors, and prednisolone on CVD risk. However, only a few patients were HLA-B27–negative, and accordingly this analysis could not be performed. There are differences between the groups regarding use of NSAID, TNF-α inhibitors, and prednisolone. However, the cross-sectional design makes it difficult to draw conclusions regarding use of these medications because of channeling bias and thus represents a limitation of our present study.

A strength of our AS cohort is the heterogeneous group of patients, which represents the entire disease spectrum. ASDAS mean in this cohort was 2.3, close to the 2.1 cutoff between moderate and high disease activity. The SD was 1.0, reflecting a wide range of disease activity.

We found elevated ADMA levels and increased AIx in patients with AS compared to controls, supporting an increased risk of CVD in AS. Patients with AS who had high ASDAS had higher AIx and BMI, indicating that high disease activity is associated with CVD risk. High ASDAS was associated with decreased atherogenic lipids, which may lead to an underestimation of the CVD risk. These results need to be confirmed in larger longitudinal studies.

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ONLINE SUPPLEMENT

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

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