

# Assessment of subclinical atherosclerotic cardiovascular disease in patients with ankylosing spondylitis

Erdoğan Hatipsoylu<sup>1</sup>, İlker Şengül<sup>1</sup>, Taciser Kaya\*, Altınay Göksel Karatepe\*, Seniz Akçay\*,  
Leyla Isayeva\*\*, Giray Bozkaya\*\*\*, Erhan Tatar\*\*\*\*

Department of Physical Medicine and Rehabilitation, Kahramanmaraş Afşin State Hospital; Kahramanmaraş-Turkey

<sup>1</sup>Department of Physical Medicine and Rehabilitation, Faculty of Medicine, İzmir Katip Çelebi University; İzmir-Turkey

Departments of \*Physical Medicine and Rehabilitation, \*\*Radiology, \*\*\*Biochemistry, \*\*\*\*Nephrology,  
İzmir Bozyaka Training and Research Hospital of University of Health Sciences; İzmir-Turkey

## ABSTRACT

**Objective:** The aim of the present study was to compare patients with ankylosing spondylitis (AS) with healthy controls with respect to subclinical atherosclerotic cardiovascular disease (CVD).

**Methods:** A total of 44 patients with AS with no history of CVD, diabetes mellitus, hypertension, chronic kidney disease, and lipid-lowering drug use were compared with 40 age- and sex-matched healthy controls with respect to carotid intima-media thickness (CIMT) and pulse wave velocity (PWV), which are surrogate markers of subclinical atherosclerosis. Correlation analysis was also performed to examine the association between surrogate markers and disease activity with inflammation [Ankylosing spondylitis disease activity score with C-reactive protein (ASDAS-CRP)].

**Results:** In addition to age and sex, both groups were comparable with respect to cigarette smoking, body mass index, and high-density lipoprotein cholesterol ( $p=0.425$ ,  $p=0.325$ , and  $p=0.103$ , respectively). The level of total cholesterol was significantly lower in patients with AS ( $p=0.002$ ). Nonsteroidal anti-inflammatory drug and tumor necrosis factor alpha inhibitor use ratios in patients with AS were 79.5% and 65.9%, respectively. There was no significant difference between both groups regarding PWV and CIMT ( $p=0.788$  and  $p=0.253$ , respectively). In patients with AS, there was a significant correlation between ASDAS-CRP and CIMT ( $r=0.315$ ,  $p=0.038$ ), but the correlation between ASDAS-CRP and PWV was not significant ( $r=-0.183$ ,  $p=0.234$ ).

**Conclusion:** The results of the present study could not provide sufficient evidence whether disease activity with inflammation caused subclinical atherosclerotic CVD in patients with AS without overt CVD. The increased atherosclerotic CVD risk is most probably multifactorial in patients with AS, but the extent of the contribution of disease activity with inflammation to increased atherosclerosis is controversial. (*Anatol J Cardiol* 2019; 22: 185-91)

**Keywords:** ankylosing spondylitis, carotid intima-media thickness, pulse wave velocity, subclinical cardiovascular disease

## Introduction

Cardiovascular disease (CVD) is the leading cause of death in patients with ankylosing spondylitis (AS) (1). The increased prevalence of cardiovascular (CV) morbidity and mortality in patients with AS has been attributed to AS-specific CV manifestations, traditional CVD risk factors, systemic inflammation, and nonsteroidal anti-inflammatory drug (NSAID) use (2, 3).

Although CVD has become the leading cause of death for patients with AS (1), the direct relationship between AS itself (sys-

temic inflammation) and increased atherosclerotic CVD risk is not as clear as in rheumatoid arthritis (4). Since it may not be exactly possible to determine the extent of the isolated effects of all risk factors associated with atherosclerosis including inflammation, to examine vascular damage biomarkers that reflect the cumulative effect of all defined and unidentified risk factors can make more sense. Of these biomarkers, carotid intima-media thickness (CIMT) and pulse wave velocity (PWV) have been suggested as independent risk factors for future CVD (5, 6). However, inconsistent results have been reported regarding the value of CIMT and PWV

**Address for correspondence:** Dr. İlker Şengül, İzmir Katip Çelebi Üniversitesi Tıp Fakültesi, Fiziksel Tıp ve Rehabilitasyon Anabilim Dalı,  
Basın Sitesi 35360 İzmir-Türkiye

Phone: +90 533 733 36 98 E-mail: ilkrsgnl@gmail.com

**Accepted Date:** 22.07.2019 **Available Online Date:** 16.09.2019

©Copyright 2019 by Turkish Society of Cardiology - Available online at [www.anatoljcardiol.com](http://www.anatoljcardiol.com)  
DOI:10.14744/AnatolJCardiol.2019.13367



in the detection of subclinical atherosclerotic CVD in patients with AS (7-15). In a recent meta-analysis, increased risk of subclinical atherosclerosis based on increased values of CIMT and PWV has been reported (16). However, it was also noted that studies included in the meta-analysis were heterogeneous, and some studies did not provide information about atherosclerotic risk factors and disease activity (16). The aim of the present study was to investigate the presence of disease-specific subclinical atherosclerosis using CIMT and PWV in patients with AS without overt CVD by controlling some main traditional risk factors for CVD including age, sex, hypertension, and diabetes mellitus.

## Methods

### Study design

This was a cross-sectional study conducted between January 2016 and December 2017. The study was approved by the Local Ethics Committee and conducted according to the Declaration of Helsinki. Written consent was obtained from each of the participants of the study.

### Patients and controls

Individuals with an age  $\geq 18$  years in a hospital cohort of patients with AS, diagnosed according to the 1984 modified New York criteria (17), were included in the study. The patient group was matched to the control group based on age and sex. The control group was examined similar to the patient group. Individuals with psoriatic arthritis, reactive arthritis, spondylarthritis related to inflammatory bowel disease, a known history of CVD (angina pectoris, myocardial infarction, cerebrovascular infarction, transitory ischemic attack, or peripheral arterial disease), diabetes mellitus, hypertension, and chronic renal disease were excluded from the study. Individuals with a family history of premature coronary heart disease and those receiving lipid-lowering drugs were also excluded. Other exclusion criteria included pregnancy, breastfeeding, and the suspicion of having any aforementioned disorder at inclusion.

### Demographics and disease characteristics

Patient demographics, including age, sex, body mass index (BMI), and smoking, were recorded. In addition to disease duration (duration since symptom onset), each patient's Ankylosing spondylitis disease activity score with C-reactive protein (AS-DAS-CRP) was calculated (18).

### Laboratory measurements

Glucose, creatinine, complete blood count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) levels were measured from venous blood samples after at least 8 h of fasting for all participants.

### Assessment of subclinical atherosclerosis Arterial stiffness

Arterial stiffness was measured via PWV by a validated (19) non-operator-dependent portable brachial cuff-based oscillometric device (Mobil\_O\_Graph PWA; I.E.M., Stolberg, Germany), which was used by an experienced clinician (E.T.). All participants were cautioned not to drink caffeine or smoke for at least 8 h prior to the analysis. All participants were asked to rest for 10 min prior to the measurement. Before starting the measurement, an appropriate cuff was selected based on the subject's upper arm circumference, and this cuff was then placed on the non-dominant arm. Thereafter, the device was set so as to obtain automatic recordings in a sitting position. The signals obtained via the oscillometric device were then transferred to a computer via an infrared wireless communication network. The data processing (pulse wave analysis) was performed independently via special software developed for this device. Then, PWV values were extracted from the pulse wave analysis parameters. PWV is used to measure the speed of the pulse wave through the arteries. It is estimated indirectly via the Mobil-O-Graph PWA device through a mathematical model based on pulse wave analysis and wave separation analysis (20). In addition to PWV, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were also extracted.

### Carotid intima-media thickness

The carotid intima-media area was described as the area between the leading edges of the lumen-intima and media-adventitia interfaces of the far wall of the common carotid artery (21). CIMT measurement was performed according to the Mannheim Carotid Intima-Media Thickness and Plaque Consensus (21) using a Toshiba Applio 300 device with a high-frequency (5–11 MHz) linear probe, which was operated by a radiologist (L.I.). Longitudinal images of the common carotid arteries were obtained, in which the subjects were in the supine position with a slight hyperextension of the neck. During diastole, intima-media thickness was measured on the far wall of the common carotid artery at least 5 mm below the carotid bifurcation. In the case of plaque detection during the examination, these patients were considered as having overt CVD and were excluded in the study. Three measurements were performed across the entire 1 cm length of a straight arterial segment; thereafter, these measurements were averaged. Finally, the mean intima-media thickness values from both sides were again averaged, and a single value was selected as the CIMT value.

### Sample size

The results of the study by Bodnár et al. (10) were used to calculate the minimum required sample size. A priori minimum required sample size that was calculated based on an alpha of 0.05, a power of 90%, and an effect size of 0.73 for CIMT was 82 (41 participants in each group).

### Statistical analysis

Data were analyzed using MedCalc Statistical Software version 18.5 (MedCalc Software bvba, Ostend, Belgium) for statistical analyses. Shapiro–Wilk test was used for the normal distribution of numerical variables. Normally distributed variables were presented as mean values and standard deviations (SDs). Non-normally distributed variables were presented as median values and interquartile ranges (IQRs). Independent samples t-test or Mann–Whitney U test was used to analyze between-group differences according to the normality. Chi-square test was used to analyze categorical variables. Pearson’s or Spearman’s correlation coefficient was used to analyze the correlation between the numerical variables, as appropriate. Point biserial correlation coefficient was used to analyze the correlation between the numerical variables and binominal categorical variables. A p-value <0.05 was considered statistically significant.

### Results

A total of 84 participants, of which 40 were volunteer controls and 44 were patients with AS, were examined. The median (IQR)

age of the study population was 43 (37–48) years. Of the 84 participants, 38 (45.2%) were female.

In addition to age and sex, both groups were comparable with regard to smoking status and BMI. CRP and ESR were significantly higher in the AS group than in the control group (p<0.001 and p=0.006, respectively), TC was significantly higher in the control group (p=0.002). Other laboratory measurements, such as PWV and CIMT, were also comparable across the groups. The median (IQR) symptom duration was 210 (120–300) months, and a mean (SD) ASDAS-CRP of 2.5 (0.9) was found in the AS group. The percentages of NSAID, disease-modifying antirheumatic drug (DMARD) (sulfasalazine or methotrexate), and tumor necrosis factor alpha (TNF-α) inhibitor use were 79.5%, 25%, and 65.9%, respectively. The demographic and clinical characteristics of the participants according to groups are presented in Table 1.

In the correlation analyses, PWV was significantly correlated with age, CIMT, and SBP in both groups. PWV was also significantly correlated with TC and LDL-C in the control group. In addition, PWV was significantly correlated with BMI, DBP, and disease duration in the AS group. CIMT was significantly correlated with age in both groups. CIMT was also significantly correlated with ASDAS-CRP, disease duration, and TG in the AS

**Table 1. Anthropometric, demographic, and clinical characteristics of the participants across the groups**

|                                      | Controls (n=40)  | AS (n=44)          | P      |
|--------------------------------------|------------------|--------------------|--------|
| Age, years, median (IQR)             | 44 (37.5-47.5)   | 42 (37.0-49.0)     | 0.993  |
| Sex, male, n (%)                     | 20 (50)          | 26 (59.1)          | 0.403  |
| Smoking, n (%)                       | 13 (32.5)        | 18 (40.9)          | 0.425  |
| BMI, kg/m <sup>2</sup> , mean (SD)   | 25.3 (3.0)       | 26.1 (4.3)         | 0.325  |
| Duration of AS, months, median (IQR) |                  | 210 (120-300)      | -      |
| ASDAS-CRP, mean (SD)                 |                  | 2.5 (0.9)          | -      |
| Current use of medication            |                  |                    |        |
| NSAID, n (%)                         |                  | 35 (79.5)          | -      |
| DMARD, n (%)                         |                  | 11 (25.0)          |        |
| TNF-α inhibitor, n (%)               |                  | 29 (65.9)          |        |
| SBP, mm Hg, mean (SD)                | 118.5 (13.1)     | 122.0 (12.7)       | 0.225  |
| DBP, mm Hg, mean (SD)                | 79.1 (10.0)      | 81.1 (11.0)        | 0.400  |
| TC, mg/dL, mean (SD)                 | 216.2 (46.6)     | 184.9 (44.5)       | 0.002  |
| HDL-C, mg/dL, median (IQR)           | 50 (45.0-63.0)   | 49.5 (41.5-56.5)   | 0.103  |
| LDL-C, mg/dL, mean (SD)              | 139.7 (38.3)     | 125.6 (37.4)       | 0.092  |
| TG, mg/dL, median (IQR)              | 117 (87.0-171.5) | 111.5 (73.5-173.5) | 0.720  |
| ESR, mm/h, median (IQR)              | 9 (6-19)         | 22.5 (6.5-35)      | 0.006  |
| CRP, mg/dL, median (IQR)             | 1.1 (0.7-2.7)    | 3.9 (2-12.6)       | <0.001 |
| Surrogate markers of subclinical CVD |                  |                    |        |
| CIMT, mm, median (IQR)               | 0.59 (0.54-0.65) | 0.56 (0.52-0.64)   | 0.253  |
| PWV, m/s, median (IQR)               | 6.3 (5.6-6.6)    | 6.0 (5.7-7.2)      | 0.788  |

AS - ankylosing spondylitis; IQR - interquartile range; BMI - body mass index; SD - standard deviation; ASDAS-CRP - ankylosing spondylitis disease activity score with C-reactive protein; NSAID - nonsteroidal anti-inflammatory drug; DMARD - disease-modifying antirheumatic drug; TNF-α - tumor necrosis factor alpha; SBP - systolic blood pressure; DBP - diastolic blood pressure; TC - total cholesterol; HDL-C - high-density lipoprotein-cholesterol; LDL - low-density lipoprotein-cholesterol; TG - triglyceride; ESR - erythrocyte sedimentation rate; CRP - C-reactive protein; CVD - cardiovascular disease; CIMT - carotid intima-media thickness; PWV - pulse wave velocity

**Table 2. Correlations between surrogate markers of cardiovascular disease, traditional risk factors, and disease activity by the groups**

|                                  | Control  |        |          |        | AS       |        |          |       |
|----------------------------------|----------|--------|----------|--------|----------|--------|----------|-------|
|                                  | PWV, m/s |        | CIMT, mm |        | PWV, m/s |        | CIMT, mm |       |
|                                  | r        | P      | r        | P      | r        | P      | r        | P     |
| Age, years                       | 0.766    | <0.001 | 0.684    | <0.001 | 0.879    | <0.001 | 0.385    | 0.010 |
| Sex, male                        | 0.058    | 0.616  | 0.078    | 0.516  | 0.002    | 0.962  | 0.104    | 0.396 |
| Smoking, yes                     | 0.097    | 0.675  | 0.186    | 0.285  | 0.248    | 0.184  | 0.119    | 0.197 |
| BMI, kg/m <sup>2</sup>           | 0.255    | 0.112  | 0.078    | 0.633  | 0.316    | 0.037  | 0.163    | 0.290 |
| Disease duration, months         | -        | -      | -        | -      | 0.582    | <0.001 | 0.456    | 0.002 |
| ASDAS-CRP                        | -        | -      | -        | -      | -0.183   | 0.234  | 0.315    | 0.038 |
| NSAID use, yes                   | -        | -      | -        | -      | 0.035    | 0.838  | 0.029    | 0.804 |
| DMARD use, yes                   | -        | -      | -        | -      | 0.244    | 0.054  | 0.201    | 0.290 |
| TNF- $\alpha$ inhibitor use, yes | -        | -      | -        | -      | 0.043    | 0.259  | 0.066    | 0.776 |
| SBP, mm Hg                       | 0.379    | 0.016  | 0.102    | 0.533  | 0.395    | 0.008  | 0.013    | 0.932 |
| DBP, mm Hg                       | -0.063   | 0.698  | -0.147   | 0.364  | 0.495    | 0.001  | 0.163    | 0.291 |
| TC, mg/dL                        | 0.489    | 0.001  | 0.243    | 0.132  | 0.064    | 0.681  | 0.150    | 0.330 |
| HDL-C, mg/dL                     | 0.038    | 0.816  | 0.004    | 0.982  | 0.136    | 0.377  | -0.181   | 0.239 |
| LDL-C, mg/dL                     | 0.470    | 0.002  | 0.218    | 0.177  | 0.045    | 0.774  | 0.113    | 0.467 |
| TG, mg/dL                        | 0.010    | 0.950  | 0.032    | 0.847  | -0.033   | 0.831  | 0.364    | 0.015 |

AS - ankylosing spondylitis; BMI- body mass index; ASDAS-CRP - ankylosing spondylitis disease activity score with C-reactive protein; NSAID - nonsteroidal anti-inflammatory drug; DMARD - disease-modifying antirheumatic drug; TNF- $\alpha$  - tumor necrosis factor alpha; SBP - systolic blood pressure; DBP - diastolic blood pressure; TC - total cholesterol; HDL-C - high-density lipoprotein-cholesterol; LDL - low density lipoprotein-cholesterol; TG - triglyceride; ESR - erythrocyte sedimentation rate; CRP - C-reactive protein; CVD - cardiovascular disease; CIMT - carotid intima-media thickness; PWV - pulse wave velocity; CVD - cardiovascular disease

group. Neither PWV nor CIMT was correlated with sex, smoking, NSAID use, DMARD use, and TNF- $\alpha$  inhibitor use in the AS group. PWV and CIMT were not correlated with sex and smoking among the controls (Table 2).

## Discussion

The purpose of the current study was to investigate whether two independent predictors of subclinical atherosclerosis and future CV events, such as CIMT and PWV, differed in patients with AS without overt CVD as compared with controls. In general, there were no differences between the controls and patients with AS with respect to PWV and CIMT. The only factor that was significantly associated with CIMT and PWV in both controls and patients with AS was age. There was no association between disease activity and PWV, whereas CIMT was poorly associated with disease activity.

PWV is the gold standard measurement of aortic stiffness and an independent predictor of future CV events (22). Inflammation has been shown to cause vascular stiffness by affecting the structural elements of the vessel wall, including the endothelium and muscular layer (23). Thus, increased arterial stiffness due to increased inflammation, as well as a concomitant increased risk of atherosclerosis, is expected in inflammatory rheumatic dis-

eases. Despite this expectation, inconsistent results have been achieved in clinical trials in patients with AS. Some have reported no difference between patients with AS and controls with respect to aortic stiffness as measured with PWV (13, 14, 24). On the other hand, Avram et al. (25) reported higher PWV in patients with AS than those in controls, as well as an association between arterial stiffness and disease activity. In addition, there was no significant PWV progression reported when inflammation and disease activity were controlled with TNF- $\alpha$  inhibitors (26, 27), with no significant improvement in PWV with such inhibitors (27). Consistent with some of these trials (13, 14), our results also failed to show an association between arterial stiffness and disease activity using CRP. The lack of association between disease activity with inflammation and arterial stiffness in the current study may have resulted from a small sample size, cross-sectional study design, and high percentage (65.9%) of TNF- $\alpha$  inhibitor use.

Another independent risk factor for future CV events is increased CIMT, an independent indicator of subclinical atherosclerosis (5). Similar to PWV, inconsistent results have been reported regarding the relationship between disease activity with inflammation and CIMT in patients with AS, especially in cross-sectional studies (8, 14, 15, 28-30). Choe et al. (8) have reported no difference between patients with AS and controls, as well as those between inactive and active patients with AS with



respect to CIMT values. Although some authors have reported significantly higher CIMT values in patients with AS than those in controls, they found no significant correlation between CIMT and disease activity (28, 29). On the other hand, Verma et al. (30) have reported a moderately positive correlation between disease activity and CIMT. In a prospective nonrandomized controlled study with a heterogenous group of patients with inflammatory arthropathies, including rheumatoid arthritis, AS, and psoriatic arthritis, who were receiving TNF- $\alpha$  inhibitors, improvements in CIMT progression was reported with long-term (1 year) TNF- $\alpha$  inhibitors (31). As with PWV, controlling inflammation via the TNF- $\alpha$  blockers may prevent the progression in CIMT (26, 32). In the current study, the only result that suggested an association between AS and subclinical atherosclerosis was the weak association between CIMT and disease activity with inflammation. Although the present study could not reveal the acceptable level of association between AS and accelerated atherosclerosis, prospective studies have consistently reported that there was a relationship between change in CIMT over time and AS (26, 31, 32).

The increased cardiovascular risk is thought to be multifactorial (2). In the present study, although there was no or a weak association between disease-specific factors and surrogate markers of atherosclerotic CVD, there was a strong association between age and both PWV and CIMT. Both PWV and CIMT are well-known to be strongly related to age (33, 34). Another traditional risk factor, TC, was lower in patients with AS than in controls, with no association with surrogate markers of CVD. A discrepancy in lipid profile, especially reduced TC and HDL-C in cases of active disease, was reported in patients with AS (35, 36).

In addition to the unmodifiable risk factors (sex and age) controlled in the present study, some modifiable risk factors, including hypertension and diabetes mellitus associated with atherosclerotic CVD, were also controlled across the groups. Even though smoking status was not controlled, groups were comparable with respect to smoking status. There were only significant group differences with respect to TC, which was lower in the AS group than in the control group. HDL-C, another risk factor for CVD, was also comparable. The control of important traditional risk factors was important to be able to demonstrate the direct relationship between the disease itself and surrogate markers of subclinical atherosclerotic CVD. However, in the present study, the association between the disease itself and atherosclerotic CVD was not shown despite the control of traditional risk factors. In addition to cross-sectional study design, another underlying reason for this lack of association may be the high rate of TNF- $\alpha$  blocker use. The use of TNF- $\alpha$  blockers might have prevented the progression of PWV and CIMT in patients with AS. NSAIDs commonly used in the treatment of AS, such as in our AS study population (79.5%), are associated with increased cardiovascular events (37). The use of single-time indomethacin has been reported to increase PWV in old but not young people (38). However, how is PWV affected in young people with continuous cyclooxygenase inhibition as in patients with AS? This question is waiting to be

answered. Capkin et al. (39) have not found a difference regarding PWV among patients with AS using NSAIDs or TNF- $\alpha$  inhibitors. Another question waiting to be answered is that how is PWV affected if two drugs are used together? Since the effect of TNF- $\alpha$  blocker and NSAID use on PWV and CIMT was not studied in the present study, we could not comment on these issues. Indeed, the causal relationship between AS itself and increased atherosclerotic CVD risk can be elicited by monitoring patients who will not be treated for years, but this is not ethical.

### Study limitations

Our study has limitations. The limitations of the present study include its small sample size and cross-sectional study design. Another limitation was the inability to isolate the effect of TNF- $\alpha$  blocker and NSAID use on PWV and CIMT. Manual measurement, instead of automatic measurement of CIMT, was also a limitation. Another limitation was related to the PWV measurement technique. Although PWV measurement with a brachial cuff-based oscillometric device has been reported to be valid (19), the gold standard method of arterial stiffness assessment is carotid-femoral PWV measurement (40).

### Conclusion

In conclusion, the present study could not provide sufficient evidence of whether the disease itself caused atherosclerotic CVD in patients with AS without overt CVD when the main traditional risk factors for CVD were controlled. The inference from the results of the present study is that the increased atherosclerotic CVD risk is most probably multifactorial in patients with AS, but the extent of the contribution of disease activity with inflammation to increased atherosclerosis is controversial. The new longitudinally controlled studies, examining the contribution of disease activity and inflammation to changes in arterial structure and function, will provide more robust evidence.

**Conflict of interest:** None declared.

**Peer-review:** Externally peer-reviewed.

**Authorship contributions:** Concept – E.H., İ.Ş., T.K., A.G.K., S.A., L.I., G.B., E.T.; Design – E.H., İ.Ş., T.K., A.G.K., S.A., L.I., G.B., E.T.; Supervision – E.H., İ.Ş., T.K., A.G.K., S.A., L.I., G.B., E.T.; Fundings – E.H., İ.Ş., L.I., E.T.; Materials – E.H., İ.Ş., L.I., G.B., E.T.; Data collection &/or processing – E.H., İ.Ş., T.K.; Analysis &/or interpretation – E.H., İ.Ş., T.K., E.T.; Literature search – E.H., İ.Ş., T.K.; Writing – E.H., İ.Ş., T.K., A.G.K., S.A., L.I., G.B., E.T.; Critical review – E.H., İ.Ş., T.K., A.G.K., S.A., L.I., G.B., E.T.

### References

1. Castañeda S, Nurmohamed MT, González-Gay MA. Cardiovascular disease in inflammatory rheumatic diseases. *Best Pract Res Clin Rheumatol* 2016; 30: 851-69.

2. 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.
3. Soubrier M, Rosenbaum D, Tatar Z, Lahaye C, Dubost JJ, Mathieu S. Vascular effects of nonsteroidal antiinflammatory drugs. *Joint Bone Spine* 2013; 80: 358-62.
4. Agca R, Heslinga SC, Rollefstad S, Heslinga M, McInnes IB, Peters MJ, et al. EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 update. *Ann Rheum Dis* 2017; 76: 17-28.
5. Greenland P, Alpert JS, Beller GA, Benjamin EJ, Budoff MJ, Fayad ZA, et al.; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2010; 122: e584-636.
6. ESH/ESC Task Force for the Management of Arterial Hypertension. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2013; 31: 1925-38.
7. Sari I, Okan T, Akar S, Cece H, Altay C, Secil M, et al. Impaired endothelial function in patients with ankylosing spondylitis. *Rheumatology (Oxford)* 2006; 45: 283-6.
8. Choe JY, Lee MY, Rheem I, Rhee MY, Park SH, Kim SK. No differences of carotid intima-media thickness between young patients with ankylosing spondylitis and healthy controls. *Joint Bone Spine* 2008; 75: 548-53.
9. Mathieu S, Joly H, Baron G, Tournadre A, Dubost JJ, Ristori JM, et al. Trend towards increased arterial stiffness or intima-media thickness in ankylosing spondylitis patients without clinically evident cardiovascular disease. *Rheumatology (Oxford)* 2008; 47: 1203-7.
10. Bodnár N, Kerekes G, Seres I, Paragh G, Kappelmayer J, Némethné ZG, et al. Assessment of subclinical vascular disease associated with ankylosing spondylitis. *J Rheumatol* 2011; 38: 723-9.
11. Cece H, Yazgan P, Karakas E, Karakas O, Demirkol A, Toru I, et al. Carotid intima-media thickness and paraoxonase activity in patients with ankylosing spondylitis. *Clin Invest Med* 2011; 34: E225.
12. Hamdi W, Chelli Bouaziz M, Zouch I, Ghannouchi MM, Haouel M, Ladeb MF, et al. Assessment of preclinical atherosclerosis in patients with ankylosing spondylitis. *J Rheumatol* 2012; 39: 322-6.
13. Berg IJ, Semb AG, van der Heijde D, Kvien TK, Olsen IC, Dagfinrud H, et al. CRP and ASDAS are associated with future elevated arterial stiffness, a risk marker of cardiovascular disease, in patients with ankylosing spondylitis: results after 5-year follow-up. *Ann Rheum Dis* 2015; 74: 1562-6.
14. Arida A, Protogerou AD, Konstantonis G, Konsta M, Delicha EM, Kitas GD, et al. Subclinical Atherosclerosis Is Not Accelerated in Patients with Ankylosing Spondylitis with Low Disease Activity: New Data and Metaanalysis of Published Studies. *J Rheumatol* 2015; 42: 2098-105.
15. Dalbeni A, Giollo A, Tagetti A, Atanasio S, Orsolini G, Cioffi G, et al. Traditional cardiovascular risk factors or inflammation: Which factors accelerate atherosclerosis in arthritis patients? *Int J Cardiol* 2017; 236: 488-92.
16. Bai R, Zhang Y, Liu W, Ma C, Chen X, Yang J, et al. The Relationship of Ankylosing Spondylitis and Subclinical Atherosclerosis: A Systemic Review and Meta-Analysis. *Angiology* 2019; 70: 492-500.
17. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum* 1984; 27: 361-8.
18. Machado P, Landewé R, Lie E, Kvien TK, Braun J, Baker D, et al. Ankylosing Spondylitis Disease Activity Score (ASDAS): defining cut-off values for disease activity states and improvement scores. *Ann Rheum Dis* 2011; 70: 47-53.
19. Wassertheurer S, Kropf J, Weber T, van der Giet M, Baulmann J, Ammer M, et al. A new oscillometric method for pulse wave analysis: comparison with a common tonometric method. *J Hum Hypertens* 2010; 24: 498-504.
20. Papaioannou TG, Argyris A, Protogerou AD, Vrachatis D, Nasothimiou EG, Sfrikakis PP, et al. Non-invasive 24 hour ambulatory monitoring of aortic wave reflection and arterial stiffness by a novel as-cillometric device: the first feasibility and reproducibility study. *Int J Cardiol* 2013; 169: 57-61.
21. Touboul PJ, Hennerici MG, Meairs S, Adams H, Amarenco P, Bornstein N, et al. Mannheim carotid intima-media thickness and plaque consensus (2004-2006-2011). An update on behalf of the advisory board of the 3rd, 4th and 5th watching the risk symposia, at the 13th, 15th and 20th European Stroke Conferences, Mannheim, Germany, 2004, Brussels, Belgium, 2006, and Hamburg, Germany, 2011. *Cerebrovasc Dis* 2012; 34: 290-6.
22. Vlachopoulos CV, Terentes-Printzios DG, Ioakeimidis NK, Aznaouridis KA, Stefanadis CI. Prediction of cardiovascular events and all-cause mortality with erectile dysfunction: a systematic review and meta-analysis of cohort studies. *Circ Cardiovasc Qual Outcomes* 2013; 6: 99-109.
23. McEniery CM, Wilkinson IB. Large artery stiffness and inflammation. *J Hum Hypertens* 2005; 19: 507-9.
24. Berg IJ, van der Heijde D, Dagfinrud H, Seljeflot I, Olsen IC, Kvien TK, et al. Disease activity in ankylosing spondylitis and associations to markers of vascular pathology and traditional cardiovascular disease risk factors: a cross-sectional study. *J Rheumatol* 2015; 42: 645-53.
25. Avram C, Drăgoi RG, Popovicu H, Drăgoi M, Avram A, Amaricai E. Association between arterial stiffness, disease activity and functional impairment in ankylosing spondylitis patients: a cross-sectional study. *Clin Rheumatol* 2016; 35: 2017-22.
26. Tam LS, Shang Q, Kun EW, Lee KL, Yip ML, Li M, et al. The effects of golimumab on subclinical atherosclerosis and arterial stiffness in ankylosing spondylitis—a randomized, placebo-controlled pilot trial. *Rheumatology (Oxford)* 2014; 53: 1065-74.
27. Mathieu S, Pereira B, Couderc M, Rabois E, Dubost JJ, Soubrier M. No significant changes in arterial stiffness in patients with ankylosing spondylitis after tumour necrosis factor alpha blockade treatment for 6 and 12 months. *Rheumatology (Oxford)* 2013; 52: 204-9.
28. Gonzalez-Juanatey C, Vazquez-Rodriguez TR, Miranda-Fillooy JA, Direrssen T, Vaqueiro I, Blanco R, et al. The high prevalence of subclinical atherosclerosis in patients with ankylosing spondylitis without clinically evident cardiovascular disease. *Medicine (Baltimore)* 2009; 88: 358-65.
29. Gupta N, Saigal R, Goyal L, Agrawal A, Bhargava R, Agrawal A. Carotid intima media thickness as a marker of atherosclerosis in ankylosing spondylitis. *Int J Rheumatol* 2014; 2014: 839135.
30. Verma I, Krishan P, Syngle A. Predictors of Atherosclerosis in Ankylosing Spondylitis. *Rheumatol Ther* 2015; 2: 173-82.

31. Angel K, Provan SA, Fagerhol MK, Mowinckel P, Kvien TK, Atar D. 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.
32. van Sijl AM, van Eijk IC, Peters MJ, Serné EH, van der Horst-Bruinsma IE, Smulders YM, et al. Tumour necrosis factor blocking agents and progression of subclinical atherosclerosis in patients with ankylosing spondylitis. *Ann Rheum Dis* 2015; 74: 119-23.
33. Engelen L, Ferreira I, Stehouwer CD, Boutouyrie P, Laurent S; Reference Values for Arterial Measurements Collaboration. Reference intervals for common carotid intima-media thickness measured with echotracking: relation with risk factors. *Eur Heart J* 2013; 34: 2368-80.
34. Reference Values for Arterial Stiffness' Collaboration. Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: 'establishing normal and reference values'. *Eur Heart J* 2010; 31: 2338-50.
35. van Halm VP, van Denderen JC, Peters MJ, Twisk JW, van der Paardt M, van der Horst-Bruinsma IE, et al. Increased disease activity is associated with a deteriorated lipid profile in patients with ankylosing spondylitis. *Ann Rheum Dis* 2006; 65: 1473-7.
36. Mathieu S, Gossec L, Dougados M, Soubrier M. Cardiovascular profile in ankylosing spondylitis: a systematic review and meta-analysis. *Arthritis Care Res (Hoboken)* 2011; 63: 557-63.
37. McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. *JAMA* 2006; 296: 1633-44.
38. Barnes JN, Casey DP, Hines CN, Nicholson WT, Joyner MJ. Cyclooxygenase inhibition augments central blood pressure and aortic wave reflection in aging humans. *Am J Physiol Heart Circ Physiol* 2012; 302: H2629-34.
39. Capkin E, Kiris A, Karkucak M, Durmus I, Gokmen F, Cansu A, et al. Investigation of effects of different treatment modalities on structural and functional vessel wall properties in patients with ankylosing spondylitis. *Joint Bone Spine* 2011; 78: 378-82.
40. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, et al.; European Network for Non-invasive Investigation of Large Arteries. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J* 2006; 27: 2588-605.