Seminars in Arthritis and Rheumatism 55 (2022) 152037

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit

Factors associated with atherosclerosis in radiographic and non-radiographic axial spondyloarthritis. A multicenter study on 838 patients

Javier Rueda-Gotor [a,b,*], Iván Ferraz-Amaro [c], Fernanda Genre [b], Iñigo González-Mazón [d], Alfonso Corrales [b,d], Vanesa Calvo-Rio [d], Virginia Portilla [d], Javier Llorca [e], Rosa Expósito [f], Vanesa Hernández-Hernández [c], Juan Carlos Quevedo-Abeledo [g], Carlos Rodríguez-Lozano [g], Clementina Lopez-Medina [h], María Lourdes Ladehesa-Pineda [h], Santos Castañeda [i], Esther F. Vicente [i], Cristina Fernández-Carballido [j], M Paz Martínez-Vidal [k], David Castro-Corredor [l], Joaquín Anino-Fernández [l], Diana Peiteado [m], Chamaida Plasencia-Rodríguez [m], María Luz García-Vivar [n], Eva Galíndez-Agirregoikoa [n], Esther Montes-Perez [o], Carlos Fernández-Díaz [p], Ricardo Blanco [b,d], Miguel Ángel González-Gay [b,d,q,r]

[a] *Rheumatology Division, Hospital Sierrallana, Torrelavega, Spain*
[b] *Epidemiology, Genetics and Atherosclerosis Research Group on Systemic Inflammatory Diseases, IDIVAL, Santander, Spain*
[c] *Rheumatology Division, Hospital Universitario de Canarias, Santa Cruz de Tenerife, Spain*
[d] *Rheumatology Division, Hospital Universitario Marqués de Valdecilla, IDIVAL, Santander, Spain*
[e] *Department of Epidemiology and Computational Biology, School of Medicine, University of Cantabria, CIBER Epidemiología y Salud Pública (CIBERESP), IDIVAL, Santander, Spain*
[f] *Division of Rheumatology, Hospital Comarcal, Laredo, Cantabria, Spain*
[g] *Rheumatology Division, Hospital Universitario de Gran Canaria Dr. Negrín, Las Palmas de Gran Canaria, Spain*
[h] *Rheumatology Division, Hospital Universitario Reina Sofía, Córdoba, Spain.*
[i] *Rheumatology Division, Hospital Universitario de La Princesa, IIS-Princesa, Madrid, Spain*
[j] *Rheumatology Division, Hospital Universitario de San Juan, Alicante, Spain.*
[k] *Rheumatology Division, Hospital General Universitario de Alicante, Alicante, Spain*
[l] *Rheumatology Division, Hospital General Universitario de Ciudad Real, Ciudad Real, Spain*
[m] *Rheumatology Division, Hospital La Paz, Madrid, Spain*
[n] *Rheumatology Division, Hospital Universitario Basurto, Bilbao, Spain*
[o] *Diagnóstico Médico Cantabria (DMC), Santander, Spain*
[p] *Rheumatology división, Hospital Universitario Reina Sofía, Murcia, Spain*
[q] *School of Medicine, University of Cantabria, Santander, Spain*
[r] *University of the Witwatersrand, Cardiovascular Pathophysiology and Genomics Research Unit, School of Physiology, Faculty of Health Sciences, South Africa.*

ARTICLE INFO

Keywords:
Ankylosing spondylitis
Non-radiographic spondyloarthritis
Atherosclerosis
Cardiovascular
Carotid ultrasound

ABSTRACT

Objectives: To identify disease-related factors associated with subclinical atherosclerosis and cardiovascular (CV) events in a large series of patients with axial spondyloarthritis (axSpA) and to identify possible differences in the effect of the potential pro-atherogenic factors between ankylosing spondylitis (AS) non-radiographic axSpA (nr-axSpA).

Methods: This is a cross-sectional observational study of the AtheSpAin cohort, a Spanish multicenter cohort to study atherosclerosis in axSpA. Subclinical atherosclerosis determined by carotid ultrasound included assessment of carotid intima-media thickness (cIMT) and plaque detection.

Results: 639 AS and 167 nr-axSpA patients were recruited. CV risk factors (CRF) and several disease-related factors showed a statistically significant association with subclinical atherosclerosis in the crude analysis. After adjustment for age, sex, and smoking (model 1), associations remained statistically significant for spinal

* Corresponding author at: Rheumatology Division, Hospital Sierrallana, Barrio de Ganzo s/n. 39300, Torrelavega, Spain
E-mail address: ruedagotor@gmail.com (J. Rueda-Gotor).

https://doi.org/10.1016/j.semarthrit.2022.152037

Available online 28 May 2022

mobility, inflammatory bowel disease, use of prednisone, and Disease-modifying antirheumatic drugs (DMARD) when assessing carotid plaques and for acute phase reactants (APR) at diagnosis, use of prednisone, DMARD, and TNF-inhibitors when measuring cIMT. In model 2, which also included classic CRF as confounding factors to identify axSpA features with a potential independent pro-atherogenic effect, the functional status was the only variable significantly associated with plaques and the use of prednisone and APR at diagnosis with cIMT. No association differences were found between both subtypes of patients. Besides, APR at diagnosis were also associated with subsequent development of CV events that had occurred in 33 patients.
Conclusion: Apart from CRF, atherosclerotic disease in AxSpA is associated with disease-related factors such as inflammatory response and disease severity, with no differences between AS and nr-axSpA.

Introduction

As occurs in other chronic inflammatory conditions such as rheumatoid arthritis (RA) [1], psoriasis [2], or inflammatory bowel disease (IBD) [3], axial spondyloarthritis (axSpA) is associated with an increased cardiovascular (CV) risk mainly due to accelerated atherosclerosis [1], with subsequent increased in CV morbidity and mortality [4,5]. A meta-analysis of longitudinal studies reported an increased frequency of myocardial infarction (risk ratio-RR=1.44; 95% confidence interval- CI 1.25 to 1.67) and stroke (RR=1.37; 95% CI 1.08 to 1.73) in ankylosing spondylitis (AS) patients when compared to the general population [6]. In a recent Spanish multicenter prospective study including 738 AS, 775 RA, 721 psoriatic arthritis, and 677 healthy controls, AS was the most common inflammatory disease associated with CV events after five years of follow-up [7].

Identifying the factors that underlie this process is crucial to advance in the prevention of CV events. Although traditional CV risk factors are highly prevalent in AS [8], they cannot fully explain the excess of CV events observed in this condition. A cohort of ankylosing spondylitis (AS) patients from Olmsted County showed a cumulative incidence of CV events three times higher than the predicted by the Framingham risk score, an algorithm exclusively based on traditional CV risk factors [9]. In the same line, a study comparing 149 axSpA with 181 healthy controls found an increased prevalence of carotid plaques in axSpA patients irrespective of sex, age, smoking, dyslipidemia, hypertension, obesity, and diabetes mellitus [10].

Several disease-related factors have been implicated in the accelerated atherosclerosis observed in patients with inflammatory rheumatic diseases (IRD), highlighting the role of the inflammatory response. Proinflammatory cytokines such as TNF-alpha, IL-6, and IL-1, promote endothelial dysfunction and vessel structural damage and have been associated with CV mortality [1]. The inflammatory process can also have an indirect pro-atherogenic effect, leading to a deleterious lipid profile characterized by an increased atherogenic index and the development of insulin resistance [11]. Treatments used, genetic factors, and other disease-related factors have also been associated with CV risk in IRD [12]. However, concerning axSpA, data about such pro-atherogenic factors are scarce and contradictory. We lack studies assessing their implication in the development of CV events, so most information available proceeds from the analysis of surrogate markers of atherosclerosis. The detection of carotid plaques and the assessment of carotid intima-media wall thickness (cIMT) measured by carotid ultrasound, both considered a reliable expression of subclinical atherosclerosis [13], have been widely used for this purpose in IRD. With regard specifically to AS, the reported findings are controversial. While most studies failed to demonstrate the link between carotid atherosclerosis and acute phase reactants (APR) or activity indexes [14–17], an association with other disease-related factors like the Bath Ankylosing Spondylitis Functional Index (BASFI) or the Bath Ankylosing Spondylitis Metrology Index (BASMI) have been reported [17–19]. However, these findings are still pending confirmation in studies with higher sample sizes and adjustments made for confounding variables. Besides, no data has been published about proatherogenic factors in nr-axSpA so far. These patients are characterized by a weaker inflammatory response measured by APR, lower values of BASMI, and higher prevalence of females compared to AS, but the exact role of such differences in the atherosclerotic burden of both conditions remains unknown.

This study aimed to identify disease-related factors associated not only with subclinical atherosclerosis but also with cardiovascular events in a large series of patients with axSpA who were specifically evaluated for the presence of atherosclerosis, the multicenter AtheSpAin cohort. We also attempted to identify possible differences in the effect of risk factors on subclinical atherosclerosis between patients with [r-axSpA] AS and patients with nr-axSpA.

Materials and methods

Patients

This is a cross-sectional analysis of the AtheSpAin cohort, a Spanish multicenter cohort designed to study atherosclerosis in axSpA.

For this purpose, consecutive patients older than 18 years who met the definitions of r-axSpA and nr-axSpA according to the ASAS criteria [20] were recruited over six years (2013-2019) in 10 different Spanish hospitals.

Two clinical indexes of disease activity (Bath Ankylosing Spondylitis Disease Activity Index, BASDAI, and Ankylosing Spondylitis Disease Activity Score, ASDAS), a functional status index (Bath Ankylosing Spondylitis Functional Index, BASFI), a metrologic index (Bath Ankylosing Spondylitis Metrology Index, BASMI), an enthesitis index (Maastricht Ankylosing Spondylitis Enthesitis Score -MASES) [21–25], and the presence of synovitis were evaluated in all patients at the time of carotid US assessment. Waist circumference, maximum body index and blood pressure data were also obtained at the time of the study.

Information on the history of hip involvement, synovitis, enthesitis, extra-articular manifestations (anterior uveitis, psoriasis, and inflammatory bowel disease), HLA-B27 status, disease duration and therapy from the disease diagnosis was also reviewed. It was also the case for information on the history of CV events (ischemic heart disease, congestive heart failure, ischemic stroke, and peripheral artery disease) and history of and traditional CV risk factors.

Identification of patients with serum CRP levels greater than 3 mg/L at the time of diagnosis and the CRP and ESR data at the time of recruitment and at the time of diagnosis, as well as the lipid profile, were reviewed. Structural damage was assessed by the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) [26] and the presence of syndesmophytes on spinal radiographs. Patients also underwent a standard anteroposterior plain radiograph of the pelvis to classify the patients as radiographic or nr-axSpA.

A subject's written consent was obtained in all the cases. The study was approved by the local Ethics Committee of Hospital Universitario Marques de Valdecilla and subsequently for Ethics Committees of the other centers.

Carotid US examination

The Carotid US examination was performed according to the same protocol in the participating hospitals. It included the measurement of

cIMT in the common carotid artery and the detection of focal plaques in the extracranial carotid tree following the Mannheim consensus [27]. Plaque was defined as a focal protrusion at least cIMT >1.5 mm in the lumen, protrusion at least 50% greater than the surrounding cIMT, or arterial lumen encroaching >0.5 mm [27]. The cIMT was determined as the average of three measurements in each common carotid artery, and the final cIMT was the largest average cIMT (left or right).

Statistical analysis

Demographic and clinical characteristics in patients with axSpA were described as mean (standard deviation) or percentage numbers for categorical variables. For non-normally distributed continuous variables, data were expressed as median and interquartile range (IQR). Univariable differences between different axSpA subgroups were assessed through the Student's T, Mann–Whitney U, Chi2 or Fisher's exact tests according to normal distribution or number of subjects. Association of axSpA disease-related data with carotid IMT and plaque was performed through, respectively, multivariable logistic and linear regression analysis.

In this sense, we designed two different models to establish whether the associations found were independent of the putative influence of inflammation on the traditional CV risk factors. In model 1, we only adjusted for age, sex, and smoking; if this model reached significant results, it would be interpreted as a pro-atherogenic effect potentially dependent on the increased risk for metabolic syndrome features associated with inflammation. In model 2, we adjusted for age, sex, smoking, and classic CV risk factors; if this model reached significant results, it would be interpreted as a pro-atherogenic effect independent of the influence of classic CV risk factors.

Differences in the relation of a given independent variable to subclinical atherosclerosis (cIMT or carotid plaque) between AS versus nr-axSpA were assessed through the addition of an interaction factor to the regression model. I. e., interaction factors were added to the regression models when we addressed the comparison of the effect (beta coefficients or ORs) between AS and nr-axSpA patients.

All the analyses used a 5% two-sided significance level and were performed using Stata software, version 17/SE (StataCorp, College Station, TX, USA). P-values <0.05 were considered statistically significant.

Results

Characteristics of AS patients

A total of 838 axSpA patients (667 AS and 171 nr-axSpA) were included in the present study. The main demographic, cardiovascular, and disease-related data are summarized in table 1. The mean ±SD age (50 ± 12 versus 43 ± 11 years, p=0.000) and the proportion of males (75 % versus 52%, p=0.000) were higher in the AS group, which also showed a higher prevalence of traditional CV risk factors.

As shown in table 1, the comparison of disease-related factors generally showed a more severe disease in AS patients than in those with nr-axSpA, with a higher mobility limitation at time of study (BASMI: 2.9 ±2.1 versus 2.0± 1.4, p = 0.000), and more severe structural damage measured both by mSASSS [median (IQR): 7 (2-22) versus 1 (0-4), p = 0.000] and by the presence of syndesmophytes (47% versus 10%, p = 0.000). AS patients had a higher prevalence of HLA-B27 (74% versus 65%, p = 0.005), history of hip involvement (21% versus 4%, p = 0.000), uveitis (24% versus 10%, p = 0.000) and a more intense inflammatory response measured by serum levels of APR both at diagnosis and at study (table 1).

No significant differences were found in the treatments received, except for TNF-inhibitors, used in 39% of AS patients and 26% of nr-axSpA patients (p = 0.003).

More severe atherosclerotic disease was observed in AS measured

Table 1
Main demographic, cardiovascular, and disease-related characteristics of 838 axSpA patients older than 18 y/o

axSpA patients older than 18 y/o Variables	axSpA n=838	Non-rx axSPA n=171	AS n=667	p value[1]
Age (years)	48 ± 12	43 ± 11	50 ± 12	0.000
Male	564 (67)	87 (52)	477 (75)	0.000
Cardiovascular data				
History of CV risk factors				
Current smoker	285 (34)	57 (34)	228 (36)	0.82
Have ever smoked	149 (18)	20 (12)	129 (20)	0.044
Obesity	188 (22)	28 (17)	160 (25)	0.027
Dyslipidemia	277 (33)	42 (25)	235 (37)	0.007
Hypertension	220 (26)	26 (16)	194 (30)	0.000
Diabetes Mellitus	58 (7)	6 (4)	52 (8)	0.049
Chronic Kidney Disease	19 (2)	2 (1)	17 (3)	0.39
History of cardiovascular events, n (%)	33 (4)	3 (2)	30 (5)	0.12
Ischemic heart disease	19 (2)	2 (1)	17 (3)	0.39
Congestive heart failure	3 (0)	0 (0)	3 (0)	1.00
Ischemic stroke	7 (1)	0 (0)	7 (1)	0.36
Peripheral artery disease	6 (1)	1 (1)	5 (1)	1.00
Lipids				
Total cholesterol	191 ± 39	192 ± 38	191 ± 39	0.75
HDL-cholesterol	54 ± 16	59 ± 20	53 ± 15	0.001
LDL-cholesterol	116 ± 33	114 ± 30	116 ± 34	0.52
Atherogenic index ≥4	298 (36)	55 (33)	243 (38)	0.21
Triglycerides	118 ± 75	115 ± 77	119 ± 74	0.51
Statins	122 (15)	11 (7)	111 (17)	0.002
Blood pressure, mm Hg				
Systolic	129 ± 17	125 ± 17	130 ± 17	0.000
Diastolic	79 ± 11	78 ± 10	80 ± 11	0.028
Disease-related data at time of study				
Mean disease duration, years				
Since first symptoms	14 (7-25)	7 (3-12)	16 (9-28)	0.000
Since diagnosis	9 (2-17)	2 (1-8)	11 (4-20)	0.000
ASDAS	2.31 ± 1.00	2.30 ± 0.99	2.31 ± 1.00	0.91
Inactive disease	133 (16)	34 (20)	99 (15)	0.39
Low disease activity	183 (22)	32 (19)	151 (24)	
High disease activity	323 (39)	68 (41)	255 (40)	
Very high disease activity (>3.5)	75 (9)	16 (10)	59 (9)	
BASDAI	3.77 ± 227	4.07 ± 2.34	3.69 ± 2.25	0.060
BASDAI>4	372 (44)	83 (50)	289 (45)	0.24
CRP at time of study, m/L	2.2 (0.6-6.2)	1.0 (0.5-4.7)	2.6 (0.9-7.0)	0.000
ESR at time of study, mm/ 1st hour	7 (3-14)	6 (3-13)	7 (4-15)	0.40
BASFI	3.6 ± 2.6	3.4 ± 2.4	3.6 ± 2.6	0.31
BASMI	2.7 ± 2.1	2.0 ± 1.4	2.9 ± 2.1	0.000
MASES	0 (0-2)	0 (0-2)	0 (0-2)	0.010
Syndesmophytes	316 (38)	16 (10)	300 (47)	0.000
mSASSS	5 (1-15)	1 (0-4)	7 (2-22)	0.000
Grade of Sacroileitis				
Grade ≥ 3 (uni or bilateral)	475 (57)	0(0)	475 (57)	0.000
Grade 4 (uni or bilateral)	210 (25)	0 (0)	210 (25)	0.000
Current drugs				
NSAIDs, n (%)	678 (81)	143 (86)	535 (84)	0.48
Currrent prednisone, n (%)	105 (13)	20 (12)	85 (13)	0.72
DMARDs, n (%)	306 (37)	62 (37)	244 (38)	0.87
Methotrexato, n (%)	138 (16)	23 (14)	115 (18)	0.23
Sulfasalazine, n (%)	185 (22)	34 (20)	151 (24)	0.43
Anti-TNF-alpha, n (%)	296 (35)	44 (26)	252 (39)	0.003
Secukinumab, n (%)	5 (1)	2 (1)	3 (0)	0.55
Historical disease-related data				
History of synovitis	294 (35)	68 (41)	226 (35)	0.15
History of enthesitis	260 (31)	66 (40)	194 (30)	0.019
History of dactilitis	50 (6)	12 (7)	38 (6)	0.54
History of hip involvement	139 (17)	7 (4)	132 (21)	0.000
Extra-articular manifestations				
Total	287 (34)	44 (26)	243 (38)	0.008

(*continued on next page*)

Table 1 (*continued*)

axSpA patients older than 18 y/o Variables	axSpA n=838	Non-rx axSPA n=171	AS n=667	p value[1]
Psoriasis	87 (10)	16 (10)	71 (11)	0.61
Uveitis	169 (20)	17 (10)	152 (24)	0.000
Inflammatory Bowel Disease	55 (7)	12 (7)	43 (7)	0.80
HLA-B27 positive	585 (70)	109 (65)	476 (74)	0.005
CRP at time of disease diagnosis, (mg/L)	4.0 (1.0-11.2)	2.0 (0.6-8.0)	4.6 (1.4-12.0)	0.11
CRP >3 mg/L at time of diagnosis	441 (53)	70 (42)	371 (58)	0.000
ESR at the time of disease diagnosis (mm/1st hour)	13 (6-27)	9 (3-21)	14 (7-29)	0.000
Drugs from the disease diagnosis				
Anti-TNF-α	64 (8)	7 (4)	57 (9)	0.64
IL-17 inhibitors	10 (1)	3 (2)	7 (1)	0.12
DMARDs	127 (15)	19 (11)	108 (17)	0.33
Subclinical atherosclerosis				
Carotid IMT, microns	643 ± 146	586 ± 116	658 ± 150	0.000
Carotid plaques, n (%)	260 (31)	38 (23)	222 (35)	0.003

P[1] for comparison between patients with AS and Non radiographic axSpA

with both cIMT (0.658± 0.250 mm versus 0.586± 0.116 mm, p = 0.000), and presence of carotid plaques (35% versus 23%, p = 0.003).

Cardiovascular and disease-related features associated with the presence of subclinical atherosclerosis

Carotid plaques

Since carotid plaques are considered the primary surrogate marker of subclinical atherosclerosis, we aimed to identify which CV and disease-related factors included in Table 1 were associated with their presence. Unilateral and bilateral plaques were analyzed independently to assess associations with different degrees of atherosclerosis severity. All significant findings are summarized in Table 2. We also analyzed the differences between AS and nr-axSpA in this regard (Table 2).

As expected, age, male sex, traditional CV risk factors, atherogenic index, and blood pressure were all associated with unilateral and, especially, bilateral carotid plaques (Table 2).

We designed two different adjusted models regarding disease-related factors to analyze whether the possible pro-atherogenic effect of axSpA features was potentially dependent (model 1) or independent (model 2) of classic CV risk factors.

Although several axSpA features were found to be related to plaques in the crude analysis, most associations disappeared in the adjusted models. Only BASMI [OR: 1.22 (1.07-1.40), p = 0.004], the coexistence of IBD [OR: 3.48 (1.32-9.19), p = 0.012] and the use of prednisone [OR: 2.42 (1.11-5.29), p = 0.027] and DMARDs [OR: 2.01 (1.15-3.52), p = 0.015] remained significant after adjusting for age, sex, and smoking, while a non-significant trend was observed for disease duration [OR: 1.02 (1.00-1.05), 0.080] (model 1). The only variable directly associated to carotid plaques without the influence of classic CV risk factors was the functional limitation measured by BASFI [OR: 1.13 (1.03-1.23), p= 0.010], while BASDAI [OR: 1.10 (0.99-1.23), p = 0.070], BASMI [OR: 1.11 (0.98-1.26), p = 0.094], and ESR at diagnosis [OR: 1.01 (1.00-1.02), p = 0.077] only showed a trend towards significance (model 2).

The crude analysis suggested a more relevant pro-atherogenic role of disease activity in the case of bilateral plaques, showing significant associations with ASDAS [1.35 (1.09-1.68), p = 0.007], very high disease activity measured by ASDAS [OR: 3.43 (1.54-7.65), p = 0.003], CRP at time of the study [OR:1.02 (1.00-1.03), p = 0.044] and history of synovitis [OR: 1.51 (1.01-2.27), p = 0.045]. However, no relevant differences were observed between unilateral and bilateral involvement in the adjusted models.

The associations mentioned above did not differ globally among radiographic and non-radiographic axSpA patients as it can be seen through the fact that interaction p values were non-significant. Only the history of previous hip involvement and the total number of extra-articular manifestations relation to carotid plaque (as an ordinal variable: no plaque, unilateral plaque and bilateral plaque) showed a different OR between nr-axSpA and AS. In this sense, the relation of hip involvement and extra-articular manifestations to carotid plaque was higher in non nr-axSpA compared to AS (data not shown in Table).

Carotid intima-media wall thickness

We then completed the search of potential pro-atherogenic factors by using cIMT as a surrogate marker of atherosclerosis. As shown in table 3, which only includes the statistically significant findings, the crude analysis reported several associations with traditional CV risk factors and many disease-related features, but only the APR and treatments used remained significant in the adjusted analysis. This was the case for CRP [ß coefficient: 0.51 (0.18-0.84), p = 0.003], CRP > 3 mg/L [ß coefficient: 18 (1-34), p = 0.035] and ESR [ß coefficient: 0.67 (0.20-1.14), p = 0.005] at diagnosis, as well as for the use of prednisone [ß coefficient: 40 (15-64), p = 0.001], methotrexate [ß coefficient: 25 (3-47), p= 0.026] and TNF-inhibitors [ß coefficient: 19 (2-36), p = 0.031] at time of study, all of them in model 1. Model 2 confirmed most of these findings, suggesting an effect on cIMT independent of traditional CV risk factors, and it also found a non-significant trend for syndesmophytes [ß coefficient: 7 (-13-28), p = 0.071]. The associations reported were comparable in both AS and nr-axSpA patients for most of the characteristics of the disease (interaction analysis in Table 3). Only DMARD intake had a higher effect on cIMT in non nr-axSpA compared to AS (data not shown).

Cardiovascular and disease-related features associated with the presence of cardiovascular events

Finally, we evaluated characteristics related to atherosclerotic CV events in 33 axSpA patients with a history of ischemic heart disease, congestive heart failure, ischemic stroke, or peripheral artery disease (Table 4). All but seven CV events occurred after the onset of axSpA.

As expected, CV events were associated with a history of traditional CV risk factors and with axSpA features related to the severity of the disease. The disease duration [OR:1.03 (1.00-1.06), p = 0.023], BASDAI > 4 [OR: 2.58 (1.16-5.73), p = 0.020], BASFI [1.25 (1.08-1.45), p = 0.003], and the structural damage at time of study both in the sacroiliac joint [grade of sacroiliitis ≥ 3, OR: 5,57 (1.94-16.00), p = 0.001] and in the spine [syndesmophytes, OR: 2.41 (1.15-5.03), p = 0.020] were associated with a history of CV events.

Besides, patients receiving prednisone [OR: 2.31 (1.02-5.28), p = 0.046], methotrexate [OR: 2.29 (1.01-4.94), p = 0.034] and anti-TNF-alpha [OR: 3.33 (1.61-6.87), p = 0.001] at time of study were more likely to have experienced CV events, as also occurred with anti-TNF at any time from the diagnosis [OR: 2.95 (1.03-8.44), 0.044].

Importantly, CRP >3 mg/L [OR: 5.27 (1.82-15.30), p = 0.002] and ESR [OR: 1.03 (1.02-1.05), p = 0.000] at diagnosis were found to be associated with subsequent development of CV events.

Discussion

The strategies for primary prevention of CV events in patients with IRD are increasingly pointing towards identifying pro-atherogenic factors other than traditional CV risk factors. In RA, specific CV risk scores that include disease-related characteristics have been designed in recent years with the aim of increasing the accuracy of their estimates. [28,29]. The Expanded Risk Score in Rheumatoid Arthritis (ERS-RA), which combines classic CV risk factors with data on disease activity, disability, disease duration, and prednisone use, showed the highest correlation with the coronary artery calcium score in comparison with other four predictive scores designed for the general population [30]. However,

Table 2
Cardiovascular and disease related features associated with unilateral or bilateral carotid plaques in 729 axSpA patients older than 35 y/o

Variables	Unilateral plaque			Bilateral plaque			Interaction p valuenr-axSpA Vs AS
	OR[c] (95% CI)	OR adjusted [1] (95% CI)	OR adjusted [2] (95% CI)	ORc (95% CI)	OR adjusted [1] (95% CI)	OR adjusted [2] (95% CI)	
Age (years)	**1.10 (1.07-1.13), 0.000[a]**			**1.15 (1.12-1.18), 0.000 [a]**			n.s.
Male	**1.78 (1.14-2.77), 0.011 [a]**			**1.75 (1.11-2.74), 0.015 [a]**			n.s.
Cardiovascular data							
History of CV risk factors							
Current smoker	1.33 (0.88-2.00), 0.18			**1.60 (1.06-2.41), 0.025 [a]**			n.s.
Have ever smoked	1.40 (0.94-2.09), 0.096			**1.86 (1.23-2.81), 0.003 [a]**			n.s.
Obesity	1.51 (0.97-2.34), 0.066			1.23 (0.77-1.94), 0.39			n.s.
Dyslipidemia	**1.90 (1.27-2.83), 0.002 [a]**			**3.37 (2.23-5.10), 0.000 [a]**			n.s.
Hypertension	**2.11 (1.39-3.20), 0.000 [a]**			**3.15 (2.07-4.78), 0.000 [a]**			n.s.
Diabetes Mellitus	**2.11 (1.00-4.44), 0.050**			**4.46 (2.35-8.49), 0.000 [a]**			n.s.
Chronic Kidney Disease	2.28 (0.63-8.22), 0.21			**3.66 (1.16-11.55),0.027[a]**			n.s.
Lipids							
Atherogenic index ≥4	**1.67 (1.11-2.50), 0.013 [a]**			1.08 (0.71-1.64), 0.73			n.s.
Triglycerides	1.00 (1.00-1.00), 0.45			**1.00 (1.00-1.01), 0.036 [a]**			n.s.
Statins	**2.57 (1.53-4.30), 0.000 [a]**			**3.96 (2.36-6.64), 0.000 [a]**			
Blood pressure, mm Hg							
Systolic	**1.04 (1.02-1.05), 0.000 [a]**			**1.04 (1.03-1.05), 0.000 [a]**			n.s.
Diastolic	**1.03 (1.01-1.04), 0.009 [a]**			0.99 (0.97-1.01), 0.23			n.s.
Carotid IMT (each 0.1 mm)	**1.84 (1.56-2.16), 0.000 [a]**			**2.19 (1.85-2.59), 0.000 [a]**			
Disease-related data at time of study							
Mean disease duration, years	**1.04 (1.03-1.06), 0.000 [a]**	1.02 (1.00-1.05), 0.080	1.01 (0.99-1.04), 0.26	**1.07 (1.05-1.09), 0.000 [a]**	1.01 (0.99-1.04), 0.7	1.01 (0.99-1.02), 0.43	n.s.
Since first symptoms	**1.04 (1.02-1.05), 0.000 [a]**	1.01 (0.98-1.03), 0.60	1.00 (0.98-1.03), 0.77	**1.05 (1.03-1.07), 0.000 [a]**	0.99 (0.97-1.02), 0.60	0.99 (0.97-1.02), 0.58	n.s.
Since diagnosis	1.21 (0.98-1.49), 0.076	1.23 (0.92-1.63), 0.16	1.20 (0.94-1.54), 0.15	**1.35 (1.09-1.68), 0.007 [a]**	1.23	1.15 (0.92-1.44), 0.23	n.s.
ASDAS	2.20 (1.00-4.43), 0.050	2.00 (0.68-5.91), 0.21	1.32 (0.54-3.26), 0.55	**3.43 (1.54-7.65), 0.003 [a]**	1.72 (0.67-4.45), 0.26	1.24 (0.54-2.83), 0.61	
ASDAS Very high disease activity (>3.5)	1.07 (0.98-1.17), 0.16	1.10 (0.97-1.245), 0.13	1.10 (0.99-1.23), 0.070	1.09 (0.99-1.19), 0.079	1.09 (0.98-1.21), 0.12	1.07 (0.97-1.18), 0.16	n.s.
BASDAI	1.00 (0.98-1.02), 0.88	1.00 (0.98-1.03), 0.72	0.99 (0.97-1.01), 0.40	**1.02 (1.00-1.03), 0.044 [a]**	1.00 (0.98-1.02), 0.71	0.99 (0.97-1.01), 0.31	n.s.
CRP at time of study, m/L	**1.19 (1.10-1.29), 0.000 [a]**	1.06 (0.95-1.18), 0.29	**1.13 (1.03-1.23), 0.010 [a]**	**1.17 (1-08-1.27), 0.000 [a]**	1.07 (0.98-1.18), 0.14	**1.12 (1.03-1.22), 0.007 [a]**	n.s.
BASFI	**1.27 (1.14-1.41), 0.000 [a]**	**1.22 (1.07-1.40), 0.004 [a]**	1.11 (0.98-1.26), 0.094	**1.45 (1.30-1.62), 0.000 [a]**	**1.21 (1.07-1.36), 0.003 [a]**	1.11 (0.99-1.25), 0.074	n.s.
BASMI	**2.09 (1.39-3.13), 0.000 [a]**	0.86 (0.48-1.54), 0.61	1.11 (0.67-1.84), 0.69	**2.17 (1.43-3.30), 0.000 [a]**	0.81 (0.48-1.37), 0.44	1.11 (0.69-1.79), 0.67	n.s.
Syndesmophytes	**1.30 (1.05-1.61), 0.015 [a]**	0.89 (0.58-1.38), 0.61	1.14 (0.81-1.61), 0.45	**1.77 (1.40-2.25), 0.000 [a]**	0.97 (0.71-1.33), 0.86	0.88 (0.67-1.16), 0.37	
log mSASSS							
Grade of Sacroileitis							
Grade ≥ 3 (uni or bilateral)	**1.53 (1.01-2.30), 0.044 [a]**	0.80 (0.43-1.49), 0.48	0.85 (0.50-1.44), 0.55	**1.83 (1.19-2.82), 0.006 [a]**	0.79 (0.46-1.34), 0.38	0.80 (0.50-1.28), 0.35	-
Grade 4 (uni or bilateral)	**2.48 (1.63-3.77), 0.000 [a]**	1.02 (0.57-1.83), 0.94	1.30 (0.78-2.17), 0.32	**2.35 (1.53-3.60), 0.000 [a]**			-
Prednisone, n (%)	1.52 (0.86-2.68), 0.15	**2.42 (1.11-5.29), 0.027 [a]**	1.56 (0.75-3.25), 0.23	**1.91 (1.10-3.29), 0.021 [a]**	**2.28 (1.19-4.39), 0.013 [a]**	1.58 (0.84-2.96), 0.16	n.s.
DMARDs, n (%)	1.32 (0.89-1.98), 0.17	**2.01 (1.15-3.52), 0.015 [a]**	1.26 (0.76-2.07), 0.37	**1.63 (1.09-2.44), 0.018 [a]**	**1.90 (1.18-3.07), 0.008 [a]**	1.53 (0.98-2.37), 0.059	n.s.
Methotrexate, n (%)	**1.61 (0.98-2.66), 0.063**	**2.20 (1.11-4.37), 0.025 [a]**	1.50 (0.80-2.81), 0.21	**2.21 (1.36-3.57), 0.001 [a]**	**2.03 (1.14-3.62), 0.016 [a]**	1.49 (0.86-2.60), 0.16	n.s.
Historical disease-related data							
History of synovitis							n.s.

(*continued on next page*)

Table 2 (*continued*)

Variables	Unilateral plaque			Bilateral plaque			Interaction p valuenr-axSpA Vs AS
	OR[c] (95% CI)	OR adjusted [1] (95% CI)	OR adjusted [2] (95% CI)	ORc (95% CI)	OR adjusted [1] (95% CI)	OR adjusted [2] (95% CI)	
	0.90 (0.59-1.36), 0.61	1.30 (0.76-2.24), 0.34	0.78 (0.48-1.27), 0.32	**1.51 (1.01-2.27), 0.045** [a]	1.21 (0.76-1.94), 0.43	0.73 (0.47-1.15), 0.73	
History of hip involvement	**1.63 (1.01-2.65), 0.047** [a]	1.05 (0.56-1.96), 0.89	0.99 (0.56-1.74), 0.96	1.55 (0.95-2.55), 0.080	0.95 (0.53-1.68), 0.85	1.04 (0.61-1.78), 0.88	0.017 (2)
Extra-articular manifestations							
Total	0.95 (0.64-1.44), 0.82	1.52 (0.88-2.63), 0.13	0.90 (0.55-1.48), 0.68	1.42 (0.95-2.12), 0.092	1.30 (0.81-2.10), 0.28	0.92 (0.59-1.43), 0.70	0.015 (1)
Inflammatory Bowel Disease	1.13 (0.54-2.39), 0.74	**3.48 (1.32-9.19), 0.012** [a]	1.96 (0.79-4.90), 0.15	1.18 (0.56-2.49), 0.66	1.82 (0.76-4.35), 0.18	1.48 (0.66-3.30), 0.34	n.s.
CRP at diagnosis, (mg/L)	1.01 (1.00-1.01), 0.056	1.00 (0.99-1.01), 0.55	1.01 (1.00-1.01), 0.19	1.00 (0.99-1.01), 0.96	1.00 (0.99-1.01), 0.39	1.00 (1.00-1.01), 0.33	n.s.
CRP >3 mg/L at diagnosis	**1.59 (1.06-2.39), 0.025** [a]	1.32 (0.75-2.33), 0.34	1.35 (0.83-2.19), 0.23	**1.84 (1.20-2.82), 0.005** [a]	1.37 (0.84-2.23), 0.21	1.29 (0.84-2.00), 0.25	n.s.
ESR at diagnosis (mm/1st hour)	**1.01 (1.00-1.03), 0.009** [a]	1.01 (0.99-1.02), 0.35	1.01 (1.00-1.02), 0.077	**1.02 (1.00-1.03), 0.008** [a]	1.00 (0.99-1.01), 0.85	1.01 (0.99-1.02), 0.38	n.s.

OR[c] : crude analysis
OR Adjusted [1]: odds ratios adjusted for age, sex, and smoking
OR Adjusted [2]: odds ratios adjusted for age, sex, smoking, obesity, hypertension, dyslipidemia, diabetes mellitus, CKD, and statins
asignificant variable ($p < 0.05$)
In the interaction analysis carotid plaque is considered an ordinal variable (0= no plaque, 1=unilateral, 2=bilateral).

data on proatherogenic factors in axSpA are scarce and similar strategies have not been developed for this condition. Despite being recognized as a condition with an increased risk of CV events in the EULAR recommendations for CV disease risk management, the authors did not include specific strategies for CV risk assessment in axSpA due to the scarce evidence available at that moment [31]. The present study provides information in this regard, since it includes the largest cohort of patients with AxSpA analyzed to date for atherosclerotic disease. Furthermore, this is the first study to identify proatherogenic factors in nr-axSpA and to evaluate the characteristics of axSpA associated not only with subclinical atherosclerosis but also with CV events.

Our results confirm the influence of the inflammatory process on atherosclerosis development in axSpA. Serum levels of ESR and CRP at diagnosis, especially the latter when exceeding 3 mg/L, were associated with the development of CV events that had occurred in 33 patients. The same link was observed by analyzing cIMT in the entire cohort even after adjusting for confounding factors. Regarding disease activity, ASDAS and BASDAI were also associated with both surrogate markers of atherosclerosis in the crude analysis, persisting a non-significant trend in the adjusted model, while high disease activity at the time of the study was related to a history of CV events. These are relevant findings since, unlike what occurs in the general population [32] and other IRD like RA [33], the link between inflammatory activity and CV risk has not been clearly demonstrated in axSpA. The weaker inflammatory response that characterizes axSpA compared with other IRD, the difficulty of objectively measuring the disease activity, and the limited sample size of the existing studies are factors that could explain the contradictory results of previous studies, most of which failed to demonstrate this association [14–17]. In this regard, a recent study by Rojas-Gimenez et al. found no association between cIMT and ASDAS-CRP, nor with the mean CRP values of the previous five years, unlike what occurred in RA [34]. It is widely accepted that systemic inflammation in IRD can significantly influence classic risk factors like dyslipidemia, insulin resistance, or obesity [35]. A recent study conducted on the AtheSpAin cohort reported that traditional CV risk factors were associated with higher disease activity also in patients with SpA [36]. It could be argued that this interconnection could explain the pro-atherogenic role played by the inflammation in our series. However, it is important to emphasize that the associations persisted after adjusting for traditional CV risk factors, thus suggesting an independent effect of the inflammatory activity on the atherosclerotic disease of axSpA.

Other axSpA features related to the severity of the disease like the functional and the mobility status, measured by BASFI and BASMI respectively, have been previously associated with subclinical atherosclerosis [17–19]. The present study confirms this point through multivariate analysis, excluding the influence of relevant confounding factors not considered in most previous studies, such as sex, age, or smoking. Besides, CV events were also associated with BASFI and BASMI scores at the study time. Inflammatory activity could be partially responsible for these findings since both indices are mainly determined by disease activity and structural damage, which is also highly conditioned by the severity of the inflammation [37,38]. The potential effect of BASFI and BASMI on atherosclerosis also seems to be independent of its putative effect on the classic CV risk factors according to the result of the multivariate analysis.

The structural damage and the disease duration are disease-related variables also associated with CV risk in IRD like RA [39]. However, the present study was not able to confirm this point in axSpa. Although both factors were associated with atherosclerotic morbidity in the subgroup of 33 patients with CV events, the multivariate analysis assessing subclinical atherosclerosis only reported a non-significant trend for disease duration with carotid plaques and for syndesmophytes with cIMT. These results on structural damage contrast with those reported by Ladehesa-Pineda et al. who found an independent association of mSASSS with carotid plaques in 144 patients with axSpA [40]. Differences in disease characteristics between both studies could explain such a discrepancy. Patients from Ladehesa-Pineda et al. registry showed more severe radiological damage than patients from our series, with mSASSS scores three times higher. Besides, they were biological-naïve, which constitutes a relevant difference considering TNF-inhibitors' influence over structural damage [41] and atherosclerosis [42].

The role of the extra-articular manifestations in the atherosclerotic burden of axSpA is another intriguing question to clarify. Psoriasis [2] and IBD [3] have been independently related to increased CV risk by themselves, and uveitis was found to be a significant risk factor for developing acute myocardial infarction in patients with AS in a recent retrospective cohort study with 5905 patients from the Taiwanese National Database [43]. However, in our series, IBD was the only

Table 3
Cardiovascular and disease related features associated with IMT in 838 axSpA patients older than 18 y/o.

Variables	Carotid IMT beta coefficient[c] (95%CI), p.	beta coefficient adjusted[1] (95% CI), p.	beta coefficient adjusted[2] (95% CI), p.	Interaction p value nr-axSpA Vs AS
Age (years)	7 (6-8), 0.000			n.s.
Male	53 (32-74), 0.000			0.000
Cardiovascular data				
History of CV risk factors				
Current smoker	0 (-21-22), 0.97			n.s.
Have ever smoked	**32 (12-54), 0.002**[a]			n.s.
Obesity	**52 (28-76), 0.000**[a]			n.s.
Dyslipidemia	**82 (62-103), 0.000**[a]			n.s.
Hypertension	**111 (90-133), 0.000**[a]			n.s.
Diabetes Mellitus	**111 (72-151), 0.000**[a]			n.s.
Chronic Kidney Disease	**96 (27-165), 0.007**[a]			
Lipids				
HDL-cholesterol x 10	**-9 (-2- -0), 0.002**[a]			n.s.
LDL-cholesterol x 10	**5 (2-8), 0.002**[a]			n.s.
Atherogenic index ≥4	**31 (10-51), 0.004**[a]			n.s.
Triglycerides x 10	**3 (1-4), 0.000**[a]			n.s.
Statins	**90 (61-119), 0.000**[a]			n.s.
Blood pressure, mm Hg				
Systolic	**3 (2-3), 0.000**[a]			n.s.
Diastolic	**2 (1-3), 0.000**[a]			n.s.
Disease related data at time of study				
Mean disease duration, years				
Since first symptoms	**4 (3-5), 0.000**[a]	-0.14 (-0.95-0.67), 0.74	-0.13 (-1.00-0.74), 0.77	n.s.
Since diagnosis	**4 (3-5), 0.000**[a]	-0.25 (-1.14-0.65), 0.59	-0.03 (-0.98-0.93), 0.96	n.s.
ASDAS				
Low disease activity	**40 (9-72), 0.012**[a]	12 (-14-38), 0.38	12 (-15-39) 0.37	
High disease activity	**42 (13-70), 0.004**[a]	19 (-5-43), 0.12	5 (-20-30), 0.69	
Very high disease activity (>3.5)	**72 (33-112), 0.000**[a]	26 (-7-59), 0.13	18 (-17-53), 0.31	
BASDAI	**5 (0-9), 0.046**[a]	2 (-2-5), 0.37	1 (-3-5), 0.54	n.s.
BASDAI>4	20 (-1-40), 0.060	10 (-7-27), 0.25	8 (-10-26), 0.38	n.s.
BASFI	**11 (7-15), 0.000**[a]	1 (-2-5), 0.49	0 (-3-4), 0.82	n.s.
BASMI	**18 (13-23), 0.000**[a]	1 (-4-6), 0.70	0 (-5-5), 0.90	n.s.
Syndesmophytes	**82 (61-103), 0.000**[a]	2 (-17-22), 0.81	7 (-13-28), 0.071	n.s.
log mSASSS	**3 (2-3), 0.000**[a]	0.63 (-9-91-11.18), 0.91	-0.19 (-0.95-0.56), 0.62	n.s.
Grade of sacroileitis Rx				
Grade ≥ 3 (uni or bilateral)	**65 (44-85), 0.000**[a]	7 (-11-25), 0.44	5 (-14-24), 0.60	-
Grade 4 (uni or bilateral)	**81 (58-104), 0.000**[a]	4 (-17-24), 0.71	8 (-14-29), 0.49	-
NSAIDs, n (%)	**-48 (-74--21), 0.000**[a]	-14 (-36-8), 0.20	-17 (-39-5), 0.13	n.s.
Currrent prednisone, n (%)	**46 (15-76), 0.003**[a]	**40 (15-64), 0.001**[a]	**33 (5-61), 0.019**[a]	n.s.
DMARDs, n (%)	**22 (1-43), 0.041**[a]	14 (-3-31), 0.10	14 (-4-32), 0.12	0.047
Methotrexate n (%)	**55 (28-82), 0.000**[a]	**25 (3-47), 0.026**[a]	15 (-9-39), 0.21	n.s.
Anti-TNF-alpha, n (%)	**37 (16-58), 0.001**[a]	**19 (2-36), 0.031**[a]	17 (-1-35), 0.063	0.053
Historical disease-related data				
History of synovitis	**37 (16-58), 0.001** [a]	11 (-6-28), 0.22	6 (-13-24), 0.54	n.s.
History of enthesitis	1 (-21-22), 0.95	3 (-15-20), 0.75	-6 (-24-13), 0.54	n.s.
History of dactilitis	14 (-29-57), 0.52	-4 (-38-30), 0.82	-1 (-37-35), 0.96	n.s.
History of hip involvement	**35 (7-62), 0.014**[a]	(-39-6), 0.16	-14 (-37-9), 0.22	n.s.
Extra-articular manifestations				
Total	**26 (4-47), 0.018**[a]	6 (-11-23), 0.49	6 (-12-24), 0.51	n.s.
Uveitis	25 (-1-50), 0.055	7 (-13-27), 0.50	12 (-9-33), 0.26	n.s.
CRP at time of disease diagnosis, (mg/L)	**1 (0-1), 0.005**[a]	**0.51 (0.18-0.84), 0.003**[a]	**0.31 (0.00-0.62), 0.047**[a]	n.s.
CRP >3 mg/L at time of diagnosis	**35 (15-56), 0.001**[a]	**18 (1-34), 0.035**[a]	17 (-1-35), 0.057	n.s.
ESR at the time of disease diagnosis (mm/1st hour)	**2 (1-2), 0.000** [a]	**0.67 (0.20-1.14), 0.005**[a]	**0.77 (0.29-1.26), 0.002**[a]	n.s.
Drugs from the disease diagnosis				
Anti-TNF-α	16 (-28-59), 0.49	5 (-31-42), 0.77	2 (-34-38), 0.91	n.s.
DMARDs	**53 (18-88), 0.003**[a]	22 (-7-51), 0.14	20 (-10-49), 0.19	0.025

beta coefficient[c] crude analysis
beta coefficient adjusted[1]: adjusted for age, sex, and smoking
beta coefficient adjusted[2]: adjusted for age, sex, smoking, obesity, hypertension, dyslipidemia, diabetes mellitus, CKD, and statins
[a] significant variable ($p < 0.05$)

extra-articular manifestation associated with carotid plaques in the age, sex and smoking adjusted model, while uveitis and extra-articular manifestations only showed a non-significant trend with cIMT in the crude analysis and CV events, respectively. It seems necessary to carry out more research to elucidate whether they confer additional CV risk to patients with AxSpA.

Table 4
Association between cardiovascular events and the main cardiovascular and disease-related features in 33 axSpA patients

Variable	OR (95% CI), p
Age (years)	1.09 (1.06-1.13), 0.000[a]
Male	2.25 (0.92-5.52), 0.076
Cardiovascular data	
History of CV risk factors	
Dyslipidemia	6.51 (2.89-14.69), 0.000[a]
Hypertension	4.37 (2.12-9.01), 0.000[a]
Diabetes Mellitus	6.85 (3.08-15.21), 0.000[a]
Lipids	
Total cholesterol	0.98 (0.97-0.99), 0.000[a]
HDL-cholesterol	0.97 (0.95-1.00), 0.047[a]
LDL-cholesterol	0.97 (0.96-0.99), 0.000[a]
Triglycerides	1.00 (1.00-1.01), 0.077[b]
Statins	7.37 (3.39-16.02), 0.000[a]
Carotid IMT, mm	1.01 (1.00-1.01), 0.000[a]
Carotid plaques, n (%)	6.59 (2.91-14.95), 0.000[a]
Disease-related data at time of study	
Mean disease duration, years	
Since first symptoms	1.03 (1.00-1.06), 0.023[a]
Since diagnosis	1.05 (1.02-1.08), 0.001[a]
BASDAI>4	2.58 (1.16-5.73), 0.020[a]
BASFI	1.25 (1.08-1.45), 0.003[a]
BASMI	1.19 (0.99-1.42), 0.063
Syndesmophytes	2.41 (1.15-5.03), 0.020[a]
Grade of sacroiliitis Rx	
Grade $\geq$ 3 (uni or bilateral)	5,57 (1.94-16.00), 0.001[a]
Grade 4 (uni or bilateral)	3.75 (1.85-7.57), 0.000[a]
Current drugs	
NSAIDs, n (%)	0.32 (0.16-0.66), 0.002[a]
Currrent prednisone, n (%)	2.31 (1.02-5.28), 0.046[a]
Methotrexate, n (%)	2.29 (1.01-4.94), 0.034[a]
Anti-TNF-alpha, n (%)	3.33 (1.61-6.87), 0.001[a]
Historical disease-related data	
History of synovitis	1.89 (0.93-3.83), 0.079
Extra-articular manifestations (total)	1.96 (0.97-3.99), 0.062
CRP at time of disease diagnosis, (mg/L)	1.01 (1.00-1.02), 0.058
CRP >3 at time of diagnosis	5.27 (1.82-15.30), 0.002[a]
ESR at the time of disease diagnosis (mm/1st hour)	1.03 (1.02-1.05), 0.000[a]
Anti-TNF-α (from the disease diagnosis)	2.95 (1.03-8.44), 0.044[a]

[a] significant variables, $p < 0.05$

Increasing evidence indicates a beneficial effect of both synthetic and biological DMARDs in the CV risk of axSpA [42]. Nevertheless, these therapies were found to be associated with subclinical atherosclerosis and CV events in our series. We believe that it is a confounding by indication effect. In this sense, we interpret these findings not so much as a possible deleterious effect of these drugs, but rather because of the greater severity of the disease that characterizes patients receiving DMARDs, more commonly affected by peripheral arthritis and extra-articular manifestations and with higher inflammatory markers.

Our group recently reported a comparable severity of atherosclerosis in radiographic and non-radiographic axSpA patients, despite the latter being characterized by a weaker inflammatory burden and lower values of BASMI [44]. ~~We~~ The present study also found no difference in the potential disease-related pro-atherogenic factors identified in both conditions, thus confirming the modest impact of these particularities in the atherosclerotic disease of axSpA.

Such differences in the inflammatory response and, above all, in spinal mobility, could be determined by the higher age and male ratio that characterizes AS in our series. This point would explain the comparable association observed between BASMI and carotid plaques in both conditions when the analysis was adjusted by age and sex. Besides, although statistically significant, the differences found between radiographic and non-radiographic axSpA in this regard might not clinically relevant enough to confer a higher CV risk to AS.

The cross-sectional design is a limitation of the present study, which does not allow us to establish a causal effect on the associations described. We are also aware that results from the group of patients with past CV events should be interpreted with caution. The scarce number of available patients constituted a serious limitation to calculate adjusted analysis, so we only showed the univariable associations, which resulted more representative. Besides, except for some historical variables like ESR or CRP at diagnosis, most of the assessed factors were dated after the CV event occurred"

In conclusion, through the analysis of both CV events and subclinical atherosclerosis in a large cohort of axSpA patients, the present study confirms the critical role of inflammation in the development of accelerated atherosclerosis, which seems to be independent of the putative effect of inflammation on the traditional CV risk factors. The functional limitation measured by BASFI, a disease severity feature also related to the cumulative inflammatory burden, was also associated with atherosclerosis, while the role of extra-articular manifestations remains unclear. Interestingly, no differences were found between radiographic and non-radiographic axSpA in the potential effects of SpA features on cIMT and carotid plaques despite the weaker inflammatory response that characterizes the latter. These results provide helpful information to design more accurate predictive tools to improve the primary prevention of CV events in axSpA and constitute an additional argument supporting a treat to target strategy with tight control of inflammation, which would predictably have beneficial consequences also in CV risk.

Declaration of Competing Interest

None.

References

[1] Castañeda S, Nurmohamed MT, González-Gay MA. Cardiovascular disease in inflammatory rheumatic diseases. Best Pract Res Clin Rheumatol 2016. https://doi.org/10.1016/j.berh.2016.10.006.

[2] Alexandroff AB, Pauriah M, Camp RDR, Lang CC, Struthers AD, Armstrong DJ. More than skin deep: atherosclerosis as a systemic manifestation of psoriasis. Br J Dermatol 2009. https://doi.org/10.1111/j.1365-2133.2009.09281.x.

[3] Cainzos-Achirica M, Glassner K, Zawahir HS, Dey AK, Agrawal T, Quigley EMM, et al. Inflammatory Bowel Disease and Atherosclerotic Cardiovascular Disease: JACC Review Topic of the Week. J Am Coll Cardiol 2020. https://doi.org/10.1016/j.jacc.2020.10.027.

[4] Haroon NN, Paterson JM, Li P, Inman RD, Haroon N. Patients with ankylosing spondylitis have increased cardiovascular and cerebrovascular mortality: a population-based study. Ann Intern Med 2015;163:409–16. https://doi.org/10.7326/M14-2470.

[5] Szabo SM, Levy AR, Rao SR, Kirbach SE, Lacaille D, Cifaldi M, et al. Increased risk of cardiovascular and cerebrovascular diseases in individuals with ankylosing spondylitis: a population-based study. Arthritis Rheum 2011;63:3294–304. https://doi.org/10.1002/art.30581.

[6] Mathieu S, Soubrier M. Cardiovascular events in ankylosing spondylitis: a 2018 meta-analysis. Ann Rheum Dis 2019;78:1–3. https://doi.org/10.1136/annrheumdis-2018-213317.

[7] Martín-Martínez MA, Castañeda S, Sánchez-Alonso F, García-Gómez C, González-Juanatey C, Sánchez-Costa JT, et al. Cardiovascular mortality and cardiovascular event rates in patients with inflammatory rheumatic diseases in the CARdiovascular in rheuMAtology (CARMA) prospective study—results at 5 years of follow-up. Rheumatology 2020. https://doi.org/10.1093/rheumatology/keaa737.

[8] 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. https://doi.org/10.1002/acr.20364.

[9] Wright KA, Crowson CS, Michet CJ, Matteson EL. Time trends in incidence, clinical features, and cardiovascular disease in ankylosing spondylitis over three decades: a population-based study. Arthritis Care Res 2015;67:836–41. https://doi.org/10.1002/acr.22512.

[10] Rueda-Gotor J, Corrales A, Blanco R, Fuentevilla P, Portilla V, Expósito R, et al. Atherosclerotic disease in axial spondyloarthritis: Increased frequency of carotid plaques. Clin Exp Rheumatol 2015:33.

[11] Guin A, Sinhamahapatra P, Misra S, Choudhury Mazumder SR, Chatterjee S, Ghosh A. Incidence and effect of insulin resistance on progression of atherosclerosis in rheumatoid arthritis patients of long disease duration. Biomed J 2019. https://doi.org/10.1016/j.bj.2019.01.007.

[12] Arida A, Protogerou AD, Kitas GD, Sfikakis PP. Systemic inflammatory response and atherosclerosis: The paradigm of chronic inflammatory rheumatic diseases. Int J Mol Sci 2018;19:1–27. https://doi.org/10.3390/ijms19071890.

[13] Nambi V, Chambless L, Folsom AR, He M, Hu Y, Mosley T, et al. Carotid intima-media thickness and presence or absence of plaque improves prediction of coronary heart disease risk. The ARIC (Atherosclerosis Risk In Communities) Study. J Am Coll Cardiol 2010;55:1600–7. https://doi.org/10.1016/j.jacc.2009.11.075.

[14] Peters MJ, Van Der Horst-Bruinsma IE, Dijkmans BA, Nurmohamed MT. Cardiovascular risk profile of patients with spondylarthropathies, particularly ankylosing spondylitis and psoriatic arthritis. Semin Arthritis Rheum 2004;34:585–92. https://doi.org/10.1016/j.semarthrit.2004.07.010.
[15] Peters MJL, Van Eijk IC, Smulders YM, Serne E, Dijkmans BAC, Van Der Horst-Bruinsma IE, et al. Signs of accelerated preclinical atherosclerosis in patients with ankylosing spondylitis. J Rheumatol 2010;37:161–6. https://doi.org/10.3899/jrheum.090667.
[16] 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 2008;47:1203–7. https://doi.org/10.1093/rheumatology/ken198.
[17] Bodnar N, Kerekes G, Seres I, Paragh G, Kappelmayer J, Nemethne ZG, et al. Assessment of subclinical vascular disease associated with ankylosing spondylitis. J Rheumatol 2011;38:723. https://doi.org/10.3899/jrheum.100668. LP –729.
[18] Hamdi W, Bouaziz MC, 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. https://doi.org/10.3899/jrheum.110792.
[19] Gupta N, Saigal R, Goyal L, Agrawal AA, Bhargava R, Agrawal AA. Carotid intima media thickness as a marker of atherosclerosis in ankylosing spondylitis. Int J Rheumatol 2014:2014. https://doi.org/10.1155/2014/839135.
[20] Rudwaleit M, Van Der Heijde D, Landewé R, Listing J, Akkoc N, Brandt J, et al. The development of assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): Validation and final selection. Ann Rheum Dis 2009;68:777–83. https://doi.org/10.1136/ard.2009.108233.
[21] Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the bath ankylosing spondylitis disease activity index. J Rheumatol 1994;21:2286–91. https://doi.org/10.1002/acr.20575.PMID.
[22] Lukas C, Landewé R, Sieper J, Dougados M, Davis J, Braun J, et al. Development of an ASAS-endorsed disease activity score (ASDAS) in patients with ankylosing spondylitis. Ann Rheum Dis 2009;68:18. https://doi.org/10.1136/ard.2008.094870. LP –24.
[23] Jenkinson TR, Mallorie PA, Whitelock HC, Kennedy LG, Garrett SL. AC. Defining spinal mobility in ankylosing spondylitis (AS). The Bath AS Metrology Index. J Rheumatol 1994;21:1694–8.
[24] Calin A, Garrett S, Whitelock H, Kennedy LG, O'Hea J, Mallorie P JT. A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. J Rheumatol 1994;21:2281–5.
[25] Heuft-Dorenbosch L, Spoorenberg A, Van Tubergen A, Landewé R, Van Der Tempel H, Mielants H, et al. Assessment of enthesitis in ankylosing spondylitis. Ann Rheum Dis 2003;62:127–32. https://doi.org/10.1136/ard.62.2.127.
[26] Creemers MCW, Franssen MJAM, Van't Hof MA, Gribnau FWJ, Van De Putte LBA, Van Riel PLCM. Assessment of outcome in ankylosing spondylitis: an extended radiographic scoring system. Ann Rheum Dis 2005. https://doi.org/10.1136/ard.2004.020503.
[27] 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). Cerebrovasc Dis 2012;34:290–6. https://doi.org/10.1159/000343145.
[28] Solomon DH, Greenberg J, Curtis JR, Liu M, Farkouh ME, Tsao P, et al. Derivation and internal validation of an expanded cardiovascular risk prediction score for rheumatoid arthritis: A consortium of rheumatology researchers of North America registry study. Arthritis Rheumatol 2015;67:1995–2003. https://doi.org/10.1002/art.39195.
[29] Crowson CS, Rollefstad S, Kitas GD, Van Riel PLCM, Gabriel SE, Semb AG. Challenges of developing a Cardiovascular risk calculator for patients with rheumatoid arthritis. PLoS One 2017;12:1–21. https://doi.org/10.1371/journal.pone.0174656.
[30] Kim SH, Lee SH, Kim HR, Min HK. Cardiovascular disease risk calculators to reflect the subclinical atherosclerosis of coronary artery in rheumatoid arthritis: a pilot study. BMC Rheumatol 2021;5:1–7. https://doi.org/10.1186/s41927-021-00213-3.
[31] Agca R, Heslinga SC, Rollefstad S, Heslinga M, McInnes IB, Peters MJL, 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 2016;76:17–28. https://doi.org/10.1136/annrheumdis-2016-209775.
[32] Bermudez EA, Rifai N, Buring J, Manson JAE, Ridker PM. Interrelationships among circulating interleukin-6, C-reactive protein, and traditional cardiovascular risk factors in women. Arterioscler Thromb Vasc Biol 2002;22:1668–73. https://doi.org/10.1161/01.ATV.0000029781.31325.66.
[33] Gonzalez-Gay MA, Gonzalez-Juanatey C, Lopez-Diaz MJ, Piñeiro A, Garcia-Porrua C, Miranda-Filloy JA, et al. HLA-DRB1 and persistent chronic inflammation contribute to cardiovascular events and cardiovascular mortality in patients with rheumatoid arthritis. Arthritis Care Res 2007;57:125–32. https://doi.org/10.1002/art.22482.
[34] Rojas-gim M, Clementina L. Subclinical atherosclerosis measure by carotid ultrasound and inflammatory activity in patients with rheumatoid arthritis and spondylarthritis 2022:1–12.
[35] Sattar N, McCarey DW, Capell H, McInnes IB. Explaining how "High-Grade" systemic inflammation accelerates vascular risk in rheumatoid arthritis. Circulation 2003;108:2957–63. https://doi.org/10.1161/01.CIR.0000099844.31524.05.
[36] Ferraz-Amaro I, Rueda-Gotor J, Genre F, Corrales A, Blanco R, Portilla V, et al. Potential relation of cardiovascular risk factors to disease activity in patients with axial spondyloarthritis. Ther Adv Musculoskelet Dis 2021;13:1–10. 10.1177/1759720x211033755.
[37] Zochling J. Measures of symptoms and disease status in ankylosing spondylitis: ankylosing spondylitis disease activity score (ASDAS), ankylosing spondylitis quality of life scale (ASQoL), bath ankylosing spondylitis disease activity index (BASDAI). Bath Ankylosing Sp. Arthritis Care Res 2011;63:S47–58. https://doi.org/10.1002/acr.20575.
[38] Landewé R, Dougados M, Mielants H, Van Der Tempel H, Van Der Heijde D. Physical function in ankylosing spondylitis is independently determined by both disease activity and radiographic damage of the spine. Ann Rheum Dis 2009;86:863–7. https://doi.org/10.1136/ard.2008.091793.
[39] Castañeda S, Martín-Martínez MA, González-Juanatey C, Llorca J, García-Yébenes MJ, Pérez-Vicente S, et al. Cardiovascular morbidity and associated risk factors in Spanish patients with chronic inflammatory rheumatic diseases attending rheumatology clinics: Baseline data of the CARMA Project. Semin Arthritis Rheum 2015;44:618–26. https://doi.org/10.1016/j.semarthrit.2014.12.002.
[40] Ladehesa-Pineda ML, Arias de la Rosa I, López Medina C, Castro-Villegas M del C, Ábalos-Aguilera M del C, Ortega-Castro R, et al. Assessment of the relationship between estimated cardiovascular risk and structural damage in patients with axial spondyloarthritis. Ther Adv Musculoskelet Dis 2020;12:1–15. https://doi.org/10.1177/1759720x20982837.
[41] Karmacharya P, Duarte-Garcia A, Dubreuil M, Murad MH, Shahukhal R, Shrestha P, et al. Effect of therapy on radiographic progression in axial spondyloarthritis: a systematic review and meta-analysis. Arthritis Rheumatol 2020;72:733–49. https://doi.org/10.1002/art.41206.
[42] Toussirot E. The risk of cardiovascular diseases in axial spondyloarthritis. Current Insights. Front Med 2021;8. https://doi.org/10.3389/fmed.2021.782150.
[43] Lai Y-F, Lin T-Y, Chien W-C, Sun C-A, Chung C-H, Chen Y-H, et al. Uveitis as a risk factor for developing acute myocardial infarction in ankylosing spondylitis: a national population-based longitudinal Cohort study. Front Immunol 2022;12:1–10. https://doi.org/10.3389/fimmu.2021.811664.
[44] González Mazón I, Rueda-Gotor J, Ferraz-Amaro I, Genre F, Corrales A, Calvo Rio V, et al. Subclinical atherosclerotic disease in ankylosing spondylitis and non-radiographic axial spondyloarthritis. A multicenter study on 806 patients. Semin Arthritis Rheum 2021;51:395–403. https://doi.org/10.1016/j.semarthrit.2021.02.003.