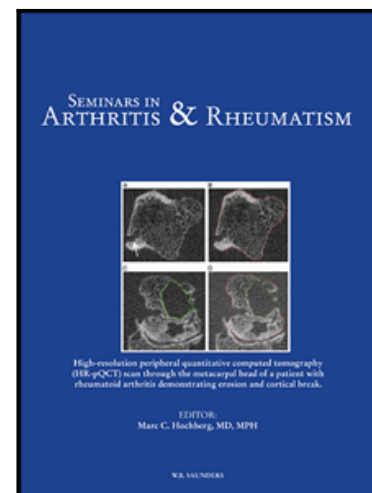Journal Pre-proof

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

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

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Highlights

- Identifying pro-atherogenic factors in rheumatic diseases can help prevent cardiovascular events.

- Axial spondyloarthritis features associated with atherosclerosis remain unclear

- Inflammation and disease severity are associated with atherosclerosis in axial spondyloarthritis

Graphical abstract

DISEASE FEATURES ASSOCIATED WITH ATHEROSCLEROSIS IN 838 PATIENTS WITH AXIAL SPONDYLOARTHRITIS
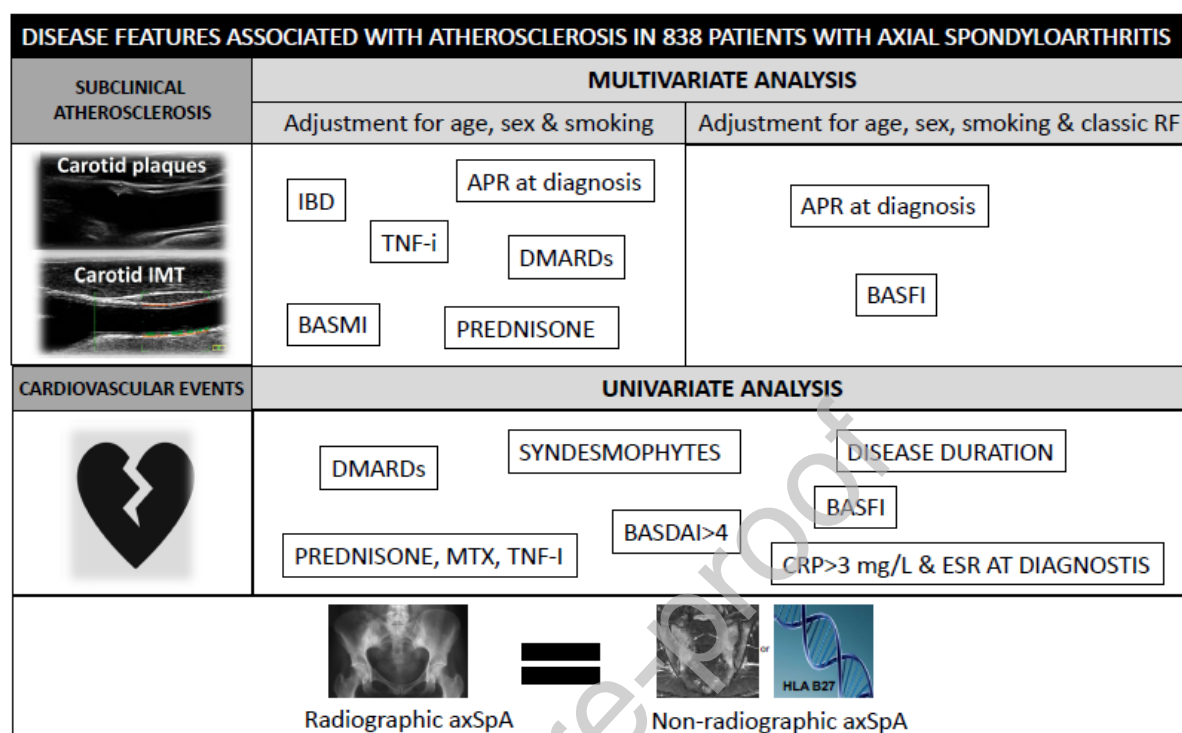
ABSTRACT

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 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.

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

1.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.

2.MATERIALS AND METHODS

2.1 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.

2.2 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).

2.3 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.

3. RESULTS

3.1 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 (table1).

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 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).

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

3.2.1 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).

3.2.2 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).

3.3 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.

4. 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, 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 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.

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.

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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 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 +	191 + 39	0.75
HDL-cholesterol	54 + 16	59 + 20	53 + 15	0.001
LDL-cholesterol	116 + 33	114 +	116 + 34	0.52
Atherogenic index >4	298 (36)	55 (33)	243 (38)	0.21
Triglycerides	118 + 75	115 +	119 + 74	0.51
Statins	122 (15)	11 (7)	111 (17)	0.002
Blood pressure, mm Hg				
Systolic	129 + 17	125 +	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 +	2.30 +	2.31 +	0.91
Inactive disease	133 (16)	34 (20)	99 (15)	
Low disease activity	183 (22)	32 (19)	151 (24)	0.39
High disease activity	323 (39)	68 (41)	255 (40)	
Very high disease activity (>3.5)	75 (9)	16 (10)	59 (9)	
BASDAI	3.77 + 2.27	4.07 +	3.69 +	0.060
BASDAI>4	372 (44)	83 (50)	289 (45)	0.24
CRP at time of study, m/L	2.2 (0.6-	1.0 (0.5-	2.6 (0.9-	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 +	3.6 + 2.6	0.31
BASMI	2.7 + 2.1	2.0 +	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
Methotrexate, 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
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-	2.0 (0.6-	4.6 (1.4-	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, mm	643 + 146	586 +	658 +	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

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			Interactio
	OR^c (95%	OR	OR	ORc (95%	OR	OR	
Age	**1.10 (1.07-**			**1.15 (1.12-**			n.s.
Male	**1.78 (1.14-**			**1.75 (1.11-**			n.s.
Cardiova							
History							
Current	1.33 (0.88-			**1.60 (1.06-**			n.s.
Have	1.40 (0.94-			**1.86 (1.23-**			n.s.
Obesity	1.51 (0.97-			1.23 (0.77-			n.s.
	1.90 (1.27-			**3.37 (2.23-**			n.s.
	2.11 (1.39-			**3.15 (2.07-**			n.s.
Diabetes	**2.11 (1.00-**			**4.46 (2.35-**			n.s.
Chronic	2.28 (0.63-			**3.66 (1.16-**			n.s.
Lipids							
Atheroge	**1.67 (1.11-**			1.08 (0.71-			n.s.
Triglycer	1.00 (1.00-			**1.00 (1.00-**			n.s.
Statins	**2.57 (1.53-**			**3.96 (2.36-**			
Blood							
Systolic	1.04 (1.02-			1.04 (1.03-			n.s.
Diastolic	1.03 (1.01-			0.99 (0.97-			n.s.
Carotid	**1.84 (1.56-**			**2.19 (1.85-**			
Disease-							
Mean							
disease	**1.04 (1.03-**	1.02 (1.00-	1.01 (0.99-	**1.07 (1.05-**	1.01 (0.99-	1.01 (0.99-	n.s.
duration.	**1.04 (1.02-**	1.01 (0.98-	1.00 (0.98-	**1.05 (1.03-**	0.99 (0.97-	0.99 (0.97-	n.s.
ASDAS	1.21 (0.98-	1.23 (0.92-	1.20 (0.94-	**1.35 (1.09-**	1.23	1.15 (0.92-	n.s.
ASDAS	2.20 (1.00-	2.00 (0.68-	1.32 (0.54-	**3.43 (1.54-**	1.72 (0.67-	1.24 (0.54-	
BASDAI	1.07 (0.98-	1.10 (0.97-	1.10 (0.99-	1.09 (0.99-	1.09 (0.98-	1.07 (0.97-	n.s.
CRP at	1.00 (0.98-	1.00 (0.98-	0.99 (0.97-	**1.02 (1.00-**	1.00 (0.98-	0.99 (0.97-	n.s.
BASFI	**1.19 (1.10-**	1.06 (0.95-	**1.13 (1.03-**	**1.17 (1.08-**	1.07 (0.98-	**1.12 (1.03-**	n.s.
BASMI	**1.27 (1.14-**	**1.22 (1.07-**	1.11 (0.98-	**1.45 (1.30-**	**1.21 (1.07-**	1.11 (0.99-	n.s.
Syndesm	**2.09 (1.39-**	0.86 (0.48-	1.11 (0.67-	**2.17 (1.43-**	0.81 (0.48-	1.11 (0.69-	n.s.
log	**1.30 (1.05-**	0.89 (0.58-	1.14 (0.81-	**1.77 (1.40-**	0.97 (0.71-	0.88 (0.67-	
Grade of							
Grade ≥	**1.53 (1.01-**	0.80 (0.43-	0.85 (0.50-	**1.83 (1.19-**	0.79 (0.46-	0.80 (0.50-	-
Grade 4	**2.48 (1.63-**	1.02 (0.57-	1.30 (0.78-	**2.35 (1.53-**			-
Prednison	1.52 (0.86-	**2.42 (1.11-**	1.56 (0.75-	**1.91 (1.10-**	**2.28 (1.19-**	1.58 (0.84-	n.s.
DMARD	1.32 (0.89-	**2.01 (1.15-**	1.26 (0.76-	**1.63 (1.09-**	**1.90 (1.18-**	1.53 (0.98-	n.s.
Methotre	**1.61 (0.98-**	**2.20 (1.11-**	1.50 (0.80-	**2.21 (1.36-**	**2.03 (1.14-**	1.49 (0.86-	n.s.
Historica							
History	0.90 (0.59-	1.30 (0.76-	0.78 (0.48-	**1.51 (1.01-**	1.21 (0.76-	0.73 (0.47-	n.s.
History	**1.63 (1.01-**	1.05 (0.56-	0.99 (0.56-	1.55 (0.95-	0.95 (0.53-	1.04 (0.61-	0.017
Extra-							
Total	0.95 (0.64-	1.52 (0.88-	0.90 (0.55-	1.42 (0.95-	1.30 (0.81-	0.92 (0.59-	0.015
Inflamm	1.13 (0.54-	**3.48 (1.32-**	1.96 (0.79-	1.18 (0.56-	1.82 (0.76-	1.48 (0.66-	n.s.
CRP at	1.01 (1.00-	1.00 (0.99-	1.01 (1.00-	1.00 (0.99-	1.00 (0.99-	1.00 (1.00-	n.s.
CRP >3	**1.59 (1.06-**	1.32 (0.75-	1.35 (0.83-	**1.84 (1.20-**	1.37 (0.84-	1.29 (0.84-	n.s.
ESR at	**1.01 (1.00-**	1.01 (0.99-	1.01 (1.00-	**1.02 (1.00-**	1.00 (0.99-	1.01 (0.99-	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

a significant variable ($p < 0.05$)

In the interaction analysis carotid plaque is considered an ordinal variable (0= no plaque, 1=unilateral, 2=bilateral).

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

Variables	Carotid IMT			Interaction p value nr-axSpA Vs AS
	beta coefficient[c] (95%CI), p.	beta coefficient adjusted [1] (95% CI), p.	beta coefficient adjusted [2] (95% CI), p.	
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-	-0.03 (-0.98-	n.s.

		0.65), 0.59	0.93), 0.96
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 ($p < 0.05$)

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 ≥ 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, $p < 0.05$