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Reclassification into very-high cardiovascular risk after carotid ultrasound in patients with axial spondyloarthritis

J. Rueda-Gotor[1], J.C. Quevedo-Abeledo[2], A. Corrales[1], F. Genre[3], V. Hernández-Hernández[4], E. Delgado-Frías[4], M.Á. González-Gay[1,3,5,6], I. Ferraz-Amaro[4]

[1]Division of Rheumatology, Hospital Universitario Marqués de Valdecilla, Santander, Spain;
[2]Division of Rheumatology, Hospital Doctor Negrín, Las Palmas de Gran Canaria, Spain;
[3]Epidemiology, Genetics and Atherosclerosis Research Group on Systemic Inflammatory Diseases, Hospital Universitario Marqués de Valdecilla, IDIVAL, Santander, Spain;
[4]Division of Rheumatology, Hospital Universitario de Canarias, Tenerife, Spain;
[5]School of Medicine, University of Cantabria, Santander, Spain;
[6]Cardiovascular Pathophysiology and Genomics Research Unit, School of Physiology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa.

Abstract

Objective

Subclinical atherosclerosis, defined as the presence of carotid plaques, is more frequently found in patients with axial spondyloarthritis (axSpA) than in healthy individuals. We sought to determine whether axSpA patients are more commonly reclassified into the very high cardiovascular risk category than controls after performing carotid ultrasound and if this can be linked to disease characteristics.

Methods

343 patients diagnosed with axSpA according to ASAS criteria and 177 controls were studied. Disease characteristics and Systematic Coronary Risk Evaluation (SCORE) were assessed in patients and controls. Presence of plaques and intima-media thickness (cIMT) was determined by carotid ultrasound. Multivariable regression analysis was performed to identify differences in the frequency of reclassification between patients and controls, as well as factors associated with reclassification in axSpA.

Results

Carotid plaques (36% vs.25%, p=0.010) and higher cIMT (0.641± 0.121 vs. 0.602± 0.115 mm, p=0.001) were more common in patients than controls. Reclassification into the high-risk category was greater in patients (34% vs. 25%, p=0.037). Age (beta coefficient 2.74 [95%CI 1.34–5.62] vs. beta coef. 0.63 (95%CI 0.40–0.99) in patients, interaction p=0.001) and serum LDL-cholesterol (beta coef. 1.03 [95%CI 1.02–1.04] vs. beta coef. 1.00 [0.99–1.01], interaction p=0.029) showed a higher effect on reclassification in controls after multivariable analysis. Although reclassification in axSpA was associated with higher ASDAS-CRP, BASFI and BASMI scores, these associations were lost after adjusting for cardiovascular risk factors.

Conclusion

Patients with axSpA are more likely to be reclassified into the very-high risk category after carotid ultrasound than controls. The influence of traditional cardiovascular risk factors on this reclassification differs between patients and controls.

Key words
axial spondyloarthritis, carotid plaques, cardiovascular risk, SCORE

*Javier Rueda-Gotor, MD, PhD**
*Juan C. Quevedo-Abeledo, MD**
Alfonso Corrales, MD, PhD
Fernanda Genre, PhD
Vanesa Hernández-Hernández, MD, PhD
Esmeralda Delgado-Frías, MD, PhD
*Miguel A. González-Gay, MD, PhD***
*Iván Ferraz-Amaro, MD, PhD***

**These authors share first authorship.*
***These authors share senior authorship and are both corresponding authors.*

Please address correspondence to:
Miguel Ángel González-Gay,
Division of Rheumatology,
Hospital Universitario Marqués de Valdecilla, IDIVAL,
Avenida de Valdecilla, s/n,
39008 Santander, Spain.
Email: miguelaggay@hotmail.com

Iván Ferraz-Amaro,
Division of Rheumatology,
Hospital Universitario de Canarias,
38320 Santa Cruz de Tenerife, Spain.
E-mail: iferrazamaro@hotmail.com

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Introduction

Patients with axial spondyloarthritis (axSpA) are prone to an increased and premature prevalence of atherosclerosis (1, 2). This is due to the compound effects of a genetic component, classic cardiovascular risk (CVR) factors, inflammation, disease severity and the therapy used to manage the disease (3). In a recent report by Terenzi *et al*. regarding axSpA comorbidities (4), the assessment by positron emission tomography disclosed that the carotid arterial wall of patients with axSpA had higher rates of (18)F-fluorodeoxyglucose uptake than age and gender-matched healthy controls (4). Moreover, as a result of disease activity and functional impairment, arterial stiffness in axSpA patients had a trend to be higher (4).

All current clinical practice guidelines on the prevention of cardiovascular disease (CVD) recommend an assessment of total CVR since atherosclerosis usually results from a number of risk factors. Composite scores, such as the Systematic Coronary Risk Evaluation (SCORE) (5), are informative tools that guide preventive and therapeutic strategies by providing estimations of CVR. Nevertheless, when applied to patients with inflammatory diseases, such as rheumatoid arthritis and systemic lupus erythematosus (SLE), these scores have been found to significantly underestimate the actual risk of CVD (6–8). With respect to axSpA, the incidence of cardiovascular events was found to be three times higher than that predicted by the Framingham Risk Score (9). However, data on axSpA are limited since this issue has not been extensively studied in these patients.

The 2016 European Society of Cardiology guidelines recommend screening for carotid artery atherosclerosis in patients with moderate CVD risk. The presence of plaque on carotid ultrasonography automatically implies a reclassification into very high risk. This approach thus helps identify patients with inflammatory arthritis who might be candidates for intensive preventive therapy (5). The probability of patient reclassification after carotid ultrasound was found to be higher in patients with SLE (8) and rheumatoid arthritis (10). Therefore, screening for asymptomatic atherosclerotic plaques by carotid ultrasound should be regarded as part of the CVD risk evaluation in these patients and in other forms of inflammatory joint disorders.

Taking all of these considerations into account, the main purpose of our study was to assess the impact of carotid ultrasound assessment on the CVR stratification of patients with axSpA who had initially been stratified according to SCORE risk charts compared to controls. We also aimed to identify disease-related characteristics or traditional CVR factors that could potentially predict such a CVR reclassification in axSpA.

Methods

Study participants

This was a cross-sectional study that included 520 individuals, 343 patients with axSpA and 177 controls. All of them were 18 years old or older and axSpA patients were enrolled if they had a clinical diagnosis of axSpA and fulfilled the Assessment of SpondyloArthritis International Society (ASAS) classification criteria for axSpA (11). All had been diagnosed by rheumatologists and were periodically followed-up at rheumatology outpatient clinics. For the purpose of inclusion in the present study, axSpA disease duration was required to be ≥1 year. Those axSpA patients undergoing biologic therapy (anti-tumour necrosis factor-TNF-alpha therapies) were not excluded from the present study. Likewise, since glucocorticoids can be used in the management of axSpA, patients taking prednisone were not excluded. None of the patients had established CVD. Diabetes mellitus patients were excluded because according to guidelines (12) these patients are considered to be in the very-high risk SCORE category when target organ damage is present. Additionally, patients were excluded if they had a history of cancer or any other chronic disease, evidence of active infection or a glomerular filtration rate <60ml/min/1.73m^2. The study protocol was approved by the Institutional Review Committees at Hospital Universitario de Canarias, Hospital Doctor Ne-

grín, Hospital Universitario Marqués de Valdecilla and Hospital de Laredo all in Spain, and all subjects provided informed written consent (approval no. 2016_64).

Assessments and data collection

Surveys in axSpA patients were performed to assess CVR factors and medication. Subjects completed a questionnaire and underwent a physical examination to determine anthropometric measurements and blood pressure. Medical records were reviewed to ascertain specific diagnoses and medications. Hypertension was defined as a systolic or a diastolic blood pressure higher than 140 and 90 mmHg, respectively. Dyslipidaemia was defined if one of the following factors was present: total cholesterol >200 mg/dl, triglyceride >150 mg/dl, HDL cholesterol <40 in men or <50 mg/dl in women, LDL cholesterol >130 mg/dl, or current use of statins. The atherogenic index was calculated using the total cholesterol/HDL cholesterol ratio. Two clinical indexes of disease activity (Bath Ankylosing Spondylitis Disease Activity Index, BASDAI and Ankylosing Spondylitis Disease Activity Score, ASDAS-C-reactive protein [CRP]) (13, 14), a functional status index (Bath Ankylosing Spondylitis Functional Index, BASFI) (15), a metrologic index (Bath Ankylosing Spondylitis Metrology Index, BASMI) (16), and an enthesitis index (Maastricht Ankylosing Spondylitis Enthesitis Score - MASES) (17) were evaluated in all patients at the time of assessment. Additionally, standard techniques were used to measure plasma glucose, C-reactive protein, and serum lipids.

Carotid ultrasound assessment

Carotid ultrasound was performed to assess carotid intima-media wall thickness (cIMT) in the common carotid artery and to detect focal plaques in the extracranial carotid tree in patients with axSpA and controls, as previously reported (10,18). A commercially available scanner, an Esaote Mylab 70 (Genoa, Italy) equipped with a 7–12 MHz linear transducer and an automated software-guided radiofrequency technique – Quality Intima Media

Table I. Demographic data of the 343 axial spondyloarthritis patients and 177 controls.

	Controls=177	axSpA=343	*p*-value
Male, n (%)	90 (51)	200 (58)	**0.048**
Age, years	45 ± 12	49 ± 12	**0.000**
BMI, mg/cm^2	26 ± 4	27 ± 5	0.058
Waist circumference, cm	90 ± 14	95 ± 13	**0.000**
Systolic pressure, mmHg	125 ± 15	129 ± 18	**0.004**
Diastolic pressure, mmHg	78 ± 9	78 ± 12	0.18
Comorbidity			
Hypertension, n (%)	20 (11)	79 (23)	**0.001**
Dyslipidaemia, n (%)	25 (14)	114 (33)	**0.000**
Current smoking, n (%)	32 (18)	134 (31)	**0.000**
SCORE	0.1 (0.0-0.4)	0.6 (0.1-2)	**0.000**
Analytical data			
Cholesterol, mg/dl	200 ± 34	194 ± 39	0.082
Triglycerides, mg/dl	102 ± 56	125 ± 83	**0.002**
LDL-cholesterol, mg/dl	120 ± 31	116 ± 33	0.13
HDL-cholesterol, mg/dl	55 ± 21	54 ± 18	0.060
Atherogenic index	3.7 ± 1.1	3.9 ± 1.2	0.068
CRP, mg/l	0.50 (0.20-1.60)	2.80 (1.00-6.20)	0.39
axSpA-related data			
Disease duration, years		7 (2-16)	
HLA-B27, n (%)		253 (79)	
Family history of axSpA, n (%)		71 (21)	
ASDAS-CRP		2.3 ± 1	
Inactive disease, n (%)		65 (19)	
Low disease activity, n (%)		80 (23)	
High disease activity, n (%)		157 (46)	
Very high disease activity, n (%)		41 (12)	
BASDAI, total score		3.7 (1.9-5.4)	
BASDAI >4, n (%)		156 (46)	
BASDAI >4 and CRP >5 mg/dl, n (%)		46 (14)	
BASFI, total score		3.3 (1.6-5.8)	
BASMI, total score		2.8 (1.2-4.2)	
MASES, total score		0 (0-2)	
ESR, mm/h		5 (2-13)	
Peripheral arthritis ever, n (%)		142 (41)	
Enthesitis, n (%)		111 (32)	
Extraarticular manifestations, n (%)		97 (28)	
Uveitis, n (%)		85 (25)	
Psoriasis, n (%)		16 (5)	
Inflammatory bowel disease, n (%)		13 (4)	
Syndesmophytes in axial x-ray		143 (42)	
Current NSAID, n (%)		270 (79)	
Current prednisone, n (%)		34 (10)	
DMARDs, n (%)		115 (34)	
Methotrexate, n (%)		61 (18)	
Sulfasalazine, n (%)		72 (21)	
anti-TNF-alpha, n (%)		119 (35)	
Carotid intima media assessment			
Carotid plaque, n (%)	45 (25)	125 (36)	**0.011**
cIMT, mm	0.602 ± 0.115	0.641 ± 0.121	**0.001**
Reclassification after carotid ultrasound, n (%)	45 (25)	118 (34)	**0.037**

Data represent mean ± SD or median (IQR) when data were not normally distributed.
BMI: body mass index; LDL: low-density lipoprotein; HDL: high-density lipoprotein; CRP: C-reactive protein.
ASDAS-CRP (Ankylosing Spondylitis Disease Activity Score) categories were defined as: <1.3 inactivity; ≥1.3 to <2.1 low disease activity; ≥2.1 to <3.5 high disease activity; ≥3.5 very high.
NSAID: non-steroidal anti-inflammatory drugs; DMARD: disease-modifying anti rheumatic drug.
cIMT, carotid intima media thickness; TNF: tumour necrosis factor. SCORE: Systematic Coronary Risk Evaluation.
BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI Bath Ankylosing Spondylitis Metrology Index.
BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score.
Reclassification refers to being reclassified into a very-high category after carotid plaque identification.
Significant *p*-values are depicted in **bold**.

Table II. Differences between reclassified and non-reclassified axial spondyloarthritis patients and controls.

	Reclassification into very-high risk SCORE after carotid ultrasound					
	axSpA patients			Controls		
	No (n=225)	Yes (n=118)	*p*-value	No (n=132)	Yes (n=45)	*p*-value
Male, n (%)	140 (62)	60 (51)	**0.043**	59 (45)	31 (69)	**0.006**
Age, years	45 ± 11	55 ± 10	**0.000**	41 ± 10	55 ± 11	**0.000**
BMI, mg/cm^2	26.5 ± 4.4	27.3 ± 4.8	0.15	25.5 ± 4.6	27.5 ± 3.1	**0.011**
Waist circumference, cm	93 ± 13	99 ± 12	**0.003**	88 ± 14	97 ± 12	**0.001**
Systolic pressure, mmHg	127 ± 17	134 ± 17	**0.000**	122 ± 14	131 ± 16	**0.001**
Diastolic pressure, mmHg	75 ± 18	78 ± 17	0.079	77 ± 9	80 ± 9	0.15
Comorbidity						
Hypertension, n (%)	39 (17)	40 (34)	**0.001**	11 (8)	9 (20)	**0.038**
Dyslipidaemia, n (%)	57 (26)	52 (44)	**0.002**	14 (11)	11 (24)	**0.021**
Current smoking, n (%)	62 (28)	49 (42)	0.38	24 (18)	8 (18)	0.079
Obesity, n (%)	34 (15)	25 (21)	0.16	18 (14)	4 (9)	0.41
Analytical data						
Cholesterol, mg/dl	191 ± 38	197 ± 40	0.20	194 ± 34	215 ± 29	**0.000**
Triglycerides, mg/dl	120 ± 77	132 ± 92	0.19	97 ± 55	116 ± 55	0.057
LDL-cholesterol, mg/dl	114 ± 32	118 ± 35	0.21	114 ± 30	137 ± 27	**0.000**
HDL-cholesterol, mg/dl	51 ± 19	52 ± 16	0.91	56 ± 23	52 ± 17	0.19
Atherogenic index	3.8 ± 1.2	4 ± 1.1	0.070	3.5 ± 1	4.1 ± 1	**0.000**
CRP, mg/l	2.40 (0.97-6.00)	3.70 (1.40-7.00)	0.80	0.50 (0.20-1.55)	0.60 (0.20-1.90)	0.55
Carotid intima media assessment						
cIMT, mm	0.604 ± 0.100	0.707 ± 0.128	**0.000**	0.570 ± 0.086	0.696 ± 0.138	**0.000**

Data represent mean±SD or median (IQR) when data were not normally distributed. CRP: C-reactive protein. BMI: body mass index; LDL: low-density lipoprotein; HDL: high-density lipoprotein; cIMT, carotid intima media thickness. Significant *p*-values are depicted in **bold**.

Thickness in real-time (QIMT, Esaote, Maastricht, Holland) – was used for this purpose. Based on the Mannheim consensus, plaque criteria in the accessible extracranial carotid tree (common carotid artery, bulb and internal carotid artery) were defined as follows: a focal protrusion in the lumen measuring at least cIMT >1.5 mm; a protrusion at least 50% greater than the surrounding cIMT; or an arterial lumen encroaching >0.5 mm (19).

Statistical analysis

Demographic and clinical characteristics were described in patients with axSpA and controls as mean ± standard deviation or percentages for categorical variables. For non-normally distributed continuous variables, data were expressed as median and interquartile range (IQR). Univariate differences between patients and controls and reclassified and non-reclassified individuals were assessed using the Student's t, Mann-Whitney, Chi squared or Fisher Exact tests, according to normal distribution or number of subjects. Logistic regression analysis adjusted for the variables with a *p*-value below 0.20 in the univariate analysis was performed to assess the relation of axSpA disease-related data with the presence of reclassification. Interaction factors were added to the regression models when we addressed the comparison of the effect (beta coefficients) between controls and axSpA patients. All of the analyses used a 5% two-sided significance level and were performed using SPSS software, v. 21 (IBM, Chicago, IL, USA) and STATA software, v. 15/SE (Stata Corp., College Station, TX, USA). A *p*-value <0.05 was considered statistically significant.

Results

Demographic, analytical and disease-related data

A total of 343 axSpA patients and 177 controls with a mean age of 49±12 and 45±12 years, respectively, were included in this study. Demographic and disease-related characteristics of the participants are shown in Table I. Male gender was more frequent in axSpA patients. Similarly, the frequency of all traditional CVR factors (hypertension, dyslipidaemia and current smoking) was higher in axSpA patients. Consequently, an increased SCORE (median 0.6 [IQR 0.1–2] *vs*.0.1 [IQR- 0.0–0.4], *p*=0.000) was also found in axSpA patients. Laboratory assessment revealed higher triglyceride serum levels in axSpA patients (125±83 *vs*.102±56 mg/dl, *p*=0.002) and a similar CRP in both populations.

The median axSpA disease duration was 7 (IQR 2-16) years. Two hundred and fifty-three (79%) of the patients were positive for HLA-B27. Nineteen percent of the patients were categorised as having inactive disease based on the ASDAS-CRP index, while 23%, 46%, and 12% were included in the low, high, and very high disease activity categories, respectively. BASDAI, BASFI and BASMI scores were, respectively, 3.7 (IQR 1.9–5.4), 3.3 (IQR 1.6–5.8) and 2.8 (1.2–4.2). Regarding therapies, 10% of the axSpA patients were taking prednisone, 79% were taking non-steroidal anti-inflammatory drugs, while 34% and 35% were receiving disease modifying antirheumatic drugs (DMARDs) and anti-TNF-alpha treatment, respectively. Additional disease-related information is shown in Table I.

With respect to carotid ultrasound assessment, 36% of the patients had carotid plaques compared to 25% of con-

Table III. Axial spondyloarthritis - related data and reclassification.

	Reclassification				
	Unadjusted model			Adjusted model for sex, age + CVR factors	
	No (n=225)	Yes (n=118)	*p*-value	OR (95% CI)	*p*-value
Disease duration, years	8 (3-17)	11 (4-20)	**0.005**	0.98 (0.95-1.01)	0.17
HLA-B27, n (%)	167 (74)	86 (73)	0.92	1.06 (0.54-2.05)	0.87
Family history of axSpA, n (%)	54 (25)	17 (14)	**0.039**	0.63 (0.32-1.24)	0.18
ASDAS-CRP	2.3 ± 1.0	2.5 ± 1.0	**0.025**	1.16 (0.88-1.51)	0.29
ASDAS-CRP disease activity state, n (%)					
Inactive disease	41 (18)	13 (11)	0.12	-	-
Low disease activity	54 (24)	28 (24)		1.34 (0.56-3.26)	0.51
High disease activity	97 (43)	52 (54)		1.33 (0.60-2.97)	0.48
Very high disease activity (>3.5)	26 (12)	23 (19)		1.88 (0.71-4.96)	0.20
BASDAI, total score	3.6 (1.7-5.2)	4.1 (2.4-5.7)	0.11	1.03 (0.91-1.15)	0.69
BASDAI >4, n (%)	97 (43)	72 (61)	0.25	1.15 (0.68-1.95)	0.59
BASDAI >4 and CRP >5 mg/dl, n (%)	29 (13)	22 (19)	0.16	1.58 (0.78-3.20)	0.21
BASFI, total score	2.7 (1.2-5.3)	4.2 (2.16.9)	**0.000**	1.03 (0.92-1.14)	0.65
BASMI, total score	2 (1-4)	3 (2-5)	**0.001**	0.96 (0.84-1.10)	0.58
MASES, total score	0 (0-2)	0 (0-2)	0.97	1.00 (0.91-1.11)	0.69
CRP, mg/l	1.4 (0.5-4.0)	2.2 (0.6-5.4)	0.80	0.99 (0.97-1.01)	0.40
ESR, mm/h	5 (2-9)	6 (2-15)	0.73	1.01 (0.99-1.02)	0.27
Peripheral arthritis ever, n (%)	97 (43)	45 (38)	0.37	**0.58 (0.34-0.99)**	**0.048**
Enthesitis, n (%)	34 (15)	35 (30)	0.36	0.80 (0.46-1.39)	0.43
Extraarticular manifestations, n (%)	59 (26)	38 (32)	0.24	1.32 (0.76-2.29)	0.33
Uveitis, n (%)	56 (25)	29 (25)	0.95	0.97 (0.54-1.73)	0.90
Psoriasis, n (%)	8 (4)	8 (7)	0.19	1.72 (0.52-5.72)	0.38
Inflammatory bowel disease, n (%)	4 (2)	9 (8)	**0.013**	**5.19 (1.33-20.24)**	**0.018**
Syndesmophytes in the axial x-ray	78 (34)	65 (55)	**0.000**	1.16 (0.67-2.00)	0.61
Current NSAID, n (%)	178 (79)	92 (78)	0.97	1.48 (0.75-2.89)	0.26
Current prednisone, n (%)	19 (8)	25 (21)	0.22	1.78 (0.78-4.04)	0.17
DMARDs, n (%)	69 (31)	46 (39)	0.14	1.53 (0.88-2.67)	0.13
Methotrexate, n (%)	35 (16)	26 (22)	0.14	1.49 (0.79-2.80)	0.22
Sulfasalazine, n (%)	46 (20)	26 (22)	0.81	1.27 (0.67-2.42)	0.47
anti-TNF-alpha, n (%)	77 (34)	42 (36)	0.72	1.02 (0.59-1.76)	0.94

Data represent means±SD or median (IQR) when data were not normally distributed.
ASDAS-CRP disease activity state were defined as: <1.3 inactivity; ≥1.3 to <2.1 low disease activity; ≥2.1 to <3.5 high disease activity; ≥3.5 very high disease activity.
BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI Bath Ankylosing Spondylitis Metrology Index.
BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score.
NSAID: non-steroidal anti-inflammatory drugs; DMARD: disease-modifying anti-rheumatic drug; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein. CVR: cardiovascular risk.
Adjusted for age, sex, BMI, waist circumference, hypertension and dyslipidaemia. Significant *p*-values are depicted in **bold**.

trols (p=0.011), and the average cIMT was higher in axSpA patients than in controls (0.641±0.121 *vs*. 0.602±0.115 mm, p=0.001). Additionally, reclassification into the very high SCORE category risk after carotid ultrasound assessment was higher in axSpA patients, with 34% of patients being reclassified compared to 25% of controls (p=0.037) (Table I).

Differences between reclassified and non-reclassified axial spondyloarthritis patients and controls after carotid ultrasound

Following carotid ultrasound examination and according to current guidelines, 118 (34%) patients and 45 (25%) controls were included in the very high-risk category. Patients and controls who were reclassified into very high risk were more commonly men and older, had a higher waist circumference, higher systolic pressure, and more often presented hypertension and dyslipidaemia than those individuals who were not reclassified into the very high-risk category. In contrast, the presence of obesity and current smoking did not yield any differences between reclassified and non-reclassified axSpA patients and controls. Finally, body mass index (BMI), total cholesterol, LDL-cholesterol, and atherogenic index were correlated with reclassification in controls but not in axSpA patients (Table II).

Axial spondyloarthritis-related data and reclassification

Regarding axSpA-related features, some associations were found in the univariate analysis (Table III). Disease duration (11 [IQR 4–20] *vs*. 8 [IQR 3–17] years, p=0.005) was found to behigher in the reclassified patients. Similarly, ASDAS-CRP (2.5±1.0 *vs*.2.3±1.0, p=0.025), BASFI and BASMI scores and syndesmophytes in the axial x-ray were found to be higher in the reclassified patients. In addition, the presence of inflammatory bowel disease was associated with an increased risk of reclassification. The remaining disease-related characteristics were not univariately different be-

Table IV. Differences in the effects of traditional cardiovascular risk factors on risk reclassification.

	OR (95% CI)			
	Reclassification into very-high risk SCORE after carotid ultrasound		Interaction	
	Controls	axSpA	Univariate	Adjusted
Male	**2.74 (1.34-5.62), 0.006**	**0.63 (0.40-0.99), 0.043**	**0.001**	
Age, years	**1.13 (1.09-1.18), 0.000**	**1.09 (1.06-1.11), 0.000**	0.10	
BMI, mg/cm^2	**1.11 (1.02-1.20), 0.011**	1.04 (0.99-1.09), 0.15	0.15	0.47
Waist circumference, cm	**1.05 (1.02-1.08), 0.001**	**1.03 (1.01-1.05), 0.003**	0.30	0.46
Comorbidity				
Hypertension	**2.75 (1.06-7.16), 0.038**	**2.45 (1.46-4.09), 0.001**	0.83	0.76
Dyslipidaemia	**2.73 (1.13-6.56), 0.025**	**2.07 (1.30-3.30), 0.002**	0.59	0.99
Current smoking	1.43 (0.96-2.14), 0.079	1.15 (0.84-1.59), 0.38	0.41	0.56
Obesity	0.62 (0.20-1.93), 0.41	1.51 (0.85-2.68), 0.16	0.17	0.17
Analytical data				
Cholesterol, mg/dl	**1.02 (1.01-1.03), 0.001**	1.00 (0.99-1.01), 0.20	**0.017**	**0.045**
Triglycerides, mg/dl	1.01 (1.00-1.01), 0.060	1.00 (0.99-1.00), 0.20	0.24	0.55
LDL-cholesterol, mg/dl	**1.03 (1.02-1.04), 0.000**	1.00 (0.99-1.01), 0.21	**0.002**	**0.029**
HDL-cholesterol, mg/dl	0.99 (0.98-1.01), 0.26	1.00 (0.99-1.01). 0.91	0.34	0.61
Atherogenic index	**1.78 (1.27-2.48), 0.001**	1.18 (0.98-1.43), 0.074	**0.039**	0.20

BMI: body mass index; LDL: low-density lipoprotein; HDL: high-density lipoprotein.
SCORE: Systematic Coronary Risk Evaluation.
Significant *p*-values are depicted in **bold**. Adjusted Interaction *p*-values are adjusted for age and sex.

tween reclassified and non-reclassified patients.

However, a multivariate regression analysis did not confirm the aforementioned results. In this sense, the relation of disease duration, ASDAS-CRP, and BASDAI and BASMI scores with reclassification was lost after adjusting for age, sex, BMI, waist circumference, and the presence of hypertension and dyslipidaemia. The only feature that remained significant was the occurrence of inflammatory bowel disease (odds ratio -OR- 5.19 [95% CI 1.33–20.24], p=0.018). In contrast, the existence of peripheral arthritis prior to the assessment became negatively associated, after the multivariable analysis, with the possibility of being reclassified (OR 0.58 [95% CI 0.34–0.99], p=0.048).

Differences in the effects of traditional CVR factors on risk reclassification

Differences in the effects of traditional CVR factors on reclassification were studied through the addition of interaction factors in this analysis (Table IV). In this respect, the effect of male sex, total cholesterol, and LDL-cholesterol serum levels over reclassification were higher in controls compared to patients (significant interaction adjusted p-values). Although the remaining associations were not statistically significant, all of the beta coefficients were higher in controls compared to patients with axSpA.

Discussion

Traditional risk factors such as age, gender, blood pressure, smoking history, cholesterol, and diabetes mellitus have been shown to predict the risk of coronary heart disease and death in the general population. Global risk algorithms, such as the SCORE, incorporate these risk factors to estimate the 10-year coronary and non-coronary heart death risk. However, in recent years, an increased risk of atherosclerotic events and premature CVD have emerged in a variety of systemic inflammatory rheumatic diseases. Although this growing awareness has stimulated intense basic science and clinical research, the precise nature of the relationship between local and systemic inflammation, their interactions with traditional CVR factors, and their role in accelerating atherogenesis remain unresolved. Moreover, CVD risk prediction models have been shown to underestimate the actual CVR in patients with these inflammatory diseases (6, 7). For this reason, there have been recent efforts to build and validate novel algorithms or scores capable of predicting the occurrence of CVD in inflammatory diseases. However, these new tools have yielded conflicting results and currently the best method for risk stratification in such patients has not been well established. We have recently shown that reclassification into a very high-risk category frequently occurs after carotid ultrasound assessment in patients with SLE, and that this is independently influenced by disease damage (8). In the present study, we have also found that reclassification into a very high-risk category in patients with axSpA after carotid ultrasound occurs more frequently in patients than in controls.

Previous attempts have been made to study CVR reclassification in spondyloarthropathies. For example, it was recently demonstrated that carotid ultrasound is useful for redefining CVR in axSpA (20). In this study, up to 61% and 20% of axSpA patients with moderate and low CVR, respectively, had carotid plaques. However, this report did not explore the determinants of this reclassifications in terms of whether traditional CVR factors or other factors related to the disease were associated with it. Another report studied the abilities of the coronary artery calcification score and carotid ultrasonography to detect very high CVR in axSpA patients (2). It found that the sensitivity to detect high/very high CVR patients using only the SCORE was very low. For example the risk chart algorithm detected only 3% of axSpA patients with high/very high CVR, whereas 30% of patients were identified as having high/very high CVR using a chart SCORE risk ≥5% in tandem with a coronary artery calcification score ≥100 Agatston units in those subjects who had a moderate SCORE (2).

In the present study we have found that male sex, age, and the presence of hypertension and dyslipidaemia were associated with the probability of being reclassified both in patients and controls. However, when the differences between beta coefficients were explored, it was found that the effects of male gender, serum levels of total cho-

lesterol, and LDL-cholesterol on reclassification after carotid ultrasound was significantly higher in controls than in axSpA. This same trend was found with age, BMI, waist circumference, and the presence of hypertension and dyslipidaemia, although statistical significance was not reached. This would mean that traditional CVR factors exert a greater effect in controls than in patients. These findings may reinforce the concept that reclassification in patients with inflammatory arthritis may be driven not only by the presence of conventional CVR factors, but also by the inflammation present in the disease.

Regarding the disease-related features of axSpA, higher disease duration, ASDAS-CRP, BASFI and BASMI scores, and the presence of inflammatory bowel disease were positively associated with reclassification. However, after multivariable regression analysis, these relations were lost with the exception of inflammatory bowel disease. This is in agreement with previous reports. For example, reclassification into a very high-risk category after carotid ultrasound assessment in patients with SLE has been shown to be independently influenced by disease damage (8). Moreover, reclassification in a previous report on patients with axSpA (2) was linked to the presence of syndesmophytes and extraarticular manifestations. In another study (21), age at onset, BASDAI, ASDAS-ESR and ASDAS-CRP, BASMI and BASFI scores, and modified Stoke Ankylosing Spondylitis Spine Score positively correlated with cIMT in patients with axSpA. However, this study did not address the issue of reclassification since this is not possible through cIMT, and no multivariable analysis adjustment was assessed (21). To our surprise, a protective effect on peripheral arthritis became statistically significant after multivariable analysis in our study. We do not have an exact explanation for this. However, the presence of peripheral arthritis has been found to delay spinal radiographic progression in axSpA (22). Therefore, we believe that this subset of axSpA patients may have a lower inflammatory burden that would explain this reduced risk of reclassification.

One limitation of our work is that controls were not age- and sex-matched because they were already collected when the axSpA recruitment was performed. It has been shown that the same and identical results are found irrespective of matching or not matching when multivariable regression analysis is applied in epidemiological case-control studies (23). We believe, therefore, that the procedure of multivariate analysis performed in our study was capable of handling confounding situations in the analysis regarding age and sex absence of matching.

In conclusion, careful evaluation of the CVR profile should be a key component of the management of patients with axSpA. Considering the findings of our study, patients with axSpA may benefit from the use of non-invasive imaging techniques to identify those at very high-risk who would otherwise go unnoticed and consequently have special requirements in term of cardiovascular disease prevention.

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