Carotid ultrasound in the cardiovascular risk stratification of patients with ankylosing spondylitis: results of a population-based study

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Abstract

Objective

To determine if the use of carotid ultrasonography (US) may improve the cardiovascular (CV) risk stratification in patients with ankylosing spondylitis (AS).

Methods

A set of 127 consecutive patients without history of CV events, diabetes mellitus or chronic kidney disease that fulfilled definitions for AS according to the 1984 modified New York criteria were recruited to assess carotid intima-media thickness and presence of plaques. CV risk was calculated according to the systematic coronary risk evaluation (SCORE), the Framingham Risk Score (FRS) and the Reynolds Risk Score (RRS).

Results

Men outnumbered women (61.4%). The mean±SD age at the time of the study was 44.5±11.6 years. The median (interquartile range-IQR) disease duration was 13 (7-22) years. The median (IQR) BASDAI at the time of the study was 3.65 (1.7- 4.9). HLA-B-27 was positive in 77.2%, and syndesmophytes were present in 38.9%. Carotid plaques were found in 43 (33.9%). Regardless of the algorithm used for CV risk stratification, more than 50% of the patients classified as having moderate CV risk had carotid plaques. Moreover, 20.8%, 24.6% and 53.3% of AS that fulfilled the category of low CV risk according to the total cholesterol (TC)-SCORE, FRS and RRS, respectively had carotid plaques. A model that included patients with a chart TC-SCORE ≥5% or TC-SCORE ≥1% <5% plus carotid plaques or TC-SCORE <1% and CRP >3 mg/L at diagnosis plus syndesmophytes and carotid plaques or TC-SCORE <1% and CRP >3 mg/L at diagnosis plus extraarticular manifestations plus carotid plaques yielded the highest sensitivity (93.0%) for high/very high CV risk in these patients. The presence of syndesmophytes was associated with increased risk of carotid plaques in AS that fulfilled definitions for low CV risk according to the TC-SCORE (OR 8.75 [95% CI 2.11–36.40]; p=0.002).

Conclusion

Our results support the use of carotid US in the assessment of CV risk in patients with AS.

Key words

ankylosing spondylitis, cardiovascular disease, ultrasonography, SCORE, carotid ultrasonography.

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Introduction

As occurs with other chronic inflammatory diseases, increased cardiovascular (CV) risk is observed in ankylosing spondylitis (AS) (1). A recent population-based retrospective study reported 36% higher risk of CV mortality in AS patients compared with the general population (2). Atherosclerotic-related CV events such as ischaemic heart disease or cerebrovascular disease were found to be increased in a cohort of 8616 AS patients (3). The elevated CV risk seems to be associated with a process of accelerated atherosclerosis.

Impairment of endothelial function, which is considered an early step in the development of atherosclerosis, is observed in patients with AS (4-6), and high prevalence of subclinical macrovascular disease, manifested by carotid plaques and increased carotid intima-media wall thickness (cIMT) (7-10), was also observed in patients with AS.

Besides higher prevalence of the traditional CV risk factors (11), different related-disease factors, such as the underlying chronic inflammatory burden (7, 10), the duration of the disease (4, 7) or the coexistence of extraaarticular manifestations (8), have been implicated in this accelerated atherosclerotic process. Because of that, adequate strategy to prevent the development of CV disease is a key issue in the management of patients with AS (12).

Risk calculators used to predict the individual's absolute risk for CV disease in the general population incorporate age, sex, lipid levels, smoking and blood pressure. In Europe, the 2012 "European Guidelines on CV disease prevention in clinical practice" recommended using the systematic coronary risk evaluation (SCORE) (13). Other CV risk calculators widely used in North America are the Framingham Risk Score (FRS) (14) and the Reynolds Risk Score (RRS) (15). In addition to the traditional CV risk factors, the RRS also includes the serum level of high sensitivity C -reactive protein (hsCRP), an indirect way to determine the presence of an inflammatory condition.

However, these risk algorithms were found to underestimate the actual CV risk of patients with rheumatoid arthritis (RA), It was especially true for the subgroups of patients included in the categories of low and intermediate CV risk (16-18). Because of that, a task force of the European League Against Rheumatism (EULAR) proposed to adapt the CV risk management calculated in RA patients according to the SCORE function by applying a multiplier factor of 1.5 in patients with disease factors identified as pro-atherogenic (19).

In keeping with reports on RA, a recent study has confirmed that the CV risk in patients with AS is often underestimated (20). The authors of this study found a 10-year cumulative incidence of CV events three times higher than the predicted based on the FRS. However, despite its recognition as a disease associated with increased CV risk, the EULAR recommendations do not suggest the use of a multiplier factor in AS just as it does in RA, because of the limited evidence available at the time of its publication (19).

Taking into account all these considerations, the search for additional tools that may identify high risk AS patients, who may benefit from active therapy to prevent CV events, is required. It may be of major importance in AS patients who are not included in the categories of high or very high CV risk according to the risk charts. In this regard, high-resolution B-mode ultrasound (US) of the carotid artery was proposed by the 2012 European Guidelines on CV disease as a validated instrument useful to redefine risk assessment in individuals with moderate CV disease risk profile (13). The detection of carotid plaques or the existence of a carotid intima-media wall thickness (cIMT)>0.90 mm by carotid US are considered as expression of subclinical organ damage and their presence automatically implies a very high CV risk (13). Both findings were found to be good predictors of CV events in low and intermediate risk groups of non-rheumatic individuals, and they have demonstrated to provide additional value also to the FRS when predicting CV events (21, 22).

The presence of subclinical atherosclerosis has demonstrated to be a predictor factor for CV events in patients

with RA. In these patients the presence of plaques in both carotid arteries has been found to multiply by four the risk of acute coronary syndromes compared with that observed in patients without carotid plaques (23).

To further investigate into this issue, we aimed to determine if the use of carotid US may improve the stratification of the CV risk of AS patients. For this purpose, we studied a series of AS patients without CV events, diabetes mellitus and chronic kidney disease seen at the reference hospitals for a defined population of Northern Spain.

Patients and methods

Patients

In this cross-sectional study, consecutive patients seen over a 2 year period at Hospital Universitario Marqués de Valdecilla and Hospital de Laredo (Cantabria, Spain) that fulfilled definitions for AS according to the 1984 modified New York criteria were recruited (24). Patients with history of CV events (ischaemic heart disease, cerebrovascular accident, peripheral arterial disease or heart failure) were excluded (25). Patients who fulfilled the 1984 modified New York criteria for AS and had psoriasis or inflammatory bowel disease were also excluded. In addition, patients with type 2 diabetes mellitus or those with two fasting plasma glucose levels on different days at the time of disease diagnosis or over the extended follow-up greater than 125 mg/dl and those with chronic kidney disease (glomerular filtration rate <60 ml/min/1.73 m^2) were considered as having high or very high CV risk according to current guidelines and, because of that, they were not included in the analysis.

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), and an enthesitis index (Maastricht Ankylosing Spondylitis Enthesitis Score -MASES) were evaluated in all patients at the time of carotid US assessment (26-30). Clinical information on hip involvement, synovitis, enthesitis and extraarticular manifestations, presence of syndesmophytes, HLA-B27 status and disease duration from the first symptoms and from the diagnosis of AS were assessed. It was also the case for information on family history of early CV events in first-degree relatives, waist circumference, body max index, blood pressure at the time of study and history of traditional CV risk factors.

Data on CRP and erythrocyte sedimentation rate (ESR) at the time of recruitment and at disease diagnosis, and total cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides at the time of the study were assessed. Information on therapy from the disease diagnosis, including treatment with anti-tumor necrosis factor (TNF)-α agents, was also reviewed.

The SCORE system estimates the 10-year risk of a first fatal atherosclerotic event, whether heart attack, stroke or other occlusive arterial disease, including sudden cardiac death. Risk estimates have been produced as charts for high and low risk regions in Europe (13). Spain was included in the low risk region of Europe. Two different SCORE charts have been designed: the SCORE recommended for the general population (13), which includes total cholesterol (TC-SCORE), and the SCORE recommended for chronic inflammatory diseases (19), which incorporates the atherogenic index total cholesterol/HDL cholesterol ratio (AI-SCORE). Other risk factors incorporated in the SCORE are the following: age, gender, smoking and systolic blood pressure. Subjects with SCORE <1% are included in the category of low risk. Those with a SCORE ≥1% and <5% are in the category of moderate risk. When the chart SCORE result is ≥5% and <10% they are classified as having high risk. Finally, those patients with SCORE results ≥10% are included in the category of very high CV risk.

Besides SCORE risk charts, predicted values for CV disease in our cohort of AS patients were also obtained using other CV risk charts; the FRS (14) and the RRS (15). The FRS predicts CV disease defined as all coronary events (myocardial infarction, coronary death, coronary insufficiency, and angina), cerebrovascular events (including ischaemic stroke, haemorrhagic stroke, and transient ischaemic attacks), peripheral artery disease (intermittent claudication), and heart failure (14). FRS includes sex, age, blood pressure, antihypertensive treatment, smoking, diabetes, and total and HDL cholesterol. RRS predicts a composite CV disease outcome defined as incident myocardial infarction, ischaemic stroke, coronary revascularisation, and CV death (15), and additionally includes hsCRP, family history of premature myocardial infarction (before age 60), and haemoglobin A1c among diabetics only.

Since FRS and RRS predict both fatal and non-fatal CV events, the final calculated risk should be higher than that provided by the SCORE. Therefore, the thresholds for dividing low CV risk from intermediate and high risk are different. The risk categories, chosen by consensus, that are widely used internationally are the followings: low risk <10%, intermediate risk: 10%–19%, and high risk 20% or more (31, 32).

The earliest age at which the CV risk scores should be used in the general population has not been rigorously established. Both European (13) and North American (33) guidelines recommend their application in individuals over 40 years old. However this cut off is not uniform and varies across the different CV risk scores: 30 years old in the FRS (14), 40 years old in the SCORE (34) and 45 years old in the RRS (15), which can only be applied from this age onwards. In Spain, the Framingham-based REGICOR adapted function, a CV risk function validated in the Spanish population (35), establishes its use at an intermediate point of 35 years old. Since patients with spondyloarthritis have early accelerated atherosclerosis, and we observed carotid plaques in many patients under 40, we included in the analysis all patients who were 35 years old and older.

Carotid US examination

Carotid US examination included the measurement of cIMT in the common carotid artery and the detection of focal

plaques in the extracranial carotid tree. Plaque was defined as a focal protrusion in the lumen at least cIMT >1.5 mm, protrusion at least 50% greater than the surrounding cIMT, or arterial lumen encroaching >0.5 mm (36). The cIMT was determined as the average of three measurements in each common carotid artery. The final cIMT was the largest average cIMT (left or right) (37). Carotid US was performed using a commercially available scanner, Mylab 70, Esaote (Genoa, Italy) equipped with 7-12 MHz linear transducer and the automated software guided technique radiofrequency -Quality Intima Media Thickness in real-time (QIMT, Esaote, Maastricht, Holland). Patients with carotid plaques and/or cIMT were considered as having very high CV risk.

A subject's written consent was obtained in all the cases. The study was approved by the local Ethics Committee

Statistical methods

Categorical variables were displayed as number (percentage) and continuous variables as mean±standard deviation (SD) or median and interquartile range (IQR) if the data were not normally distributed. To estimate the sensitivity, we considered patients having TC-SCORE ≥5% or the presence of carotid plaques as the gold standard for high or very high CV risk. Odds ratios (OR) with their 95% confidence intervals (CI) were estimated to study the association between carotid plaques and clinical variables. All statistical analyses were performed using the package Stata 14/SE.

Results

A set of 163 consecutive AS patients were recruited in the present study. Thirty-six of them were excluded, 24 because of psoriasis or inflammatory bowel disease, 6 with a history of CV disease, 3 with type 2 diabetes mellitus and 3 with chronic kidney disease. Therefore, 127 patients were finally included in the analysis.

The main features of the 127 patients included in the study are summarised in Table I. Men outnumbered women (n= 78; 61.4%). The mean±SD age at the time of the study was 44.5±11.6 years. The median (IQR) delay to the diagnosis was 5 (1-12) years and the median (IQR) disease duration since the onset of symptoms 13 (7-22) years. The median (IQR) BASDAI and BASFI were 3.65 (1.7–4.9) and 2.95 (1.7–5.8), respectively. Twenty-six patients had uveitis (20.5%). HLA-B27 was positive in 98 (77.2%) patients, and syndesmophytes were present in 49 (38.9%). Sixty-four (50.4%) and 47 (37.6%) patients had received synthetic disease modifying anti-rheumatic drugs (DMARDs), mainly sulfasalazine, and TNF-α inhibitors, respectively. Serum levels of CRP at diagnosis were higher than 3 mg/l in 76 (59.8%) patients. Regarding carotid US results, a cIMT>0.90 mm was only disclosed

Table I. Main clinical, epidemiologic and carotid ultrasound features of a series of 127 patients with AS without cardiovascular events, diabetes mellitus or chronic kidney disease.

Variable	AS (n=127)
Men/Women, n	78/49
Age at the time of study (years), mean ± SD	44.5 ± 11.6
Age at the time of disease diagnosis (years), mean ± SD	36.7 ± 10.6
Delay to the diagnosis (years), median (IQR)	5 (1-12)
Disease duration (years), median (IQR)	
Since the first symptoms	13 (7-22)
Since the diagnosis of AS	5 (1-11)
BASDAI, mean ±SD	3.64 ± 2.22
median (IQR)	3.65 (1.7- 4.9)
ASDAS, mean ±SD	2.36 ± 1.04
BASFI, mean ±SD	3.66 ± 2.56
median (IQR)	2.95 (1.7- 5.8)
BASMI, mean ±SD	2.98 ± 1.65
MASES, median (IQR)	1 (0-4)
Uveitis, n (%)	26 (20.5%)
History of synovitis or enthesitis, n (%)	45 (35.4%)
History of hip involvement, n (%)	10 (7.9%)
Syndesmophytes, n (%)	49 (38.9%)
Therapy, n (%)	
Anti-TNF	47 (37.6%)
Synthetic DMARDs	64 (50.4%)
Non-steroidal anti-inflammatory drugs	120 (95.2%)
HLA-B27 positive, n (%)	98 (77.2%)
CRP (mg/L), median (IQR)	
At the time of study	2.3 (0.6-8.0)
At the time of disease diagnosis	5 (2-12)
CRP >3 mg/L at diagnosis, n (%)	76 (59.8%)
ESR (mm/1st hour), median (IQR)	
At time of study	6 (3-16)
At time of disease diagnosis	11 (4.5-18.5)
History of classic cardiovascular risk factors, n (%)	
Current smokers	40 (31.5%)
Have ever smoked	30 (23.6%)
Obesity	25 (19.7%)
Dyslipidaemia	26 (20.5%)
Hypertension	18 (14.2%)
Family history of early cardiovascular events, n (%)	15 (12.0%)
Body mass index (kg/m^2), mean ±SD	26.1 ± 4.4
Blood pressure (mm Hg), mean ±SD	
Systolic	130 ± 14
Diastolic	78 ± 10
Waist circumference (cm), mean ±SD	93.3 ± 13.2
Cholesterol or triglycerides (mg/dl), mean ±SD	
Total cholesterol	194 ± 35
HDL-cholesterol	54 ± 15
LDL-cholesterol	120 ± 32
Triglycerides	101 ± 59
Carotid IMT (mm), mean ±SD	0.62 ± 0.13
Carotid IMT >0.90 mm, n (%)	3 (2.4%)
Carotid plaques, n (%)	43 (33.9%)

in 3 patients whereas carotid plaques were found in 43 (33.9%). All patients with cIMT>0.90 mm had carotid plaques. Other characteristics of this series of patients with AS are shown in Table I.

AI-SCORE, TC-SCORE, FRS, RRS, and carotid US findings in patients with AS

Based on the criterion of age discussed above, SCORE and FRS were used in 102 of the 127 AS patients who were 35 years old and older. However, the RRS is designed to calculate the CV risk in individuals older than 45 years old. Because of that, the application of RRS was only performed in 57 patients (Table II).

The CV risk was calculated using 4 different algorithms: the AI-SCORE and TC-SCORE, recommended for European countries, and the FRS and RRS more commonly used in North American individuals. All patients were classified in three different CV risk categories (low, moderate and high or very high) according to these 4 equations. The frequency of carotid plaques in each category was then calculated to compare the ability of each algorithm to correctly classify patients as having high/very high CV risk (Table II).

Regardless of the algorithm used for CV risk stratification, more than 50% of the patients classified as having moderate CV risk using the different risk charts had plaques in the carotid US assessment. Moreover, 20.8% of AS that fulfilled the category of low CV risk according to the TC-SCORE had plaques. It was even worse for FRS and RRS as 24.6% and 53.3% of the patients that fulfilled definitions of low CV risk according to these risk charts exhibited carotid plaques when the carotid US assessment was performed (Table II).

Patients with moderate and high/very high CV risk according to TC-SCORE, AI-SCORE and FRS had higher values of BASDAI and BASFI than those categorised as having low CV risk using these risk charts (Table II). It was not the case for the RRS. This contradictory result may be due to the small number of patients assessed by the RRS algorithm (Table II).

Table II. Presence of carotid plaques in 102 AS patients 35 years old and older without cardiovascular events, diabetes mellitus or chronic kidney disease who were categorised as having low, moderate or high/very high cardiovascular risk according to the TC-SCORE, the AI-SCORE and the Framingham Risk Score. The same procedure was performed using the Reynolds Risk Score in 57 AS patients older than 45 years old without cardiovascular events, diabetes mellitus or chronic kidney disease.

	Low CV risk*	Moderate CV risk**	High/very high CV risk***
TC-SCORE	11/53 (20.8%)	27/44 (61.4%)	5/5 (100%)
BASDAI (median IQR)	3.3 (1.2 – 4.6)	3.8 (2.6 – 5.0)	4.8 (2.6 – 5.7)
BASFI (median IQR)	2.1 (1.1 – 4.4)	4.7 (3.3 – 7.1)	5.3 (2.6 – 6.3)
AI-SCORE	10/51 (19.6%)	31/49 (63.3%)	2/2 (100%)
BASDAI (median IQR)	3.6 (1.3 – 4.6)	3.8 (2.0 – 5.5)	3.7 (2.6 – 4.8)
BASFI (median IQR)	2.3 (1.2 – 4.6)	4.8 (2.2 – 7.1)	4.0 (2.6 – 5.3)
Framingham Risk Score	14/57 (24.6%)	18/31 (58.1%)	10/13 (76.9%)
BASDAI (median IQR)	3.2 (1.3 – 4.6)	4.3 (2.9 – 6.0)	4.8 (1.7 – 5.7)
BASFI (median IQR)	2.3 (1.2 – 4.7)	4.8 (3.1 – 7.0)	5.8 (2.6 – 7.7)
Reynolds Risk Score	24/45 (53.3%)	8/10 (80.0%)	2/2 (100%)
BASDAI (median IQR)	4.2 (2.6 – 5.5)	4.6 (1.7 – 5.7)	3.7 (2.6 – 4.8)
BASFI (median IQR)	4.7 (2.8 – 6.9)	5.7 (2.2 – 6.4)	4.0 (2.6 – 5.3)

TC-SCORE: SCORE calculated using total cholesterol. AI-SCORE: SCORE calculated using the atherogenic index: Total cholesterol/HDL-cholesterol. *Low risk: <1% according to TC-SCORE and AI-SCORE; <10% according to Reynolds and Framingham Risk Scores. **Moderate risk: ≥1% and <5% according to TC-SCORE and AI-SCORE; ≥10% and <20% according to Reynolds and Framingham Risk Scores. ***High or very high risk: >5% according to TC-SCORE and AI-SCORE; ≥20% according to Reynolds and Framingham Risk Scores. IQR: Interquartile range.

Predictive model to establish the presence of high or very high CV risk in patients with AS

Since a great number patients with carotid plaques were included in the categories of low and moderate/intermediate CV risk, we set up a predictive model that may help us to disclose the highest number of AS with severe subclinical atherosclerosis and, therefore, with high risk of CV events. For this purpose we used the TC-SCORE that is commonly used in the Spanish general population.

As shown in Table III, the sensitivity to detect high or very high CV risk using the TC-SCORE was very low (11.6%) as the charts only detected 5 of 43 patients with SCORE ≥5% or carotid plaques (Model 1).

Using a chart TC-SCORE risk ≥5% plus the presence of severe carotid US findings (carotid plaques) in patients with moderate SCORE risk (≥1% and <5%), we disclosed a higher sensitivity as 32 AS patients were detected as having high or very high CV risk (74.4%) (Model 3) (Table III).

We built another predictive model (Model 4) that included patients with TC-SCORE ≥5% or patients with TC-SCORE ≥1% <5% plus carotid plaques or those with TC-SCORE <1% and disease duration since the onset of symptoms >10 years plus CRP >3 mg/L at disease diagnosis who had carotid plaques. This new model yielded higher sensitivity to disclose high or very high CV risk (88.4%) (Model 4) (Table III).

The sensitivity to detect high or very high CV risk did not change when we included in the model the presence of syndesmophytes instead of disease duration >10 years (88.4%) (Model 5) (Table III).

Finally, we set up a new model (Model 6) that included TC-SCORE ≥5% or patients with SCORE-TC ≥1% <5% plus carotid plaques or TC-SCORE <1% and CRP >3 mg/L at diagnosis plus syndesmophytes and carotid plaques or TC-SCORE <1% and CRP >3 mg/L at diagnosis plus extraarticular manifestation plus carotid plaques. This Model 6 yielded the highest sensitivity (93.0%) (Table III).

Association between the main clinical variables and the presence of carotid plaques in AS patients with low CV risk according to the TC-SCORE calculator

We also aimed to determine whether some clinical features may be associ-

Table III. Sensitivity to establish the presence of high/very high cardiovascular risk in 102 AS patients 35 years old and older without cardiovascular events, diabetes mellitus or chronic kidney disease using the TC-SCORE calculator or the presence of severe carotid ultrasound findings (carotid plaques).

Model	Sensitivity
Gold standard*	n= 43 (100%)
1. TC-SCORE ≥5%	n=5/43 (11.6%)
2. Carotid plaques	n=43/43 (100%)
3. TC-SCORE ≥5% or TC-SCORE ≥1% and <5% plus carotid plaques	n=32/43 (74.4%)
4. TC-SCORE ≥5% or TC-SCORE ≥1% and <5% plus carotid plaques or TC-SCORE <1% and: Disease duration since the onset of symptoms >10 years plus CRP >3 mg/L at diagnosis plus carotid plaques	n=38/43 (88.4%)
5. TC-SCORE ≥5% or TC-SCORE ≥1% and <5% plus carotid plaques or TC-SCORE <1% and : Syndesmophytes plus CRP >3 mg/L at diagnosis plus carotid plaques	n= 8/43 (88.4%)
6. TC-SCORE ≥5% or TC-SCORE ≥1% and <5% plus carotid plaques or TC-SCORE <1% and : CRP >3 mg/L at diagnosis plus syndesmophytes plus carotid plaques or CRP >3 mg/L at diagnosis plus extraarticular manifestations plus carotid plaques	n=40/43 (93.0%)

*Gold standard for high/very high cardiovascular risk: SCORE ≥5% or carotid plaques.

Table IV. Association between the main clinical variables and the presence of carotid plaques in 53 AS patients who were 35 years old and older and had low CV risk according to the TC-SCORE calculator.

Variable	OR (95% CI)	*p*
Disease duration >10 years	1.09 (0.30 – 3.92)	0.90
Disease duration >15 years	2.35 (0.63 – 8.88)	0.22
CRP >3 mg/L at the time of diagnosis	3.56 (0.88 – 14.11)	0.08
Presence of syndesmophytes	**8.75 (2.11 – 36.40)**	**0.002**
Presence of extraarticular manifestations (uveitis)	3.43 (0.82 – 14.69)	0.10

Table V. Presence of carotid plaques in 102 AS patients 35 years old and older without cardiovascular events, diabetes mellitus or chronic kidney disease who were categorised as having low, moderate or high/very high cardiovascular risk using the TC-SCORE calculator. Patients were stratified according to the use of anti TNF therapy.

TC-SCORE	Low CV risk	Moderate CV risk	High/ very high CV risk
Patients with carotid plaques	11/53 (20.8%)	27/44 (61.4%)	5/5 (100%)
Carotid plaques in patients with anti-TNF therapy	3/22 (13.6%)	14/20 (70.0%)	1/1 (100%)
Carotid plaques in patients without anti-TNF therapy	8/31 (25.8%)	13/24 (54.2%)	4/4 (100%)

ated with an increased risk of carotid plaques in patients with AS that are included in the category of low CV risk according to the TC-SCORE calculator. Interestingly, we observed that the presence of syndesmophytes was associated with an increased risk of carotid plaques in patients with AS that fulfilled definitions for low CV risk (OR 8.75 [95% CI 2.11–36.40]; *p*=0.002). Other potential associations did not achieve statistical significance (Table IV).

Influence of the effect of anti-TNF therapy on the presence of carotid plaques in the study population of patients with AS

When patients with AS undergoing anti-TNF therapy were assessed for the presence of carotid plaques, we observed that the subgroup of patients categorised as having low CV risk according to the TC-SCORE calculator had lower frequency of plaques than the remaining patients with moderate or high/very CV risk (Table V). It was also the case when carotid plaques were assessed in AS patients who did not receive anti-TNF therapy (Table V).

Discussion

The present study confirms that the CV risk algorithms available for general population underestimate the CV risk in AS patients. This finding has potential relevance since the presence of cIMT>0.90 mm or carotid plaques are considered reliable predictors of CV events (21, 38) and patients with these US findings must be considered as individuals with very high CV risk according the 2012 European Guidelines on CV disease prevention in clinical practice (13). With respect to this, an adequate stratification of individuals would promote a better control of CV risk factors (13).

Although a potential limitation of our study may be the absence of a control population, our results in patients with AS are in agreement with data reported in other types of inflammatory arthritis. In this regard, a recent study disclosed carotid plaques in 63% of RA patients with moderate SCORE (37). Also, in psoriasis, 55.9% of patients with intermediate CV risk according to the FRS were found to have carotid plaques (39). Our study indicates that carotid US may be useful to improve the sensitivity of the CV risk algorithms to detect AS patients at very high CV risk. Therefore, our results support the use of carotid US in AS patients categorised as having moderate CV according to the classic risk charts. Our results also disclosed that the carotid US assessment in AS patients at low risk according to risk charts who had CRP at diagnosis >3 mg/L plus the presence of syndesmophytes or extraarticular manifestations increases the sensitivity to disclose individuals at high CV risk. With respect to this, a value of CRP higher than 3 mg/L is also considered as a predictive factor of CV events in the general population (40), and its utility to improve the CV assessment was also recognised in

the 2012 European guidelines in cases of uncertain CV risk (13). CRP serum levels have also associated with both clinical and subclinical atherosclerosis in patients with inflammatory arthritis (1, 10, 41, 42).

Extraarticular manifestations in patients with axial spondyloarthritis, such as psoriasis (43) and inflammatory bowel disease (44), have also demonstrated to be associated with an increased risk of CV events. On the other hand, the existence of syndesmophytes is considered an indicator of severity and duration of the disease. The importance of disease-related activity and chronic inflammation in subclinical atherosclerotic risk has been demonstrated in a recent study in non-diabetic, CV disease -free patients with AS (45). In this series of 67 middle-aged patients with AS patients, the median (IQR) BASDAI) was 1.8 (0.4–3.6), and 66% of them were receiving anti-TNF treatment (45). Interestingly, low AS disease activity was not associated with accelerated atherosclerosis (45). Both disease severity and disease duration were found to be associated with an increased CV morbimortality in other chronic inflammatory rheumatic diseases such as RA (19) and systemic lupus erythematosus (46).

The use of carotid US to improve the CV risk assessment is a feasible procedure in the clinical practice. It may be performed with the same US scan that we use for musculoskeletal studies and the technique has been validated to determine subclinical atherosclerosis (47). With respect to this, an interesting result of our study was the high number of patients included in the low and moderate CV risk categories who had carotid plaques. This information is of potential relevance when considering CV risk stratification in AS patients. With respect to this, patients included in these categories were found to suffer from the highest underestimation of the CV risk in a recent study on early RA where up to 32% of CV events occurred in patients at low CV risk (17). Also, the fact that so few patients of our series had abnormal cIMT compared with those with plaques (2.4% *vs*. 33.9%) was interesting and would support using plaque as a predictor of high CV risk rather than cIMT in future studies in AS. This finding is in agreement with reports that considered that carotid plaques are more reliable indicators of severe atherosclerosis than increased cIMT (38).

In conclusion, this is the first study that assessed the utility of carotid US in the CV risk stratification of patients with AS. We observed that traditional risk charts underestimate the CV risk of patients with AS. Because of that, we propose the use of carotid US as a useful tool to improve the detection of AS patients at very high CV risk, in particular among those who are considered as having moderate CV risk according to risk score charts. However, a longitudinal study with clinical outcomes will be required to fully establish the utility of the carotid US in predicting CV disease in patients with AS.

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