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Carotid plaques as predictors of cardiovascular events in patients with Rheumatoid Arthritis. Results from a 5-year-prospective follow-up study

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ABSTRACT

Objective: To investigate if the Systematic Coronary Risk Evaluation (SCORE) and the QRISK3 algorithms as well as the carotid ultrasound are useful predictors of cardiovascular (CV) events and death in a prospectively defined population-based rheumatoid arthritis (RA) inception cohort.

Methods: A set of 327 consecutive RA patients without history of diabetes, chronic kidney disease or CV events were studied by carotid ultrasound between 2012 and 2013. At that time, CV risk was calculated according to the modified EULAR systematic coronary risk evaluation (mSCORE) for RA. A five-year prospective follow-up study was conducted by survival analysis models. The EULAR mSCORE based on the 2015/2016 updated EULAR recommendations and the QRISK3 algorithms were retrospectively tested using baseline data.

Results: After 1,984.25 patient-years of follow-up, 23 had died and 27 had experienced CV events. Linearized mortality rate was 1.16/100 patient-years (95% confidence interval [CI]: 0.74––1.73). Adjusting for age, gender and disease duration, a model with carotid plaques (Hazard ratio [HR]: 6.10 [95% CI:0.74––50.0]; p = 0.09) and another model with carotid plaques and QRISK3 (HR for carotid plaques: 6.12 [95% CI: 0.74––50.5]; p = 0.09 and HR for each 1% in QRISK3: 1.03 [95% CI: 0.99––1.07], p = 0.11, respectively were the best predictors of death whereas a model with carotid plaques (HR: 5.25 [95% CI:1.41––19.50]; p = 0.01) and another model with carotid plaques and QRISK3 (HR for carotid plaques: 5.13 [95% CI: 1.36––19.3]; p = 0.02 and HR for each 1% in QRISK3: 1.03 [95% CI: 0.99––1.07], p = 0.12, respectively, were the best predictors of CV events. In contrast, the mSCORE was a weaker predictor of the risk of death or CV events.

Conclusions: The presence of carotid plaques predicts the development of CV events and death in patients with RA. The predictable capacity of carotid plaques and QRISK3 is higher than that of mSCORE in RA patients.

Introduction

Patients with rheumatoid arthritis (RA) have an increased risk of cardiovascular (CV) events and CV mortality [1]. This is the result of vascular damage and accelerated atherosclerosis [2]. Traditional cardiovascular risk factors, a genetic component and the presence of chronic inflammatory burden account for the development of CV disease in these patients [3–5]. Identification of individuals at high risk of CV events is of main importance in RA. However, current CV risk screening and management strategies often underestimate the actual

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CV risk in patients with RA. In this regard, we observed that the use of non-invasive surrogate markers such as carotid ultrasound (US) [6] or the Coronary Artery Calcification Score [7] allowed to detect subclinical atherosclerosis in patients with RA included in the category of moderate CV risk when the systematic coronary risk evaluation (SCORE) algorithm and the modified SCORE according to the 2010 EULAR recommendations were applied [8–10]. With respect to this, experts in the field highlighted the potential relevance of imaging techniques to improve risk stratification in RA [11]. However, as they pointed out, longitudinal data with hard CV disease outcomes are scarce [11].

Taking into account these considerations, the purpose of the present study was to investigate if the SCORE, a widely used algorithm aimed to determine the 10-year risk of fatal CV event in the European population, modified according to the EULAR recommendations, the QRISK3, a score on 10-year risk of fatal or non-fatal CV event developed in England, Hippisley-Cox et al.[12] and the carotid US are useful predictors of CV events and death in a prospectively defined population-based RA inception cohort. For this purpose, we performed a prospective 5-year follow-up study of a series of 327 patients with RA without history of CV events, diabetes mellitus or chronic kidney disease.

Patients and methods

Patients

Baseline data of this series of 327 patients were previously reported [6]. Briefly, a set of 370 consecutive Spanish RA patients without a history of CV events (ischemic heart disease, cerebrovascular accident, peripheral arterial disease or heart failure) were recruited from Hospital Universitario Marqués de Valdecilla (Santander, Spain) over 1year period (2012––2013) [6]. Forty-three of them were excluded from the prospective follow-up study because 31 fulfilled definitions for type 2 diabetes mellitus and 12 had chronic kidney disease. Therefore, 327 were followed-up to determine development of CV events or death. All of them met the 1987 American College of Rheumatology classification criteria for RA and also fulfilled the 2010 classification criteria for RA [13,14].

Carotid US examination

Carotid US examination included the measurement of the carotid intima-media wall thickness (cIMT) in the common carotid artery and the detection of focal plaques in the extracranial carotid tree. 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) was used [6,7]. 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). In all cases a single rheumatologist (AC) who was blinded to clinical information performed the studies. This investigator is an expert in musculoskeletal US and has experience in measuring cIMT in RA patients. The reproducibility of the cIMT measurements was evaluated in 20 patients within 1 week of the first US examination. The correlation coefficient for cIMT was 0.97.

The presence of focal carotid plaques was detected by high resolution B-mode US scanner, with 10 MHz linear array transducer in a longitudinal view. Plaque criteria in the accessible extracranial carotid tree (common carotid artery, bulb and internal carotid artery) were 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, according to Mannheim consensus criteria [15].

CV risk algorithms, prospective follow-up and survival analysis

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 [6]. SCORE chart assessment is based on the following risk factors: age, gender, systolic blood pressure, total cholesterol and smoking status. Patients underwent carotid US assessment. At that time, CV risk was calculated according to the systematic coronary risk evaluation (SCORE) and the 2010 modified EULAR SCORE (mSCORE) for RA [8-10]. Patients were prospectively followed-up from the time of carotid US and SCORE assessment until patient's death or at least 5 years of follow-up. Using the baseline data, we also retrospectively applied the most recent EULAR mSCORE based on the 2015/2016 updated EULAR recommendations (2015/2016 EULAR mSCORE) [16].

The QRISK3 algorithm calculates a person's risk of developing a heart attack or stroke over the next 10 years. It presents the average risk of people with the same risk factors as those entered for that person [12]. This CV risk algorithm was developed by physicians and academics working in the UK National Health Service. It was based on routinely collected data from many thousands of general practitioners across the UK [12]. However, it has not been validated in the Spanish population. As occurred for the 2015/2016 EULAR mSCORE, the QRISK3 algorithm was retrospectively tested using baseline data.

We studied if the following baseline variables were predictors of CV events and death in these patients: sex, age and disease duration and the time of carotid US examination. SCORE, and the mSCORE according to the 2010 and the 2015/2016 EULAR recommendations and the QRISK3 risk prediction algorithm. Moreover, we aimed to determine the predictive capacity of the cIMT and the presence of carotid plaques at the onset of the study.

We performed three survival analyses as follows:

Event 1: We assessed death by any cause. The follow-up period was the time between the basal carotid US and CV risk evaluation and death or the last contact with the Rheumatology Division registered in the medical records. Patients alive were considered censored.

Event 2: We defined a combined event as any major CV event or death by any cause. The follow-up was the period of time between the basal carotid US and CV risk evaluation and the first occurrence of a major CV event or death. Patients alive and without a major CV event in their last contact with the Rheumatology Division registered in the medical records were censored in that date.

Event 3: We defined CV event as any major CV event. The follow-up was the time between the between the basal carotid US and CV risk evaluation and the first occurrence of a major CV event or death. Patients without any major CV event and alive at their last registered contact with the Rheumatology Division were censored in that date. Patients who died due to non-CV cause and having no CV event were considered censored in their date of death.

Statistical analysis

Models via Cox regression were performed using CV risk parameters as regressors (SCORE, 2010 EULAR mSCORE, 2015/2016 mSCORE, QRISK3, carotid plaques, cIMT as continuous variable and cIMT dichotomized in 0.9 mm). All models were adjusted by age at the time of the carotid US study, gender and disease duration at the time of the carotid US study. Results were presented as hazard ratio (HR) with 95% confidence interval (CI). For each model, we estimated the Akaike information criterion (AIC) and the Bayesian information criterion (BIC). AIC and BIC are useful indicators for selecting between several models; both AIC and BIC can be interpreted in the same way: the lower their estimations, the better the model.

To further explore the improvement in predicting events when adding carotid US results to SCORE or QRISK3 models, we estimated the net discrimination index; its 95% CI was obtained via bootstrapping with 1000 repetitions.

All statistical tests were performed with the package Stata 16/SE (Stata Corp, College Station, Tx).

The Ethical Committee of Cantabria (Spain) approved the prospective study (reference: 17/2012). Informed consent was requested to all the patients who participated in the study.

Results

Most patients from this series of 327 patients without CV events, diabetes or chronic kidney disease were women 267 (82%). The age and disease duration (mean ± SD) at the time of the carotid US assessment were 58.3 ± 13.9 and 9.7 ± 8.3 years respectively. Rheumatoid factor and/or anti-CCP positivity was found in 226 (69.1%) patients. Fifty-six (17.2%) had extra-articular manifestations. They included the presence of nodular disease in 21 patients, secondary Sjogren's syndrome in 26, pleuritis/pericarditis in 6, pulmonary fibrosis in 5, rheumatoid vasculitis in 2, scleritis/episcleritis in 2, Raynaud's phenomenon in 2, and sclerosing cholangitis in 1 case.

The SCORE (mean ± SD) was 1.68 ± 1.98 and the mSCORE calculated according the 2010 EULAR recommendations was 1.98 ± 2.48. The retrospectively recalculated 2015/2016 EULAR mSCORE was 2.52 ± 2.96. Only 23 patients were classified as having high or very high CV risk, defined as a 2015/2016 EULAR mSCORE ≥ 5%.

According to QRISK3 (mean ± SD: 15.1 ± 13.6), 179 patients were classified as having high or very high CV risk defined as a QRISK3 ≥ 10%.

Regarding baseline carotid US results; cIMT > 0.90 mm was observed in 27 (8.3%) patients. In 4 of them cIMT > 0.90 was bilateral (found in both carotids). Carotid plaques were disclosed in 161 (49.2%) patients, being bilateral in 104 of them. Also, 26 of the 27 patients with cIMT > 0.90 had carotid plaques.

Interestingly, 146 patients included in the categories of low and moderate CV risk according to the 2015/2016 EULAR mSCORE were reclassified as having very high CV risk based on the results of the carotid US assessment. In contrast, only 35 of the patients in whom QRISK3 was tested were reclassified as having very high CV risk based on results of the carotid US study. Therefore, the QRISK allowed us to identify high/very high CV risk RA patients risk better than the 2015/2016 EULAR mSCORE.

After 1984.25 patient-years of follow-up, 23 patients had died (4 because of CV events, including 1 case of fatal myocardial infarction, 2 with heart failure and with 1 aortic dissection, 5 because of malignancies, 8 because of infections and the remaining 6 patients due to other causes). The linearized mortality rate was 1.16/100 patient-years (95%confidence interval-CI: 0.74––1.73). (Table 1). After adjusting for age, gender and disease duration, model 5 including carotid plaques (HR: 6.10 [95% CI: 0.74–50.0]; p = 0.09) and model 9 including carotid plaques and QRISK3 (HR for carotid plaques: 6.12 [95% CI: 0.74––50.5]; p = 0.09 and HR for each 1% in QRISK3: 1.03 [95% CI: 0.99––1.07], p = 0.11, respectively, were the best predictors of death by any cause (Table 1).

After 1900.65 patient-years of follow-up, 44 patients suffered a CV event and or had died (linearized CV events or death rate 2.31/100 patient-years [95% CI: 1.69––3.09]). The best set of predictors of CV events or death were model 5 incorporating the presence of carotid plaques (HR: 5.25 [95% CI: 1.75–16.40]; p = 0.003), and model 9 including carotid plaques and QRISK3 (HR for carotid plaques: 5.26 [95% CI: 1.71––16.2]; p = 0.004 and HR for each 1% in QRISK3: 1.03 [95% CI: 1.00––1.06], p = 0.09, respectively) (Table 2).

After 1900.65 patient-years of follow-up, 27 patients had experienced CV events. The linearized event rate was 1.42/100 patient-years (95% CI: 0.94––2.06) (Table 3). Model 5, involving carotid plaques (HR:5.25 [95% CI:1.41–19.50]; p = 0.01), and model 9 that includes carotid plaques and QRISK3 (HR for carotid plaques: 5.13 [95% CI: 1.36––19.3]; p = 0.02 and HR for each 1% in QRISK3: 1.03 [95% CI: 0.99––1.07], p = 0.12, respectively, were the best predictors of CV events (Table 3). The presence of bilateral carotid plaques was not associated with a higher risk of CV events than the presence of unilateral plaques (**Suppl. Table 1**).

The incorporation of data from the basal carotid US assessment to models that included age, gender, disease duration and 2015/2016 EULAR mSCORE or QRISK3 increased the model predictive capacity -as measured by net reclassification index- of CV event or death and CV event, but not of death alone (**Suppl. Table 2**).

Table 1
Relationship between carotid US data, disease duration and SCORE risk charts with death occurring by any cause in 327 patients with RA.

Predictors	Variable	HR (95% CI)	p	AIC	BIC
1	SCORE	1.11 (0.88––1.40)	0.37	220.97	236.11
	Age*	1.13 (1.08––1.18)	<0.001		
	Gender (ref.: woman)	0.91 (0.22––3.86)	0.90		
	Disease duration*	1.01 (0.99––1.02)	0.37		
2	2010 EULAR mSCORE	1.14 (0.99––1.31)	0.06	219.06	234.21
	Age	1.13 (1.08––1.18)	<0.001		
	Gender	0.77 (0.22––2.76)	0.69		
	Disease duration	1.01 (0.99––1.02)	0.41		
3	2015/2016 EULAR mSCORE	1.07 (0.92––1.25)	0.37	220.97	236.11
	Age	1.13 (1.08––1.18)	<0.001		
	Gender	0.91 (0.22––3.86)	0.90		
	Disease duration	1.01 (0.99––1.02)	0.37		
4	QRISK3	1.03 (0.99––1.08)	0.11	219.36	234.49
	Age	1.09 (1.02––1.16)	0.01		
	Gender	0.96 (0.31––2.98)	0.94		
	Disease duration	1.01 (0.99––1.02)	0.99		
5	**Carotid plaque**	6.10 (0.74––50.0)	0.09	217.22	232.36
	Age	1.11 (1.06-1.16)	<0.001		
	Gender	1.34 (0.49––3.68)	0.58		
	Disease duration	1.01 (0.99––1.02)	0.28		
6	cIMT (continuous)	0.52 (0.02––11.5)	0.68	221.51	236.66
	Age	1.14 (1.08––1.20)	<0.001		
	Gender	1.44 (0.52––4.01)	0.48		
	Disease duration	1.01 (0.99––1.02)	0.42		
7	cIMT >0.9	1.19 (0.44––3.26)	0.73	221.56	236.71
	Age	1.13 (1.08––1.18)	<0.001		
	Gender	1.41 (0.51––3.89)	0.51		
	Disease duration	1.01 (0.99––1.02)	0.37		
8	Carotid plaque	5.87 (0.71––48.4)	0.10	218.76	237.68
	2015/2016 EULAR mSCORE	1.06 (0.91––1.23)	0.48		
	Age	1.10 (1.05––1.16)	<0.001		
	Gender	0.95 (0.23––3.97)	0.95		
	Disease duration	1.01 (0.99––1.02)	0.26		
9	**Carotid plaque**	6.12 (0.74––50.5)	0.09	216.87	235.77
	QRISK3	1.03 (0.99––1.07)	0.11		
	Age	1.06 (1.00––1.14)	0.07		
	Gender	0.90 (0.29––2.80)	0.86		
	Disease duration	1.01 (0.99––1.02)	0.27		
10	cIMT (continuous)	0.44 (0.02––9.96)	0.61	222.70	241.63
	2015/2016 EULAR mSCORE	1.08 (0.92––1.27)	0.34		
	Age	1.13 (1.08––1.19)	<0.001		
	Gender	0.91 (0.21––3.88)	0.90		
	Disease duration	1.01 (0.99––1.02)	0.39		
11	cIMT >0.9	1.15 (0.42––3.14)	0.78	222.89	241.82
	2015/2016 EULAR mSCORE	1.07 (0.92––1.25)	0.39		
	Age	1.13 (1.07––1.18)	<0.001		
	Gender	0.93 (0.22––3.93)	0.92		
	Disease duration	1.01 (0.99––1.02)	0.36		

* At the time of CV risk and carotid US assessment.

Table 2
Relationship between carotid US data, disease duration and SCORE risk charts with CV events or death occurring by any cause in 327 patients with RA.

Predictors	Variable	HR (95% CI)	p	AIC	BIC
1	SCORE	1.06 (0.89––1.27)	0.50	443.93	459.08
	Age*	1.10 (1.06––1.13)	<0.001		
	Gender (ref.: woman)	1.06 (0.40––2.81)	0.91		
	Disease duration*	1.01 (1.00––1.02)	0.02		
2	2010 EULAR mSCORE	1.07 (0.95––1.20)	0.28	443.36	458.51
	Age	1.09 (1.06––1.13)	<0.001		
	Gender	1.01 (0.41––2.49)	0.98		
	Disease duration	1.01 (1.00––1.02)	0.02		
3	2015/2016 EULAR mSCORE	1.04 (0.93––1.17)	0.50	443.93	459.08
	Age	1.10 (1.06––1.13)	<0.001		
	Gender	1.06 (0.40––2.81)	0.91		
	Disease duration	1.01 (1.00––1.02)	0.02		
4	QRISK3	1.03 (1.00––1.06)	0.08	441.35	456.48
	Age	1.07 (1.02-–1.11)	0.004		
	Gender	1.04 (0.47––2.29)	0.93		
	Disease duration	1.01 (1.00––1.02)	0.01		
5	**Carotid plaque**	5.25 (1.75––16.4)	0.003	432.65	447.79
	Age	1.07 (1.04––1.11)	<0.001		
	Gender	1.21 (0.57––2.53)	0.62		
	Disease duration	1.02 (1.01––1.03)	0.002		
6	cIMT (continuous)	2.70 (0.30––24.6)	0.38	443.60	458.75
	Age	1.09 (1.06––1.13)	<0.001		
	Gender	1.24 (0.58––2.63)	0.58		
	Disease duration	1.01 (1.00––1.02)	0.02		
7	cIMT >0.9	1.29 (0.59––2.81)	0.52	443.95	459.10
	Age	1.10 (1.06––1.13)	<0.001		
	Gender	1.29 (0.61––2.72)	0.51		
	Disease duration	1.01 (1.00––1.02)	0.01		
8	Carotid plaque	5.30 (1.73––16.3)	0.004	434.44	453.35
	2015/2016 EULAR mSCORE	1.03 (0.92––1.15)	0.63		
	Age	1.07 (1.03––1.11)	<0.001		
	Gender	1.05 (0.40––2.72)	0.92		
	Disease duration	1.02 (1.01––1.03)	0.002		
9	**Carotid plaque**	5.26 (1.71––16.2)	0.004	431.99	450.89
	QRISK3	1.03 (1.00––1.06)	0.09		
	Age	1.04 (1.00––1.09)	0.07		
	Gender	0.97 (0.44––2.13)	0.94		
	Disease duration	1.02 (1.01––1.03)	0.002		
10	cIMT (continuous)	2.44 (0.26––22.8)	0.43	445.33	464.27
	2015/2016 EULAR mSCORE	1.03 (0.92––1.16)	0.59		
	Age	1.09 (1.05––1.13)	<0.001		
	Gender	1.05 (0.40––2.79)	0.91		
	Disease duration	1.01 (1.00––1.02)	0.01		
11	cIMT >0.9	1.26 (0.57––2.75)	0.57	445.61	464.55
	2015/2016 EULAR mSCORE	1.04 (0.92––1.17)	0.55		
	Age	1.09 (1.06––1.13)	<0.001		
	Gender	1.07 (0.41––2.83)	0.89		
	Disease duration	1.01 (1.00––1.02)	0.01		

* At the time of CV risk and carotid US assessment.

Table 3
Relationship between carotid US data, disease duration and SCORE risk charts with CV events in 327 patients with RA.

Predictors	Variable	HR (95% CI)	p	AIC	BIC
1	SCORE	1.07 (0.86––1.34)	0.55	286.54	301.68
	Age*	1.08 (1.04––1.12)	<0.001		
	Gender (ref.: woman)	0.89 (0.25––3.19)	0.86		
	Disease duration*	1.01 (1.00––1.02)	0.03		
2	2010 EULAR mSCORE	1.04 (0.88––1.23)	0.65	286.67	301.82
	Age	1.08 (1.04––1.12)	<0.001		
	Gender	0.97 (0.30––3.18)	0.96		
	Disease duration	1.01 (1.00––1.02)	0.03		
3	2015/2016 EULAR mSCORE	1.05 (0.90––1.22)	0.55	286.54	301.68
	Age	1.08 (1.04––1.12)	<0.001		
	Gender	0.89 (0.25––3.19)	0.86		
	Disease duration	1.01 (1.00––1.02)	0.03		
4	QRISK3	1.03 (0.99––1.07)	0.10	284.34	299.48
	Age	1.05 (0.99––1.10)	0.09		
	Gender	0.85 (0.30––2.44)	0.77		
	Disease duration	1.01 (1.00––1.03)	0.02		
5	**Carotid plaque**	5.25 (1.41––19.5)	0.01	278.86	293.99
	Age	1.05 (1.02––1.09)	0.006		
	Gender	1.02 (0.38––2.73)	0.96		
	Disease duration	1.02 (1.00––1.03)	0.005		
6	cIMT (continuous)	4.90 (0.30––79.7)	0.26	285.67	300.82
	Age	1.07 (1.03––1.11)	0.001		
	Gender	1.03 (0.38––2.80)	0.95		
	Disease duration	1.01 (1.00––1.02)	0.03		
7	cIMT >0.9	1.66 (0.62––4.41)	0.31	285.90	301.05
	Age	1.08 (1.04––1.12)	<0.001		
	Gender	1.09 (0.40––2.92)	0.87		
	Disease duration	1.01 (1.00––1.03)	0.02		
8	Carotid plaque	5.21 (1.40––19.4)	0.01	280.65	299.57
	2015/2016 EULAR mSCORE	1.04 (0.89––1.20)	0.64		
	Age	1.05 (1.01––1.09)	0.02		
	Gender	0.86 (0.25––3.00)	0.81		
	Disease duration	1.02 (1.01––1.03)	0.005		
9	**Carotid plaque**	5.13 (1.36––19.3)	0.02	278.72	297.62
	QRISK3	1.03 (0.99––1.07)	0.12		
	Age	1.02 (0.97––1.08)	0.39		
	Gender	0.80 (0.28––2.26)	0.68		
	Disease duration	1.02 (1.00––1.03)	0.005		
10	cIMT (continuous)	4.40 (0.26––74.6)	0.31	287.52	306.46
	2015/2016 EULAR mSCORE	1.03 (0.89––1.20)	0.69		
	Age at ECO	1.07 (1.03––1.11)	<0.001		
	Gender	0.89 (0.25––3.16)	0.85		
	Disease duration	1.01 (1.00––1.02)	0.02		
11	cIMT >0.9	1.61 (0.60––4.31)	0.35	287.70	306.64
	2015/2016 EULAR mSCORE	1.04 (0.89––1.20)	0.65		
	Age	1.07 (1.03––1.11)	<0.001		
	Gender	0.91 (0.25––3.24)	0.88		
	Disease duration	1.01 (1.00––1.03)	0.02		

* At the time of CV risk and carotid US assessment.

Discussion

CV risk stratification is of pivotal importance in patients with RA due to the increased risk of CV disease. Several non-invasive techniques are available to determine the presence of subclinical atherosclerosis in patients with RA. [17] The combined assessment of cIMT and plaques by carotid US is considered of potential interest to identify RA patients at high risk of CV events. [17] However, the number of studies aimed to determine the prognostic outcome using carotid US are scarce. With respect to this, we previously performed a prospective study on a series of 47 patients with RA. At the time of recruitment none of them had traditional CV risk factors or CV disease. After 5 years of follow-up since the carotid US assessment 17 had suffered CV events. In this small series cIMT was found to predict CV events [18]. Patients who experienced CV events had greater baseline cIMT than those who did not have CV events (1.01 ± 0.16 mm versus 0.74 ± 0.12 mm) [18]. None of the patients with cIMT less than 0.77 mm had CV events. However, 6 of the 10 patients with cIMT greater than 0.91 mm experienced CV events. The area under the receiver operating characteristic curve (AUC) was 0.93. Interestingly, the presence of carotid plaques yielded similar results with an AUC of 0.90 [18]. More recently, Ikdahl *et al.* supported the potential role of cIMT as a predictor of CV events in a series of 138 patients with RA [19]. However, in our present study that encompassed a larger series of patients with RA we could not confirm the implication of cIMT as a predictor of future CV events in patients with RA. It is possible that higher concern among rheumatologists on tight control of the disease and better management of traditional CV risk

factors in recent years may account for these contradictory results. However, this controversy on the implication of the measurement of cIMT as a predictor of CV events is not new as it was also raised by the experts who participated in the 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines on the evaluation of CV disease risk [20]. They did not recommend using cIMT for the assessment of the risk for the first CV event [20]. The reason for that was based on the results from a meta-analysis in which cIMT was associated with future CV events in the general population. However, such a meta-analysis did not disclose an additional predictive value for CV events when results of cIMT were added to the Framingham Risk [21].

Of special relevance was the study conducted by Evans *et al.*, who prospectively evaluated 599 patients with RA without a history of acute coronary syndrome after undergoing carotid US. Patients with no atherosclerotic plaque showed a new incidence of acute coronary syndrome of 1.1 per 100 patient-years and those with unilateral and bilateral atherosclerotic plaques had acute coronary syndrome incidence rates of 2.5 and 4.3, respectively [22]. Similar results were found in a retrospective analysis of 105 patients with new-onset, treatment-naive RA [23]. Bilateral atherosclerotic plaque was associated with a HR of 6.3 of developing acute coronary syndrome compared to patients without atherosclerotic plaque [23].

A prospective cross-sectional, observational study that included 103 patients with RA and 106 controls showed that bilateral carotid plaques were found more than twice in RA (15.5%) than controls (6.6%). Unilateral carotid plaques were more common in either side evaluated. The prevalence of increased cIMT was also found higher in patients with RA either in both sides [24]. In keeping with these findings, we already reported an increased cIMT and augmented frequency of plaques in Spanish RA patients when compared with matched controls [25]. In the present study, the presence of plaques conferred an increased risk of CV events and death in patients with RA after 5 years of follow-up. However, this increased risk of CV events and death was similar in patients with unilateral or bilateral plaques. According to that, we feel that the presence of plaque by itself may be a marker of severe atherosclerotic disease and, consequently, very high risk of a CV event.

Clinical assessment of CV risk in patients with RA was performed by Wah-Suarez using seven calculators and carotid US measurement of cIMT and plaque in 97 patients 40 to 75 years old [26]. In this study the tests with the highest sensitivity for cIMT were the Framingham BMI, Framingham lipids, ACC/AHA 2013, and QRISK2. However, for the presence of carotid plaque the highest sensitivity was in QRISK2, SCORE, and ACC/AHA 2013 [26]. In the present study we performed a comparative analysis between the QRISK3 and the 2015/2016 EULAR mSCORE in our cohort of patients with RA. We observed that the QRISK3 showed higher sensitivity to identify high or very high CV risk RA patients than the 2015/2016 EULAR mSCORE.

In conclusion, the present study supports the claim that carotid plaques are good predictors of CV events and death in the follow-up of patients with RA. The predictable capacity of the QRISK3 was higher than that of the 2015/2016 EULAR mSCORE in these patients. In this regard, the modified EULAR SCORE system, which was proposed as a means to improve CV risk stratification, proved to be less useful in patients with RA prospectively evaluated for at least 5 years. Combination of risk charts and non-invasive surrogate markers along with new biomarkers may help us to identify those patients with RA who may benefit of intensive therapy to achieve reduction of CV disease.

Contributors AC performed the US study, recruited patients for the study, contributed to the elaboration of the protocol of study, helped in the interpretation of data and in the elaboration of the manuscript. NV-R contributed to the elaboration of the protocol of study, helped in the interpretation of data, performed the prospective follow-up of the patients and the elaboration of the manuscript. JR-G recruited patients for the study, helped in the interpretation of data and in the elaboration of the manuscript. VP performed the prospective follow-up of the patients and helped in the interpretation of data and in the elaboration of the manuscript. BM-A helped in the interpretation of data and in the elaboration of the manuscript. RB recruited patients for the study and contributed to the elaboration of the manuscript. SC and IF-A helped in the interpretation of data and in the elaboration of the manuscript. JL contributed to the elaboration of the protocol of study, helped in the interpretation of data and the elaboration of the manuscript and performed the statistical analysis. MAG-G recruited patients for the study, contributed to the elaboration of the protocol of study, helped in the interpretation of data and was responsible of the final drafting and elaboration of the manuscript.

Declaration of Competing Interest

Disclosures that might be interpreted as constituting of possible conflict(s) of interest for the study:

Dr. Corrales had consultation fees/participation in company sponsored speaker's from AbbVie and Sanofi.

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Supplementary materials

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