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# Combined use of QRISK3 and SCORE2 increases identification of ankylosing spondylitis patients at high cardiovascular risk: Results from the CARMA Project cohort after 7.5 years of follow-up

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ABSTRACT

*Objective:* To establish the predictive value of the QRESEARCH risk estimator version 3 (QRISK3) algorithm in identifying Spanish patients with ankylosing spondylitis (AS) at high risk of cardiovascular (CV) events and CV mortality. We also sought to determine whether to combine QRISK3 with another CV risk algorithm: the traditional SCORE, the modified SCORE (mSCORE) EULAR 2015/2016 or the SCORE2 may increase the identification of AS patients with high-risk CV disease.

*Methods:* Information of 684 patients with AS from the Spanish prospective CARdiovascular in ReuMAtology (CARMA) project who at the time of the initial visit had no history of CV events and were followed in rheumatology outpatient clinics of tertiary centers for 7.5 years was reviewed. The risk chart algorithms were retrospectively tested using baseline data.

*Results:* After 4,907 years of follow-up, 33 AS patients had experienced CV events. Linearized rate=6.73 per 1000 person-years (95 % CI: 4.63, 9.44). The four CV risk scales were strongly correlated. QRISK3 correctly discriminated between people with lower and higher CV risk, although the percentage of accumulated events over 7.5 years was clearly lower than expected according to the risk established by QRISK3. Also, mSCORE EULAR 2015/2016 showed the same discrimination ability as SCORE, although the percentage of predicted events was clearly higher than the percentage of actual events. SCORE2 also had a strong discrimination capacity according to CV risk. Combining QRISK3 with any other scale improved the model. This was especially true for

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the combination of QRISK3 and SCORE2 which achieved the lowest AIC (406.70) and BIC (415.66), so this combination would be the best predictive model.
*Conclusions:* In patients from the Spanish CARMA project, the four algorithms tested accurately discriminated those AS patients with higher CV risk and those with lower CV risk. Moreover, a model that includes QRISK3 and SCORE2 combined the best discrimination ability of QRISK3 with the best calibration of SCORE2.

## Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory arthritis primarily involving the axial skeleton y sacroiliac joints [1]. Different studies have described that patients with AS have higher morbidity and mortality due to a higher frequency of cardiovascular (CV) events compared to the general population [2–5]. Because of this, the European Alliance of Associations for Rheumatology (EULAR) group recommends CV risk assessment at least every 5 years in this group of patients [6]. This higher frequency of CV events has been related to classic CV risk factors, genetic factors, and the inflammatory burden related to the disease [2–5,7,8].

Patients with AS have a higher frequency of subclinical atherosclerosis, which confers a high CV risk to the patients [9]. Therefore, it is of interest to identify those patients with AS who are at high risk of developing CV events. These patients must have tight control of modifiable CV risk factors and disease activity.

So far there are no specific indices developed for patients with rheumatic diseases. The Systematic Coronary Risk Assessment (SCORE) developed for the general population was used in European individuals with rheumatic diseases to estimate the CV risk over many years [10,11]. This algorithm estimates the 10-year risk of death from CV disease based on classic CV risk factors (age, sex, systolic blood pressure, total cholesterol, and smoking). The SCORE does not include diabetes mellitus or chronic kidney disease, since patients with these entities were considered to have a high CV risk [12].

Given the need to have reliable indices that estimate CV risk in rheumatic diseases, the EULAR study group on CV disease in rheumatic diseases established and recommended the use of the modified SCORE EULAR 2015/2016 (mSCORE 2015/2016). This is an adaptation of the SCORE that resulted from multiplying by a factor of 1.5 to compensate for the excess CV mortality in patients with rheumatoid arthritis (RA) and other inflammatory arthropathies, compared to the general population [6,13].

The SCORE CV risk algorithm was updated to a new predictive model called SCORE2 in 2021 [14]. SCORE2 has been calibrated and validated to predict the 10-year risk of first-onset CV disease in European populations. SCORE2 has some differences with respect to the traditional SCORE. In this regard, SCORE2 provides risk estimates for the combined outcome of fatal and nonfatal CV disease events. SCORE2 also accounts for the impact of competing risks by non-CV disease deaths whereas SCORE does not. SCORE2 was recalibrated to four distinct European regions rather than the two-level regional stratification provided by SCORE [14], and it has been systematically recalibrated using the contemporary CV disease rates available, whereas the original SCORE model was based on data collected before 1986.

There are other indices such as the QRESEARCH risk estimator version 3 (QRISK3) that calculates the risk of presenting a fatal and nonfatal CV event at 10 years [15]. QRISK3 was developed by clinicians and academics from the United Kingdom National Health Service, and has been shown to be a good predictor of 10-year CV disease in British and international cohorts [15] (https://qrisk.org/lifetime). QRISK3 incorporates several improvements over its predecessors, specifically QRISK2. In this regard, QRISK3 includes a broader range of clinical and demographic factors compared to previous versions. In this sense, QRISK3 incorporates additional variables such as ethnic origin, and socioeconomic level, which were not included in previous versions. In addition to conventional CV risk factors, it includes information on chronic kidney disease, atrial fibrillation, history of migraines, serious mental illness, atypical antipsychotic medication, regular use of glucocorticoid tablets, and diagnosis or treatment of erectile dysfunction. In addition, it offers the possibility of including whether the patient has RA or systemic lupus erythematosus. QRISK3 also covers a wider age range compared to QRISK2. While QRISK2 was primarily designed for people ages 35 to 74, QRISK3 extends its applicability to people ages 25 to 84. QRISK3 uses updated algorithms and risk equations to estimate the risk of CV disease. QRISK3 has been shown to have better calibration compared to previous versions. This approach tailors CV risk estimation to each individual's specific risk factors rather than relying solely on population-level data. QRISK3 integrates contemporary data from large population-based studies to ensure its risk estimates reflect current epidemiological trends. Rigorous validation processes ensure the accuracy and reliability of QRISK3 in predicting CV risk in diverse populations and settings. Furthermore, continuous refinement and updates based on new evidence and advances in CV risk assessment ensure the continued relevance and effectiveness of QRISK3 in clinical practice [15].

There is great concern that indices developed for the general population may underestimate CV risk in patients with rheumatic diseases [16]. In this sense, as occurred in patients with RA [17] and psoriatic arthritis (PsA) [18], different studies have described that the SCORE underestimates the CV risk in patients with AS since carotid plaques, which are the expression of a high CV risk, are frequently observed when a carotid ultrasound is performed on patients with AS included in the low and moderate CV risk categories according to the SCORE algorithm (19,20). In this regard, a recent study showed that the mSCORE EULAR 2015/2016 did not add any improvement in the ability to predict CV disease in this group of patients [21].

Of note, a study performed in patients with RA, which demonstrated that the presence of atheromatous plaques in the carotid artery is a good predictor of CV disease and mortality, showed that the QRISK3 was superior to the mSCORE EULAR 2015/2016 to identify patients with RA who are at high or very high risk of CV events [22]. Likewise, another study pointed out that the combined use of the mSCORE EULAR 2015/2016 and QRISK3 indices made it possible to identify those RA patients with a high probability of presenting atheromatous plaques in the carotid artery [23].

Taking these considerations together, we aimed to establish the predictive value of the United Kingdom CV risk algorithm QRISK3 in identifying Spanish AS patients at high risk of CV events and CV mortality. We also aimed to determine whether to combine QRISK3 with another CV risk algorithm; the traditional SCORE, the mSCORE EULAR 2015/2016, or the SCORE2 may increase the identification of AS patients with high-risk CV disease. To this end, we evaluated patients from the prospective Spanish CARdiovascular in RheuMAtology (CARMA) project, which included a cohort of patients with AS followed up in rheumatology outpatient clinics for 7.5 years.

## Patients and methods

### *Study design*

The CARMA project is a prospective cohort study aimed to identify the CV disease risk profile in patients with chronic inflammatory rheumatic diseases after 10 years of follow-up. It includes patients with AS, PsA and RA as well as a cohort of patients without inflammatory disease,

who have been recruited in 67 Spanish hospitals [24]. The period of recruitment was July 2010 to January 2012 [24]. In this report, we describe information on AS patients at 7.5 years from the onset of the study.

*Population*

Data from a set of 684 consecutive Spanish patients diagnosed with AS in the CARMA project [24] were evaluated. Initial (baseline) recruitment included 738 patients. As previously reported [24], all of them met the modified New York criteria diagnosis for AS [25]. Fifty-four patients with a history of CV events (ischemic heart disease, cerebrovascular accident, peripheral arterial disease, or heart failure) prior to the onset of the study (before the baseline visit) were excluded. Six hundred and ten patients had been assessed at the 5-year follow-up visit because they attended the 5-year visit or had died before that time. Most of them were prospectively followed up in rheumatology outpatient clinics. At 7.5 years, information on the patients included the initial cohort was obtained by consulting their medical records or by calling patients or family members directly. When it was not available, we requested information from the Spanish National Statistics Institute, which is the institution in charge of keeping records of vital events, such as births and deaths. This allowed us to determine information from 684 AS patients who at the time of the initial visit had no history of CV events.

Information on this cohort is included in the supplementary Table 1.

SCORE, mSCORE EULAR 2015/2016, SCORE2 and QRISK3 risk algorithms were retrospectively tested using baseline data obtained at the time of the patient's entry into the CARMA project.

The study was performed following the principles outlined in the Helsinki Declaration, and a written informed consent was obtained from all subjects before their inclusion into the project. It was approved by the Clinical Research Ethics Committee of Lugo, Galicia (Spain) (protocol No. 2009/077), and the Ethics Committee of each participating hospital.

*Variables and operative definitions*

1. CV events and CV mortality

The occurrence of CV events and CV mortality were analyzed. The following CV events were assessed: ischemic heart disease, stroke, peripheral arterial disease, and heart failure. The operational definitions of the variables analyzed were reported elsewhere [24].

2. Cardiovascular risk algorithms

The SCORE and SCORE2 were calculated as previously described [9,13]. SCORE was assessed with age, gender, smoking status, systolic blood pressure, and total cholesterol. SCORE2 was calculated using age, gender, smoking status, systolic blood pressure, and non-HDL-cholesterol.

SCORE2 was calculated using the score2risk command for Stata, available in http://www.phpc.cam.ac.uk/ceu/erfc/programs// [14,26]. SCORE was calculated using the algorithm described by Conroy et al. [10]. The SCORE calculates the 10-year risk of death from CV disease. However, since CV disease morbidity, when combined with CV disease mortality, better reflects the total burden of atherosclerotic CV disease, SCORE2 now estimates an individual's 10-year risk of fatal and non-fatal CV disease events in individuals aged 40 to 69 years. For healthy people aged ⩾ 70years, the SCORE2-OP (older persons) algorithm estimates 5-year and 10-year fatal and nonfatal CV disease events.

The mSCORE EULAR 2015/2016 was calculated according to the updated recommendations of the EULAR group of 2015/2016 [6,13].

The QRISK3 were calculated as described elsewhere [15]. This includes the variables analyzed: conventional CV risk factors, diabetes mellitus, chronic kidney disease, emerging CV risk factors and other inflammatory rheumatic diseases. The QRISK3 calculates a person's risk of developing a heart attack or stroke over the next 10 years. It represents the average risk of people with the same risk factors as those entered for that person [15]. It defines a cut-off point of 10 %, after which (≥10 %) the CV risk is high-very high, and below that level being low-moderate CV risk.

*Statistical analysis*

The demographic and clinical variables of the patients were shown as mean and standard deviation (SD), or median and interquartile range [IQR] in case of asymmetry, for the quantitative variables, and in absolute number and relative frequencies (%) for the variables qualitative.

Correlation between CV risk scales was measured with Pearson correlation coefficient.

Survival analysis was carried out in two ways: (a) Firstly, we considered as failure the compound of CV event or death due to any cause. Patients without CV event and alive at the end of follow-up were considered censored. Time of follow-up was the time until the first CV event or until death for failures and time until the last visit for censored patients. The discriminative ability of any CV scale to identify failures in this analysis was established using Cox regression. (b) Secondly, we considered as failure any CV event, with death due to any non-CV cause as competitive risk. Time of follow-up was the same as in analysis (a). The association of CV scale with CV event was studied with Cox regression. We did not adjust any model for age or sex as they are included in the CV scales. Results of the survival analysis were presented as hazard ratios with their 95 % confidence intervals and two-tailed p values. For each survival analysis (a–b), we built seven models. Models 1–4 included a CV scale each. Then, to ascertain if adding a CV risk scale to QRISK3 would improve the model, we built models 5–7. As SCORE, mSCORE EULAR 2015/2016 and SCORE2 are all variants of each other; we did not study their combination, so we limited models 5–7 to combinations of QRISK3 with any scale of the "SCORE family". As QRISK3 was strongly correlated with any other CV scale, we used the so-called "residual method". We illustrated it here for the combination QRISK3-SCORE, but the method was similar for QRISK3- mSCORE EULAR 2015/2016 and QRISK3-SCORE2 combinations.

The residual method was intended to separate SCORE in two parts: one linearly depending on QRISK3 ("linear prediction") and another which is independent from QRISK3 ("residuals"). To do it, a linear regression model was estimated between SCORE (as Y variable) and QRISK3 (as regressor). The residuals obtained from this regression were the part of SCORE which is independent of QRISK3. Then, we carried out the survival analysis including as regressors both QRISK3 and residual of SCORE.

To compare all seven models obtained in each survival analysis, we estimated the Akaike Information Criterium (AIC) and the Bayesian Information Criterium (BIC). Both criteria work in the same way: they penalize the introduction of new variables, so they tend to favor parsimonious models unless the inclusion of a new variable relevantly improves the model likelihood. Altogether, models with lower AIC or BIC are preferable.

All statistical analyses were carried out with the software Stata 18/SE (Stata Corp, College Station, Tx, US).

## Results

*Correlation between cardiovascular risk scales*

All four CV risk scales were strongly correlated (Table 1). Of note, as SCORE and the mSCORE EULAR 2015/2016 only differed by a factor of 1.5, they statistically act as a simple change of units, so their correlation with each other is 1.

**Table 1**
Correlation between cardiovascular risk scales.

| | QRISK3 | SCORE | mSCORE EULAR 2015/2016 | SCORE2 |
|---|---|---|---|---|
| QRISK3 | 1 | | | |
| SCORE | 0.7059 | 1 | | |
| mSCORE 2015/2016 | 0.7059 | 1 | 1 | |
| SCORE2 | 0.8585 | 0.8848 | 0.8848 | 1 |

SCORE: Systematic Coronary Risk Assessment; mSCORE 2015/2016: modified SCORE EULAR 2015/2016; SCORE2: Systematic Coronary Risk Assessment 2; QRISK3: QRESEARCH risk estimator version 3.

*Performance of cardiovascular risk scales*

There were 36 compound events (CV event or death by any cause) and 4907 years of follow-up. Linearized rate=7.34 per 1000 person-years (95 % CI: 5.14, 10.16).

Prediction of CV event or death by any cause is shown in Table 2 and Figs. 1a-1d. When comparing several scales, we should consider two characteristics: discrimination and calibration.

Discrimination is the ability to differentiate between people with high and low CV risk. Discrimination can be assessed with hazard ratios in Table 2 (the higher the hazard ratio, the better the discrimination) and with the separation between lines in Fig. 1 (a-d) (the wider the separation, the better the discrimination).

Calibration is the ascertainment of the predicted risk. For instance, if a scale predicts a group of patients have 10 % CV event risk in 10 years, it would be well calibrated if about 10 % of the patients in that group actually had a CV event in 10 years of follow-up, but it would be bad calibrated if a CV event appeared in the follow-up in 5 % or 15 % of the patients. Calibration can be assessed in Fig. 1 (a-d) comparing each line with the background grid. For instance, if the red line -which represents people with predicted risk of 10 %- reaches about the 10 % line in the grid by the end of follow-up, then that scale would be well calibrated. Otherwise, if the red line is far the 10 % line in the grid, then that scale would be bad calibrated.

**Table 2**
Cardiovascular (CV) risk scales performance with the compound event death by any cause or CV event.

| Model | CV risk scale | Hazard ratio (95 % CI) | P | AIC | BIC | Figure |
|---|---|---|---|---|---|---|
| 1 | QRISK3 | 1.05 (1.03, 1.07) | <0.001 | 447.02 | 451.53 | Fig. 1a |
| 2 | SCORE | 1.09 (1.06, 1.12) | <0.001 | 574.34 | 578.91 | Fig. 1b |
| 3 | mSCORE2015/16 | 1.06 (1.04, 1.08) | <0.001 | 574.34 | 578.91 | Fig. 1c |
| 4 | SCORE2 | 1.15 (1.10, 1.19) | <0.001 | 560.66 | 565.22 | Fig. 1d |
| 5 | QRISK3 | 1.06 (1.04, 1.08) | <0.001 | 440.76 | 449.76 | |
| | SCORE residual | 1.07 (1.03, 1.12) | =0.001 | | | |
| 6 | QRISK3 | 1.06 (1.04, 1.08) | <0.001 | 440.76 | 449.76 | |
| | mSCORE2015/16 residual | 1.05 (1.02, 1.08) | =0.001 | | | |
| 7 | QRISK3 | 1.06 (1.04, 1.09) | <0.001 | 439.53 | 448.50 | |
| | SCORE2 residual | 1.14 (1.04, 1.24) | =0.004 | | | |

Abbreviations: CI: Confidence interval. AIC: Akaike Information Criteria. BIC: Bayesian Information Criteria.

All four scales were associated with events (Table 2), with hazard ratios 1.05 (1.03, 1.07) for QRISK3, 1.09 (1.06, 1.12) for SCORE, 1.06 (1.04, 1.08) for mSCORE EULAR 2015/2016 and 1.15 (1.10, 1.19) for SCORE2.

QRISK3 correctly discriminated between people with lower and higher risk (Fig. 1a), although the percentage of events accumulated in 7.5 years was clearly lower than the expected according to the risk established by QRISK3. For instance, people whose QRISK3 = 20 % in ten years, after 7.5 years had only about 8 % events (Fig. 1a, yellow line).

SCORE correctly discriminated between people with lower and higher risk (Fig. 1b). After 7.5 years of follow-up, the cumulative risk was approximately equal to the expected percentage of events. For instance, people whose SCORE = 20 %, had about 20 % events (Fig. 1b, yellow line). mSCORE EULAR 2015/2016 showed the same discrimination ability than SCORE, although the percentage of events predicted was clearly higher than the percentage that actually occurred. For instance, people whose mSCORE EULAR 2015/2016 = 20 %, had about 13 % events (Fig. 1c, yellow line).

SCORE2 had strong discrimination ability according to the CV risk, as shown in the widely separated lines in Fig. 1d. For people with SCORE2= 5 %, 10 % or 15 %, the percentage of events occurred by year 7.5 of follow-up was about the same that was predicted (blue, red and green lines in Fig. 1d, respectively). However, SCORE2 underestimated the risk for people with SCORE2= 20 % (yellow line in Fig. 1d, the cumulative hazard reached 30 % in 7.5 years).

Combining QRISK3 with any other scale improved the model, as shown in Table 2 (AIC and BIC for any model with two scales were lower than for any model with just one scale). Combining QRISK3 and SCORE2 reached the lower AIC and BIC, so this combination would be the best predictive model.

There were 33 CV events, 4907 years of follow-up. Linearized rate=6.73 per 1000 person-years (95 % CI: 4.63, 9.44). Prediction of CV event when death by non-CV cause was considered a competitive event is shown in Table 3 and Fig. 2a-2d. All four scales showed discriminative power, as described in Fig. 2a-2d and p values were lower than 0.001 in Table 3, although QRISK3 reached clearly lower AIC and BIC values. Therefore, among the four scales QRISK3 would be that of election.

Discriminative ability of QRISK3 improved when combined with any other scale (as shown in AIC and BIC lower for models in combination than for the QRISK-alone model). However, a model combining QRISK3 and SCORE2 had lower AIC and BIC than any other, making this combination preferable.

## Discussion

In the present study we provide information on a large series of patients with AS included in the prospective Spanish CARMA project that evaluated the CV outcome of patients with inflammatory arthritis. The results shown in this cohort analysis included 684 AS patients with data 7.5 years after enrollment. Four CV risk chart algorithms were tested. In addition to the different modalities of SCORE, which is the algorithm commonly used to establish CV risk in the Spanish population, we also tested QRISK3, used in the United Kingdom to establish CV risk, in our cohort of patients with AS. The results of the study indicate that the four CV risk algorithms, namely QRISK3, SCORE, mSCORE EULAR 2015/2016 and SCORE2, can be successfully applied in AS patients. In all cases, the risk chart algorithms accurately discriminated those AS patients with higher CV risk and those with lower CV risk. However, although the four scales were highly correlated with each other, none provided all the information about CV risk. This fact makes it useful to

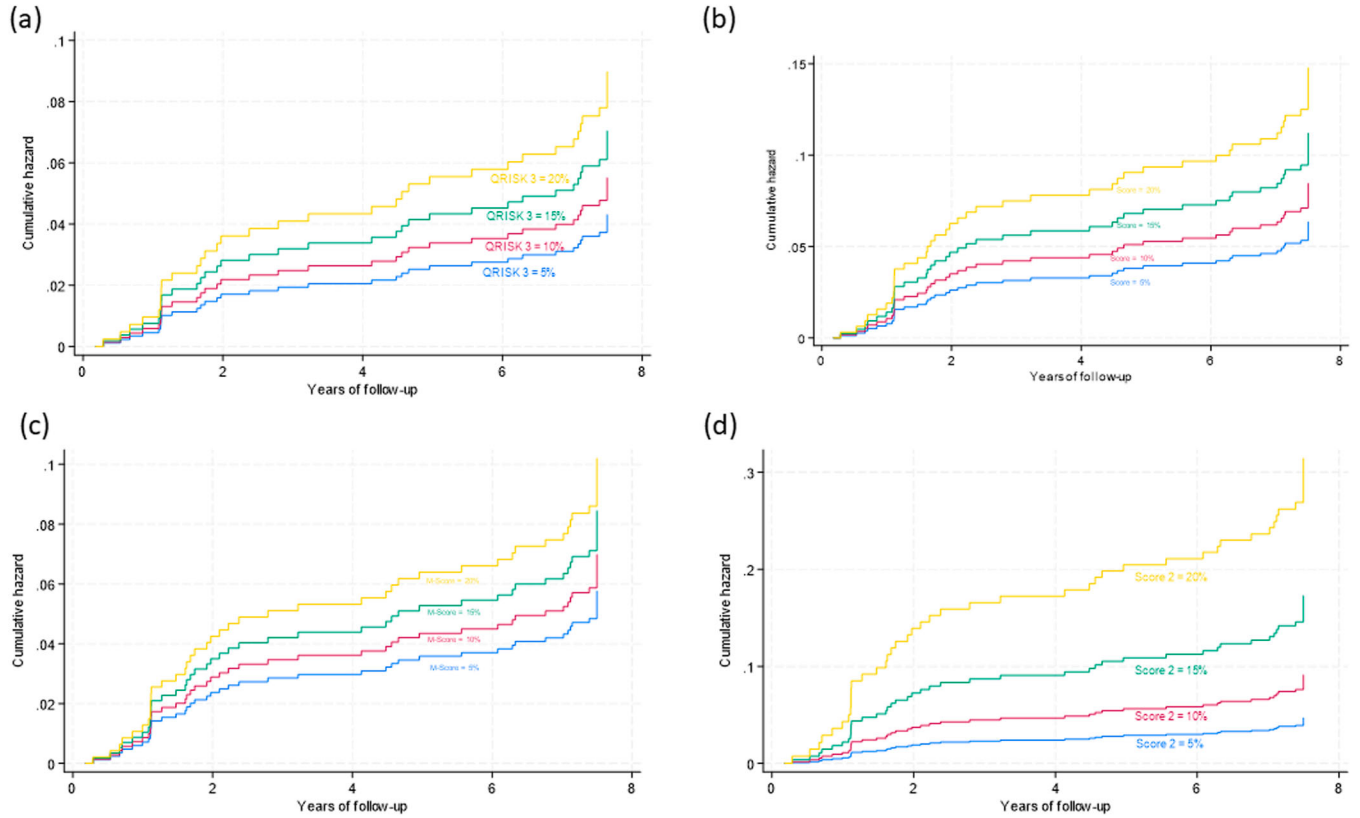


**Fig. 1.** Cardiovascular event or death by any cause: prediction using (a) QRISK3, (b) SCORE, (c) EULAR-modified SCORE, (d) SCORE-2.

**Table 3**
Cardiovascular (CV) risk scales performance with the CV event. Death by non-CV cause was considered as competing event.

| Model | Variables | Hazard ratio (95 % CI) | P | AIC | BIC | Figure |
|---|---|---|---|---|---|---|
| 1 | QRISK3 | 1.05 (1.03, 1.07) | <0.001 | 413.08 | 417.58 | Fig. 2a |
| 2 | SCORE | 1.07 (1.05, 1.10) | <0.001 | 532.91 | 537.48 | Fig. 2b |
| 3 | mSCORE2015/16 | 1.05 (1.03, 1.07) | <0.001 | 532.91 | 537.48 | Fig. 2c |
| 4 | SCORE2 | 1.14 (1.10, 1.17) | <0.001 | 518.12 | 522.68 | Fig. 2d |
| 5 | QRISK3 | 1.05 (1.03, 1.07) | <0.001 | 411.41 | 420.41 | |
| | SCORE residual | 1.05 (1.01, 1.09) | 0.02 | | | |
| 6 | QRISK3 | 1.05 (1.03, 1.07) | <0.001 | 411.41 | 420.41 | |
| | mSCORE2015/16 residual | 1.03 (1.01, 1.06) | 0.02 | | | |
| 7 | QRISK3 | 1.06 (1.04, 1.08) | <0.001 | 406.70 | 415.66 | |
| | SCORE2 residual | 1.14 (1.05, 1.23) | 0.001 | | | |

Abbreviations: CI: Confidence interval. AIC: Akaike Information Criteria. BIC: Bayesian Information Criteria.

combine two of them. In this sense, a model that included both QRISK3 and SCORE2 seems to combine the better discrimination ability of QRISK3 with a better calibration of SCORE2. However, we recognize the time constraints faced by rheumatologists in their daily clinical practice, which may pose a limitation in the use of two CV risk scores. However, based on the findings from our AS cohort, we recommend using both scores in combination whenever possible. In cases where it is not possible to test both, we suggest prioritizing QRISK3 over SCORE.

Information on the performance of different CV risk algorithms in patients with AS is scarce. In this regard, Navarini et al. performed a retrospective analysis of prospectively collected data from an AS cohort from six Italian Rheumatology Units [20]. To this end, these authors reviewed data from 133 consecutive AS patients with no personal history of CV disease who, as in our cohort, met the 1984 Modified New York Criteria in November 2008. The patients were evaluated ten years later (November 2018). During follow-up, 18 patients experienced a CV event [21]. They evaluated the performance of Framingham Score, SCORE, QRISK2, QRISK3, Reynold's Risk Score, the CV risk score developed in Dundee University, ASSIGN, and the Italian Progetto CUORE individual score [21]. According to their data, all CV risk algorithms showed poor discriminative capacity, except the Reynold's Risk Score, which includes C-reactive protein values (CRP) but is not applicable to patients with diabetes or those under 45 years of age, and the SCORE, which showed a fair performance [21]. These results are in some contradiction with our current data since, according to our results, QRISK3, SCORE, mSCORE EULAR 2015/2016 and SCORE-2 can be successfully applied in AS patients. Furthermore, we disclosed that a model including both QRISK3 and SCORE2 would be the best for identifying AS with high CV risk.

Discrepancies between the results reported by Navarini et al. and our data could be due to the different number of patients included in these studies and some differences in periods of recruitment. However, we believe that these reasons may be unlikely and that factors related to the

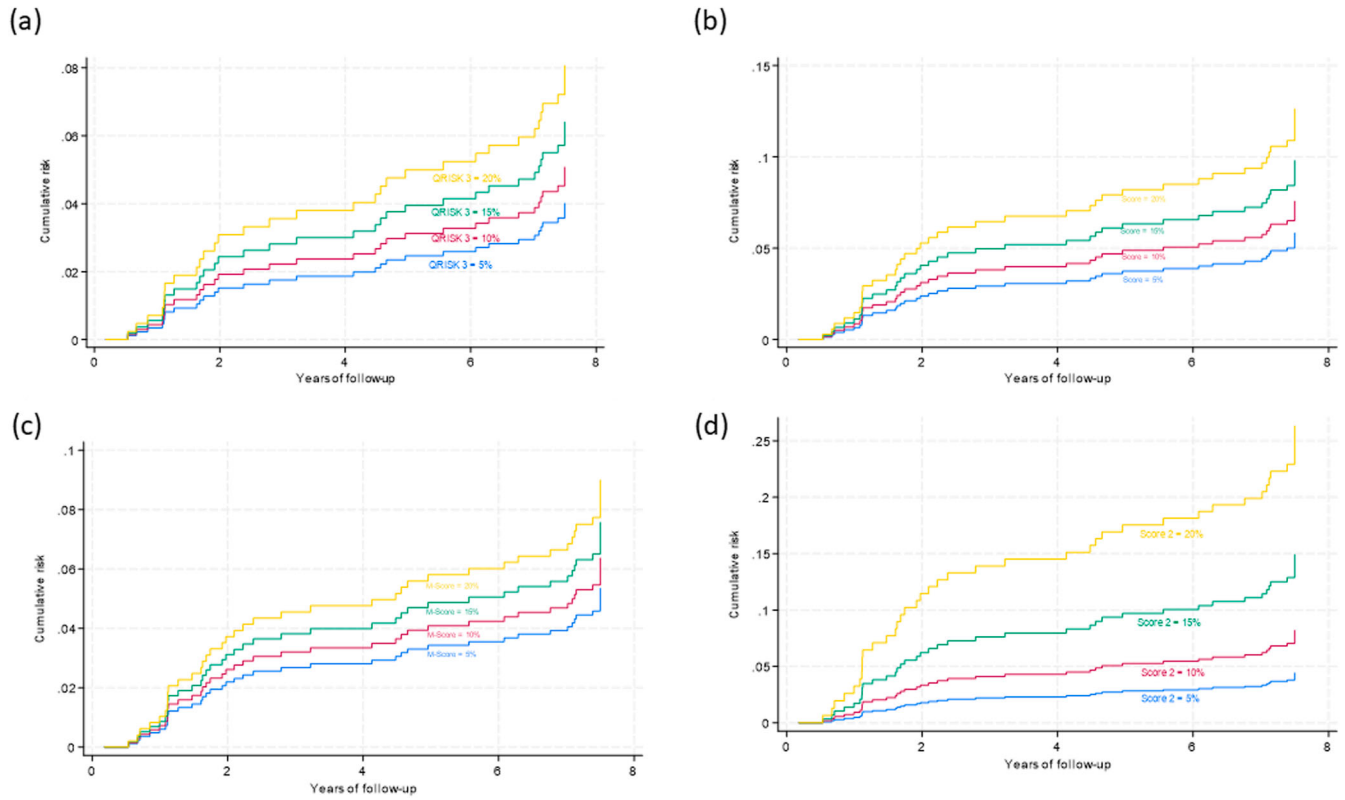


**Fig. 2.** Cardiovascular event when death by non-CV cause was considered a competitive event: prediction using (a) QRISK3, (b) SCORE, (c) EULAR-modified SCORE, (d) SCORE-2.

special characteristics of the CARMA cohort that included patients periodically followed up at rheumatology clinics from tertiary referral hospitals, subjected to strict disease control and active management of traditional CV risk factors during the follow-up, may explain this difference. In this regard, although previous studies of our group indicated that risk chart algorithms underestimated the actual CV risk in both RA and AS when we used the presence of carotid plaque as the expression of high-CV risk [19,27], it is important to highlight that plaque is an indirect marker of CV disease and the algorithms tested in our present study are focused on identifying patients at risk for CV events Furthermore, in a previous study on the CARMA cohort, a low number of fatal CV events was observed at 5 years of follow-up [28]. We feel that one of the possible explanations could be the protective effect of biologic therapy, by favorably influencing insulin sensitivity, lipid profile and metabolic changes mediated by inflammatory cytokines, all of which are involved in the development of accelerated atherogenesis in this population [28]. In this respect, endothelial dysfunction, an early step in the atherogenesis process that is present in patients with inflammatory arthritis [29], is improved by the use of anti-tumor necrosis factor (TNF)-α therapy in these patients [30]. In this sense, the information recovered from our files showed that 331 (48.4 %) of the AS patients assessed in the present study were on biologic therapy, the vast majority of them with anti-TNF-α agents, at the time of recruitment.

Interestingly, Navarini et al. highlighted the role of Reynold's Risk Score to identify AS patients at high risk of CV events [21]. This score includes CRP, a marker of inflammation frequently elevated in patients with chronic inflammatory rheumatic diseases. With respect to this, we previously reported that the median CRP over a extended follow-up of patients with RA was found to be a marker of CV events and CV mortality in patients with RA [31]. In this respect, Navarini et al. confirmed that persistence of elevated CRP and high disease activity may be considered predictive factors of CV disease in patients with axial spondylarthritis [32]. These authors assessed 295 patients without personal history of CV disease and observed that persistency of increased CRP levels at each visit and high values of clinical parameters of disease activity help to identify patients with axial spondylarthritis at higher risk of CV disease [32]. In keeping with that, we also observed that disease activity influences the reclassification of patients with RA into the category of very high CV risk [33].

In line with the above, a systematic review and meta-analysis showed that anti-TNF-α therapy was associated with a reduction in the risk of CV events including myocardial infarction and cerebrovascular accidents in patients with RA [34]. Interestingly, Karpouzas et al. described that the use of biological therapy was associated with a reduction of the CV disease in patients with RA, preventing CV events by the inhibition of coronary plaque formation and the stabilization of high-risk coronary lesions [35]. Moreover, Karpouzas et al. also demonstrated that treatment with statins modified the impact of inflammation on the formation of new coronary plaque and predicted both regression and calcification of the non-calcified lesions in patients with RA yielding a reduction in the long-term CV risk of these patients [36]. In this regard, as previously discussed when we assessed mortality after 5 years of follow-up [28], patients with the CARMA cohort were regularly followed at tertiary referral centers and had good control good control of CV risk factors. Therefore, adequate control of the disease, including frequent use of biologic therapy as well as good control of traditional CV risk factors may favor that the patients with AS have a reduction of the atherogenic burden, and, therefore, being somehow similar in terms of CV risk to those of the general population.

The main limitation of our study was that we evaluated CV events after 7.5 years of follow-up, while risk table algorithms establish the risk of CV events and CV mortality at 10 years. However, our study had several strengths, mainly related to the prospective design. In this regard, we evaluated a large cohort of AS patients undergoing scheduled follow-up visits to standardize data collection and minimize losses.

In conclusion, in patients from the prospective Spanish CARMA

project that included patients followed at rheumatology clinics from tertiary referral centers, data obtained 7.5 years after enrollment indicate that four CV risk chart algorithms, namely QRISK3, SCORE, mSCORE EULAR 2015/2016 and SCORE2, can be successfully applied in patients with AS. All of them accurately discriminated those AS patients with higher CV risk and those with lower CV risk. Moreover, a model that includes QRISK3 and SCORE2 combines the best discrimination ability of QRISK3 with the best calibration of SCORE2.

## Authors' contributions

Jessica Polo y La Borda performed the data analysis and drafted the manuscript. Santos Castañeda, Carmen García-Gómez, Iván Ferraz-Amaro and Carlos Gonzalez-Juanatey helped develop the study protocol and the manuscript, and also assisted in data interpretation. Fernando Sánchez-Alonso and Zulema Plaza helped interpret the data and improve the manuscript. Celia Erausquin Ramón Valls-García, María D. Fábregas, Esmeralda Delgado-Frías and Antonio J. Mas and helped in the search and collection of patients, cleaning of the databases, interpretation of the results and corrections and approval of the final version of the manuscript. Javier Llorca helped to design the study protocol, interpret the data, strengthen the manuscript and also performed the statistical analysis. Miguel A. Gonzalez-Gay helped design and developed the CARMA project, assisted in data interpretation, and was responsible for the final draft of the manuscript. All of the authors have given their approval to the final version.

## Ethics in publishing

As noted in the manuscript, the authors of this study declare that their study was approved by the appropriate IRB and that the participant provided written informed consent for publication.

## CRediT authorship contribution statement

**Jessica Polo y la Borda:** Formal analysis, Data curation, Investigation. **Santos Castañeda:** Conceptualization, Methodology, Writing – original draft. **Fernando Sánchez-Alonso:** Data curation, Investigation, Writing – original draft. **Zulema Plaza:** Data curation, Investigation, Writing – original draft. **Carmen García-Gómez:** Conceptualization, Methodology, Writing – original draft. **Iván Ferraz-Amaro:** Conceptualization, Methodology, Writing – original draft. **Celia Erausquin:** Data curation, Investigation, Resources. **Ramón Valls-García:** Data curation, Investigation, Resources. **María D. Fábregas:** Data curation, Investigation, Resources. **Esmeralda Delgado-Frías:** Resources, Investigation, Data curation. **Antonio J. Mas:** Resources, Investigation, Data curation. **Carlos González-Juanatey:** Writing – original draft, Investigation, Conceptualization. **Javier Llorca:** Methodology, Formal analysis, Conceptualization, Supervision, Validation, Writing – original draft. **Miguel A. González-Gay:** Writing – original draft, Conceptualization, Formal analysis, Investigation, Methodology, Supervision.

## Declaration of competing interest

The authors declare they do not have financial interests, which could create a potential conflict of interest or the appearance of a conflict of interest with regard to the current work.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2024.152442.

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