## RESEARCH ARTICLE

# Disease activity influences the reclassification of rheumatoid arthritis into very high cardiovascular risk

Iván Ferraz-Amaro[1][*] , Alfonso Corrales[2,3], Juan Carlos Quevedo-Abeledo[4], Nuria Vegas-Revenga[2,3], Ricardo Blanco[2,3], Virginia Portilla[2,3], Belén Atienza-Mateo[2,3] and Miguel Á. González-Gay[2,3,5]

## Abstract

**Background:** Previous studies have shown that risk chart algorithms, such as the Systematic Coronary Risk Assessment (SCORE), often underestimate the actual cardiovascular (CV) risk of patients with rheumatoid arthritis (RA). In contrast, carotid ultrasound was found to be useful to identify RA patients at high CV. In the present study, we aimed to determine if specific disease features influence the CV risk reclassification of RA patients assessed by SCORE risk charts and carotid ultrasound.

**Methods:** 1279 RA patients without previous CV events, diabetes, or chronic kidney disease were studied. Disease characteristics including disease activity scores, CV comorbidity, SCORE calculation, and the presence of carotid plaque by carotid ultrasound were assessed. A multivariable regression analysis was performed to evaluate if the reclassification into very high CV risk category was independently associated with specific features of the disease including disease activity. Additionally, a prediction model for reclassification was constructed in RA patients.

**Results:** After carotid ultrasound assessments, 54% of the patients had carotid plaque and consequently fulfilled definition for very high CV risk. Disease activity was statistically significantly associated with reclassification after fully multivariable analysis. A predictive model containing the presence of dyslipidemia and hypertension, an age exceeding 54 years, and a DAS28-ESR score equal or higher than 2.6 yielded the highest discrimination for reclassification.

**Conclusion:** Reclassification into very high CV risk after carotid ultrasound assessment occurs in more than the half of patients with RA. This reclassification can be independently explained by the activity of the disease.

**Keywords:** Rheumatoid arthritis, Cardiovascular disease, Carotid plaque

* Correspondence: iferrazamaro@hotmail.com
[1]Division of Rheumatology, Hospital Universitario de Canarias, Tenerife, Spain
Full list of author information is available at the end of the article

## Background

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease that leads to irreversible joint damage and systemic complications, and the age-adjusted mortality of those affected exceeds that of the general population. This increased risk of premature death in patients with RA is largely due to cardiovascular disease (CVD), particularly coronary artery disease [1]. Increase of carotid artery intima-media wall thickness (cIMT) and higher frequency of carotid plaques have been described in patients with RA [2–5]. Moreover, coronary artery calcification, a finding that is correlated with an increased risk of clinical and angiographic coronary atherosclerosis, is more prevalent in patients with established RA than in patients with early RA or healthy controls [6–8].

Prediction score algorithms for CVD, such as the Systematic Coronary Risk Evaluation (SCORE), was reported to have a suboptimal performance and to underestimate high CV risk in RA [9]. Moreover, according to the 2016 European Guidelines on Cardiovascular Disease Prevention in Clinical Practice [10], carotid artery plaque assessment using ultrasound may be considered a way of reclassifying those patients for whom the SCORE is thought to underestimate their actual CV risk. Although formal reclassification analyses have not been undertaken, it is believed that the presence of carotid plaque may be a modifier of SCORE risk prediction. In keeping with that, a recent 5-year prospective follow-up study has shown that the presence of carotid plaques predicts the development of CV events and death in patients with RA. In this study, the predictable capacity of carotid plaques was higher than that of the SCORE [11].

In the present study, we aimed to determine if specific disease features influence the CV risk reclassification of RA patients assessed by SCORE risk charts and carotid ultrasound.

## Materials and methods

### Study participants

This was a cross-sectional study that included 1279 patients with RA. They were all 18 years or older and were included in the study if they fulfilled the 2010 ACR/EULAR classification criteria for RA [12]. For the purpose of inclusion in the present study, RA disease duration needed to be ≥ 1 year. Patients taking glucocorticoids were included only if they were taking an equivalent dose ≤ 10 mg/day of prednisone. However, patients were excluded if they had diabetes, a history of cancer or any other chronic disease, evidence of active infection, or a glomerular filtration rate < 60 ml/min/1.73 m$^2$. The study protocol was approved by the Institutional Review Committees at Hospital Universitario de Canarias, Hospital Doctor Negrín, and Hospital Marqués de Valdecilla, Spain (approval number 17/2012). All subjects provided informed written consent.

### Data collection and laboratory assessments

The subjects completed a CV risk factor and medication use questionnaire and underwent a physical examination. Weight, height, body mass index, abdominal circumference, and systolic and diastolic blood pressure (measured with the participant in a supine position) were assessed under standardized conditions. Information regarding smoking status (current smoker versus non-smoker) and hypertension was obtained from the questionnaire. Medical records were reviewed to ascertain specific diagnoses and medications. Dyslipidemia was defined if one of the following was present: total cholesterol > 200 mg/dl, triglycerides > 150 mg/dl, HDL cholesterol < 40 in men or < 50 mg/dl in women, or LDL cholesterol > 130 mg/dl. Cholesterol, triglycerides, and HDL cholesterol were measured using the enzymatic colorimetric assay. LDL cholesterol was calculated using the Friedewald formula. A standard technique was used to measure the erythrocyte sedimentation rate (ESR) and high-sensitivity C-reactive protein (CRP). Disease activity in patients with RA was measured using the Disease Activity Score (DAS28) in 28 joints [13], the Clinical Disease Activity Index (CDAI) [14], and the Simple Disease Activity Index (SDAI) [15]. Patients with RA were defined as being in clinical remission (DAS28 < 2.6) or having low (DAS28 in the range of 2.6 to 3.2), moderate (DAS28 of > 3.2 to 5.1), or high disease activity (DAS28 > 5.1) as previously described [16]. Function, pain, and patient global estimate of status was measured through the Routine Assessment of Patient Index (RAPID) [17], and disease disability through the Health Assessment Questionnaire (HAQ) score [18].

### Carotid ultrasound assessment

A carotid ultrasound examination was used to assess cIMT in the common carotid artery and to detect focal plaques in the extracranial carotid tree in patients with RA [19]. A commercially available scanner, the Esaote Mylab 70 (Genoa, Italy), equipped with a 7–12-MHz linear transducer and an automated software-guided radiofrequency technique, Quality Intima Media Thickness in real-time (QIMT, Esaote, Maastricht, Holland), was used for this purpose. As previously reported [19], based on the Mannheim consensus, plaque criteria in the accessible extracranial carotid tree (common carotid artery, bulb, and internal carotid artery) were defined as follows: a focal protrusion in the lumen measuring at least cIMT > 1.5 mm, a protrusion at least 50% greater than the surrounding cIMT, or arterial lumen encroaching > 0.5 mm [20].

## Statistical analysis

Demographic and clinical characteristics are shown as frequencies for binary variables.

Continuous variables data are expressed as mean ± standard deviation (SD) or as a median and interquartile range (IQR) for non-normally distributed variables. Patients and controls with carotid plaques based on ultrasound assessment were reclassified into very high-SCORE risk category. Subjects without plaques were maintained in their original SCORE category. cIMT was not used to determine reclassification because according to current guidelines cIMT is not considered an unequivocal CVD on imaging [10]. Univariate differences between reclassified and non-reclassified patients were assessed through Student's t, Mann-Whitney U, chi-square, or Fisher's exact tests according to normal distribution or the number of subjects. Logistic regression analysis adjusted for the variables with a *p* value < 0.20 in the univariate analysis was performed to assess the relationship between RA disease-related data and the presence of reclassification. An all-sets logistic regression model was constructed to describe the most parsimonious combination of risk reclassification predictors according to Akaike Information Criteria, Schwarz Bayesian Criterion, area under the curve (AUC), and Hosmer-Lemeshow goodness-of-fit statistics. For characteristics associated with reclassification and that were included in the predictive model, sensitivity versus false-positive frequency (1-specificity) was analyzed using receiver-operating characteristic curves (ROC). To determine the optimal cutoff value of baseline characteristics in predicting reclassification, we calculated the Youden index using the following formula: sensitivity + specificity − 1, with the maximum obtained value corresponding to the optimal cutoff point. To estimate the increase in prediction accuracy between models, we used logistic regression to calculate the ROC curves and the area under the ROC curves (AUC). The SCORE AUC was thus considered the reference and was compared to the other model when adding RA-related data (age, dyslipidemia, hypertension, and DAS28 score). A comparison of ROC curves to test the statistical significance of the difference between the areas under two dependent ROC curves (derived from the same cases) was conducted using the method of DeLong et al. [21]. Reclassification differences between models were studied through the net reclassification index (NRI) and integrated discrimination improvement (IDI) as previously described [22]. Similarly, calibration of the models was calculated using the Hosmer-Lemeshow goodness-of-fit test by grouping individuals on the basis of deciles [23, 24]. All the analyses used a 5% two-sided significance level and were performed using SPSS software, version 24 (IBM Corp.). A *p* value < 0.05 was considered statistically significant.

## Results

### Demographic, laboratory, and disease-related data and SCORE risk category reclassification after carotid sonography

A total of 1279 patients with RA were included in this study. Demographic and disease-related characteristics of the participants are shown in Table 1. Mean ± SD age was 58 ± 13 years and 72% of the patients were female. Current smoking, obesity, dyslipidemia, and hypertension were present in respectively 25, 28, 48, and 37% of the patients. Disease duration was 5 (IQR 2–12) years. RA patients had moderately active disease as shown by the mean DAS28 (3.09 ± 1.49). Half of the patients (50%) were taking prednisone (the median dose of those patients on prednisone was 5 [IQR 4–6] mg/day at the time of the study). Fifty-nine percent of patients were found to be positive for rheumatoid factor and 53% for anti-citrullinated protein antibody (ACPA). Besides, 77% were on disease-modifying antirheumatic drugs and 13% were receiving anti-TNF-alpha therapy. Regarding carotid ultrasound assessment, 53% of the patients with RA had carotid plaques and the average cIMT in patients was 690 ± 140 μm. Additional information regarding RA patient characteristics is shown in Table 1.

Following SCORE risk chart stratification, 533 (42%) patients were included in the low risk category. Contrary, 487 (39%), 139 (11%), and 103 (8%) of the patients were included in the moderate-, high-, and very high-risk categories, respectively. Following carotid ultrasound assessment, 54% of the patients were found to have carotid plaque and consequently were reclassified into the very high SCORE category risk. Specifically, 26% of the patients in the low category, 65% of those in the moderate risk category, and 86% of the ones in the high category moved into the very high SCORE risk category (Table 2).

### Differences between reclassified and non-reclassified patients into very high CV risk categories after carotid ultrasound assessment

Several differences were observed in the recorded characteristics of patients with RA who were reclassified following the carotid ultrasound assessment and those who were not reclassified (Table 3). Reclassified patients were older (62 ± 9 vs. 54 ± 14 years, *p* = 0.000), and more commonly had hypertension (47% vs. 28%, *p* = 0.000) and dyslipidemia (57% vs. 40%, *p* = 0.000).

As expected, patients with RA who were reclassified following a carotid ultrasound had greater cIMT than those who were not reclassified (740 ± 140 vs. 650 ± 140 μm, *p* = 0.000). However, CRP values did not reveal any differences between reclassified and non-reclassified patients.

Regarding RA-related features, some differences were observed between these two groups of patients

**Table 1** Demographics, cardiovascular risk factors, and disease-related data in RA patients

|  | RA (*n* = 1279) |
|---|---|
| Age, years | 58 ± 13 |
| Female, n (%) | 982 (72) |
| BMI, kg/m$^2$ | 28 ± 5 |
| Abdominal circumference, cm | 94 ± 15 |
| Cardiovascular data | |
| CV risk factors, n (%) | |
| Current smoker | 326 (25) |
| Obesity | 354 (28) |
| Dyslipidemia | 611 (48) |
| Hypertension | 468 (37) |
| Diabetes mellitus | 0 (0) |
| Blood pressure, mmHg | |
| Systolic | 131 ± 17 |
| Diastolic | 78 ± 10 |
| Lipids | |
| Total cholesterol, mmol/l | 5.28 ± 0.96 |
| Triglycerides, mmol/l | 1.27 ± 0.70 |
| HDL cholesterol, mmol/l | 1.58 ± 0.44 |
| LDL cholesterol, mmol/l | 3.10 ± 0.80 |
| Atherogenic index | 3.56 ± 1.06 |
| Statins, n (%) | 303 (24) |
| Aspirin, n (%) | 43 (3) |
| Antihypertensive treatment, n (%) | 335 (26) |
| Disease-related data | |
| Disease duration, years | 5 (2–12) |
| CRP at time of study, mg/l | 2.7 (0.9–6.7) |
| ESR at time of study, mm/1° h | 12 (5–23) |
| Rheumatoid factor, n (%) | 753 (59) |
| ACPA, n (%) | 682 (53) |
| DAS28-ESR | 3.09 ± 1.49 |
| DAS28-PCR | 2.99 ± 1.28 |
| SDAI | 10 (5–18) |
| CDAI | 9 (4–16) |
| HAQ | 0.750 (0.250–1.250) |
| RAPID | 3.15 ± 2.03 |
| Current drugs, n (%) | |
| Prednisone | 636 (50) |
| Prednisone doses, mg/day | 5 (4–6) |
| NSAIDs | 498 (39) |
| DMARDs | 983 (77) |
| Methotrexate | 730 (57) |
| Leflunomide | 141 (11) |
| Hydroxychloroquine | 282 (22) |

**Table 1** Demographics, cardiovascular risk factors, and disease-related data in RA patients *(Continued)*

|  | RA (*n* = 1279) |
|---|---|
| Sulphasalazine | 44 (3) |
| Anti-TNF therapy | 166 (13) |
| Adalimumab | 56 (4) |
| Infliximab | 18 (1) |
| Etanercept | 66 (5) |
| Golimumab | 5 (0) |
| Tocilizumab | 65 (5) |
| Rituximab | 21 (2) |
| Abatacept | 22 (2) |
| Baricitinib | 12 (1) |
| Tofacitinib | 14 (1) |
| Historical disease-related data | |
| History of extraarticular manifestations, n (%) | 232 (18) |
| Erosions, n (%) | 453 (35) |
| CRP at time of disease diagnosis, mg/l | 7.0 (2.0–20.0) |
| CRP > 3 at time of diagnosis, n (%) | 685 (54) |
| ESR at the time of disease diagnosis, mm/1° h | 21 (11.38) |
| Subclinical atherosclerosis | |
| Carotid IMT, μm | 690 ± 140 |
| Carotid plaques, n (%) | 678 (53) |

Data represent means ± SD or median (IQR) when data were not normally distributed

*CV* cardiovascular, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *CRP* C-reactive protein, *NSAID* nonsteroidal anti-inflammatory drugs, *DMARD* disease-modifying antirheumatic drug, *TNF* tumor necrosis factor, *Obesity*, *ESR* erythrocyte sedimentation rate, *BMI* body mass index, *DAS28* Disease Activity Score in 28 joints, *ACPA* anti-citrullinated protein antibodies, *RAPID* routine assessment of patient index, *CDAI* Clinical Disease Activity Index, *SDAI* Simple Disease Activity Index, *HAQ* Health Assessment Questionnaire

(Table 3). Although disease duration was not found to be more frequent in the reclassified patients, both rheumatoid factor and ACPA were more commonly found in the reclassified patients compared to those non-reclassified. The odds ratio (OR) of rheumatoid factor and ACPA for reclassification were, respectively, 1.58 (95% CI 1.19–2.11) and 1.46 (95% CI 1.09–1.94). These associations were observed after multivariable analysis adjusting for age, dyslipidemia, hypertension, and statins and aspirin intake. Additionally, the DAS28-ESR score was statistically significantly associated with reclassification after fully multivariable analysis (OR 1.09 [95% CI 1.02–1.19], *p* = 0.028). It was observed a similar trend for DAS28-CRP and CDAI scores although, in these cases, statistical significance was not reached. Other associations that were significant in the univariable analysis, like those related to the presence of erosions and current use of NSAIDs, did not remain significant after adjustment for covariables (Table 3).

**Table 2** SCORE risk category reclassification after carotid ultrasound assessment

| | | SCORE risk category after carotid ultrasound assessment | | | | % patients reclassified |
| --- | --- | --- | --- | --- | --- | --- |
| | | Low | Moderate | High | Very high | |
| Initial SCORE risk category | | | | | | |
| Low | 533 | 392 | | | 141 | 26% |
| Moderate | 487 | | 170 | | 317 | 65% |
| High | 139 | | | 19 | 120 | 86% |
| Very high | 103 | | | | 103 | - |
| | 1262 | 392 | 170 | 19 | 681 | 54% |

SCORE risk reclassification data was not available for 17 patients
*SCORE* Systematic Coronary Risk Evaluation

## Predictive model for reclassifying patients into the very high CV risk category following carotid ultrasound assessment

A predictive model was constructed only for those patients with RA who had been included in the low and moderate risk SCORE categories (< 5%) prior to a carotid ultrasound assessment (Table 4). These variables conjointly represented the most parsimonious model capable of predicting the reclassification of patients with RA into the very high CV risk category (Table 4): age, the presence of hypertension and dyslipidemia, and DAS28-ESR score. Moreover, an age exceeding 54 years and a DAS28-ESR score ≥ 2.6 were the cutoffs among the continuous variables that reached the highest Youden indices.

Table 5 represents the discrimination, reclassification, and calibration assessment of the model using clinical data (age, dyslipidemia, hypertension, and DAS28-ESR score) versus the reference SCORE model. The SCORE, which included traditional CV risk factors, showed a statistically significant discrimination of reclassification (AUC 0.766, 95% CI 0.737–0.794). The AUC of the model, which contained SCORE plus age, dyslipidemia, hypertension, and DAS28-ESR, was found to have higher discrimination (0.775, 95% CI 0.747–0.803) although statistical significance was not reached ($p$ = 0.23). The addition of clinically related data represented a significant change in NRI versus the SCORE reference model (NRI 0.07, 95% CI 0.01–0.12, $p$ = 0.018). Similarly, IDI was significantly higher in this model compared to that of the SCORE reference (0.07, 95% CI 0.05–0.08, $p$ = 0.000). Model calibration (through a Hosmer-Lemeshow chi-square test) was found to be optimal in the final model ($p$ = 0.80).

## Discussion

The present work, which included a large series of patients studied by carotid ultrasound, aimed to determine if specific disease features influence the CV risk reclassification of RA patients. It confirmed that reclassification is very common in patients with RA and that disease activity increases the risk for this reclassification. This work also defines several predictors that may be used in the routine clinical practice for the identification of patients with a high probability for being reclassified.

The role of carotid ultrasound in the reclassification of CV risk has been previously studied in other inflammatory diseases. For example, in an earlier work in 343 patients diagnosed with axial spondyloarthritis and 177 controls, patients were more likely reclassified into the very high-risk category than controls after carotid ultrasound [25]. Interestingly, the influence of traditional cardiovascular risk factors on this reclassification was higher in controls compared to patients. However, in this report, although reclassification was associated with higher disease activity and functional and metrological scores, these associations were lost after adjusting for covariables [25]. Similarly, patients with psoriatic arthritis are more frequently reclassified into the very high SCORE risk category following carotid ultrasound assessment than controls [26]. In this case, reclassification was independently explained by the disease activity. Likewise, in a cross-sectional study that included 276 patients with systemic lupus erythematosus, following carotid ultrasound assessment, 32% of the patients were reclassified as very high-risk category [27]. In these SLE patients, disease duration and damage were independently associated with a higher risk of reclassification. The fact that RA shares this higher reclassification frequency with the aforementioned diseases suggests that the SCORE is not a useful instrument for assessing CV risk in patients with RA or other inflammatory diseases. This reclassification can be influenced by the inflammatory activity or damage that these disorders exert.

In our study, a predictive model containing age, two traditional CV risk factors (dyslipidemia and hypertension), and DAS28-ESR higher or equal to 2.6 was capable to show a high discrimination for reclassification. According to our results, in patients with low or moderate CV risk (< 5%), the addition of these predictor variables to SCORE yielded a discrimination higher than that of the SCORE model alone. However, the size effect

**Table 3** Multivariable analysis of the differences between reclassified or not reclassified patients

| | Not reclassified (*n* = 684) | Reclassified (*n* = 578) | *p* | Reclassification OR (95% CI), *p** |
|---|---|---|---|---|
| cIMT, μm | 650 ± 140 | 740 ± 140 | **0.000** | |
| Age, years | 54 ± 14 | 62 ± 9 | **0.000** | |
| Female, n (%) | 531 (78) | 437 (76) | 0.40 | |
| BMI, kg/m$^2$ | 27 ± 6 | 28 ± 5 | 0.39 | |
| Abdominal circumference, cm | 94 ± 15 | 94 ± 14 | 0.92 | |
| Cardiovascular data | | | | |
| CV risk factors, n (%) | | | | |
| Current smoker | 169 (25) | 153 (26) | 0.47 | |
| Obesity | 193 (28) | 155 (27) | 0.58 | |
| Dyslipidemia | 275 (40) | 332 (57) | **0.000** | |
| Hypertension | 192 (28) | 271 (47) | **0.000** | |
| Blood pressure, mmHg | | | | |
| Systolic | 130 ± 18 | 132 ± 16 | **0.024** | |
| Diastolic | 78 ± 10 | 79 ± 9 | 0.58 | |
| Lipids | | | | |
| Total cholesterol, mmol/l | 5.26 ± 0.96 | 5.28 ± 0.96 | 0.66 | |
| Triglycerides, mmol/l | 1.24 ± 0.71 | 1.28 ± 0.68 | 0.35 | |
| HDL cholesterol, mmol/l | 1.58 ± 0.44 | 1.58 ± 0.44 | 0.90 | |
| LDL cholesterol, mmol/l | 3.10 ± 0.80 | 3.10 ± 0.83 | 0.94 | |
| Atherogenic index | 3.56 ± 1.11 | 3.53 ± 0.97 | 0.63 | |
| Statins, n (%) | 113 (17) | 188 (33) | **0.000** | |
| Aspirin, n (%) | 16 (2) | 27 (5) | **0.018** | |
| Antihypertensive treatment, n (%) | 140 (20) | 190 (33) | **0.000** | |
| Disease-related data | | | | |
| Disease duration, years | 5 (2–12) | 5 (2–12) | 0.62 | |
| CRP at time of study, mg/l | 2.5 (0.9–6.4) | 3.0 (1.0–7.0) | 0.71 | |
| ESR at time of study, mm/ 1° hour | 11 (5 − 21) | 13 (6–25) | **0.007** | 1.00 (0.99–1.01), 0.79 |
| Rheumatoid factor, n (%) | 380 (56) | 360 (62) | **0.019** | **1.58 (1.19–2.11), 0.002** |
| ACPA, n (%) | 352 (51) | 320 (55) | 0.097 | **1.46 (1.09–1.94), 0.011** |
| DAS28-ESR | 2.96 ± 1.50 | 3.27 ± 1.46 | **0.000** | **1.09 (1.02–1.19), 0.028** |
| DAS28-PCR | 2.91 ± 1.28 | 3.10 ± 1.28 | **0.010** | 1.04 (0.93–1.16), 0.095 |
| SDAI | 3.20 ± 2.05 | 3.10 ± 2.02 | 0.73 | |
| CDAI | 8 (3–16) | 9 (4–17) | 0.078 | 1.00 (0.99–1.02), 0.52 |
| HAQ | 0.690 (0250–1.250) | 0.750 (0250–1.250) | 0.36 | |
| RAPID | 3.20 ± 2.05 | 3.10 ± 2.02 | 0.61 | |
| Current drugs, n (%) | | | | |
| Prednisone | 330 (48) | 291 (50) | 0.46 | |
| Prednisone doses, mg/day | 5 (2.5–6) | 5 (5–7.5) | 0.42 | |
| NSAIDs | 282 (41) | 205 (35) | **0.036** | 0.93 (0.70–1.24), 0.62 |
| DMARDs | 525 (77) | 444 (77) | 0.98 | |
| Methotrexate | 395 (58) | 324 (56) | 0.55 | |
| Leflunomide | 70 (10) | 68 (12) | 0.39 | |
| Hydroxychloroquine | 147 (21) | 132 (23) | 0.57 | |

**Table 3** Multivariable analysis of the differences between reclassified or not reclassified patients *(Continued)*

| | Not reclassified (*n* = 684) | Reclassified (*n* = 578) | *p* | Reclassification OR (95% CI), *p\** |
|---|---|---|---|---|
| Sulphasalazine | 19 (3) | 24 (4) | 0.18 | 1.69 (0.84–3.41), 0.15 |
| Anti-TNF therapy | 91 (13) | 72 (12) | 0.66 | |
| Adalimumab | 26 (4) | 28 (5) | 0.36 | |
| Infliximab | 12 (2) | 6 (1) | 0.29 | |
| Etanercept | 40 (6) | 26 (4) | 0.28 | |
| Golimumab | 1 (0) | 3 (1) | 0.34 | |
| Tocilizumab | 37 (5) | 27 (5) | 0.56 | |
| Rituximab | 9 (1) | 11 (2) | 0.40 | |
| Abatacept | 8 (1) | 13 (2) | 0.14 | 2.13 (0.77–5.97), 0.15 |
| Baricitinib | 5 (1) | 6 (1) | 0.56 | |
| Tofacitinib | 9 (1) | 5 (1) | 0.45 | |
| Historical disease-related data | | | | |
| History of extraarticular manif., n (%) | 112 (16) | 119 (21) | 0.058 | 1.07 (0.75–1.52), 0.72 |
| Erosions, n (%) | 230 (34) | 216 (37) | **0.048** | 1.26 (0.93–1.72), 0.13 |
| CRP at time of disease diagnosis, mg/l | 7 (2–19) | 8 (3–22) | 0.28 | |
| CRP > 3 at time of diagnosis, n (%) | 354 (52) | 324 (56) | 0.068 | 1.13 (0.78–1.64), 0.52 |
| ESR at the time of diagnosis, mm/1st hour | 20 (11–37) | 23 (12–40) | 0.28 | |

Data represent means ± SD or median (IQR) when data were not normally distributed
*CV* cardiovascular, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *CRP* C-reactive protein, *NSAID* nonsteroidal anti-inflammatory drugs, *DMARD* disease-modifying antirheumatic drug, *TNF* tumor necrosis factor, obesity, *ESR* erythrocyte sedimentation rate, *BMI* body mass index, *DAS28* Disease Activity Score in 28 joints, *ACPA* anti-citrullinated protein antibodies, *RAPID* routine assessment of patient index, *CDAI* Clinical Disease Activity Index, *SDAI* Simple Disease Activity Index, *HAQ* Health Assessment Questionnaire
*Multivariable analysis is adjusted for age, dyslipidemia, hypertension, and statins and aspirin intake

of this improvement was small and statistical significance was not reached.

In our study, NRI and IDI were significant for the improvement of prediction. For this reason, we believe that the selected variables could be used in the routine clinical practice to choose those patients who, after carotid ultrasound, would probably be reclassified. The fact that our predictive model included not only CV risk factors, but also a variable related to disease activity, supports the fact that reclassification is also driven by factors associated with the disease and not only by factors of traditional CV risk. Interestingly, both rheumatoid factor

**Table 4** All the logistic regression model subsets for the prediction of reclassification in patients with RA included in the low and moderate cardiovascular risk category according to the SCORE prior to carotid ultrasound assessment

| Variables | OR (95% CI) | *p* | Optimal cutoff | Sensitivity, % | Specificity, % |
|---|---|---|---|---|---|
| Age, years | 1.11 (1.09–1.13) | **0.000** | 54 | 78 | 63 |
| Hypertension | 1.61 (1.18–2.21) | **0.003** | | | |
| Dyslipidemia | 1.37 (1.03–1.83) | **0.033** | | | |
| DAS28-ESR | 1.07 (0.97–1.18) | 0.16 | 2.6 | 63 | 46 |
| Pseudo R2 | 0.188 | | | | |
| AIC | 1104 | | | | |
| BIC | 1128 | | | | |
| AUC | 0.774 | | | | |
| Sensitivity | 62% | | | | |
| Specificity | 74% | | | | |
| pfitHL | 0.111 | | | | |

Values in boldface are statistically significant. *AIC* Akaike information criterion, *BIC* Schwarz Bayesian criterion, *AUC* area under the curve, *pfitHL* Hosmer-Lemeshow goodness-of-fit, *DAS28-ESR* Disease Activity Erythrocyte Sedimentation Rate in 28 joints

Ferraz-Amaro et al. Arthritis Research & Therapy        (2021) 23:162

Page 8 of 10

**Table 5** Discrimination, reclassification, and calibration assessment of SCORE versus model adding clinical data

|  | SCORE | SCORE + predictors | p |
|---|---|---|---|
| Reclassification in patients with SCORE < 5% |  |  |  |
| Discrimination |  |  |  |
| AUC | 0.766 (0.737–0.794) | 0.775 (0.747–0.803) | 0.23 |
| Reclassification |  |  |  |
| NRI | - | **0.07 (0.01–0.12)** | **0.018** |
| IDI | - | **0.07 (0.05–0.08)** | **0.000** |
| Calibration |  |  |  |
| H-L test | 0.35 | 0.80 |  |

Clinical data represents age, dyslipidemia, hypertension, and DAS28-ESR
p values in AUC rows represent the comparison between both AUC
NRI and IDI are expressed as their values (95% confidence interval) and p value
p value in H-L test expresses the p value of the Hosmer-Lemeshow chi-square statistical test
Predictors are age, hypertension, dyslipidemia, and DAS28-ESR
SCORE Systematic Coronary Risk Evaluation, AUC area under the curve, NRI net reclassification index, IDI integrated discrimination improvement

and ACPA were independently associated with reclassification. This finding is in agreement with previous reports supporting the role of immune dysregulation of autoantibodies in the etiology of CV disease in RA. For example, rheumatoid factor and ACPA have been found to be significant predictors of CV events and mortality in both those with and those without rheumatic diseases [28]. Similarly, in RA, the risk of developing heart failure has been described twice in patients with positive rheumatoid factor than in seronegative patients [29]. ACPA has not been solely linked to RA development and severity, but also plays a role as an additional risk factor in CV disease [30]. It is also believed that citrullination is part of many chronic inflammatory processes and therefore ACPA might act as an independent pro-atherogenic factor in patients with and without RA [31]. Additionally, we understand that in our report probably rheumatoid factor and ACPA are reflecting a subpopulation with higher disease activity which eventually would prone these patients to a higher likelihood of being reclassified.

Interestingly, in our work, both the presence of dyslipidemia and high disease activity were related to the probability of reclassification. It has been recognized that in RA, increased disease activity causes a decrease in lipid-related molecules serum levels. However, it is also known that high levels of LDL cholesterol maintain a positive relation to CV events in patients with RA [32]. That is, the deleterious association between elevated lipid levels and CV events found in the general population is also observed in RA. Therefore, we believe that it is not surprising, and it is completely plausible, to find that both disease activity and the presence of dyslipidemia were related to the probability of reclassification in our study.

We acknowledge the limitation of the cross-sectional nature of the present study that does not allow us to know if patients in whom their risk was reclassified will develop CV events. However, since high/very high CV risk according to the SCORE and the presence of carotid plaque have undoubtedly been linked to CV events, the fact that a patient may be reclassified as having high CV risk is of potential interest. We also acknowledge that some patients were taking CV risk preventive medications such as aspirin, statins, and antihypertensive treatment. We understand that they have probably modified the CV risk of some patients.

## Conclusion

In conclusion, CV risk reclassification after carotid ultrasound is highly frequent in patients with RA. Disease activity is related to this reclassification. We have recently reported that the presence of carotid plaques predicts the development of CV events and death in patients with RA [11]. However, further prospective studies are required to determine the degree of relevance of the additive value of the carotid plaque assessment for the prediction of CVD risk in patients with RA.

**Abbreviations**
ACPA: Anti-citrullinated peptide/protein antibody; AUC: Area under the curve; BMI: Body mass index; CDAI: Clinical Disease Activity Index; CI: Confidence of interval; cIMT: Carotid intima-media thickness; CRP: C-reactive protein; CVD: Cardiovascular disease; DAS28: Disease Activity Score in 28 joints; DMARD: Disease-modifying antirheumatic drug; ESR: Erythrocyte sedimentation rate; HAQ: Health Assessment Questionnaire; HL: Hosmer-Lemeshow; HDL: High-density lipoprotein; IDI: Integrated discrimination improvement; IQR: Inter quartile range; LDL: Low-density lipoprotein; NRI: Net reclassification index; NSAID: Nonsteroidal anti-inflammatory drug; OR: Odds ratio; RAPID: Routine Assessment of Patient Index; RA: Rheumatoid arthritis; ROC: Receiver-operating characteristic curves; SCORE: Systematic Coronary Risk Evaluation; SD: Standard deviation; SDAI: Simplified Disease Activity Index; TNF-α: Tumor necrosis factor-α

Ferraz-Amaro *et al. Arthritis Research & Therapy*     (2021) 23:162

Page 9 of 10

## Authors' contributions

## Funding

## Availability of data and materials

The datasets used and/or analyzed in the present study are available from the corresponding author upon request.

# Declarations

## Ethics approval and consent to participate

The study protocol was approved by the institutional review committees at Hospital Universitario de Canarias, Hospital Universitario Doctor Negrín, and Hospital Universitario Marqués de Valdecilla (all in Spain), and all subjects provided written informed consent.

## Consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests. Nevertheless, Dr. Iván Ferraz-Amaro would like to acknowledge that he has received grants/research supports from Abbott, MSD, Jansen, and Roche, as well as consultation fees from company-sponsored speakers' bureaus associated with Abbott, Pfizer, Roche, Sanofi, Celgene, and MSD. Prof. M.A. González-Gay has received grants/research supports from AbbVie, MSD, Jansen, and Roche, as well as consultation fees/participation from company-sponsored speakers bureaus organized by AbbVie, Pfizer, Roche, Sanofi, Lilly, Celgene, Sobi, Amgen, and MSD.

## Author details

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

## References

1. Aviña-Zubieta JA, Choi HK, Sadatsafavi M, Etminan M, Esdaile JM, Lacaille D. Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies. Arthritis Care Res Arthritis Rheum. 2008;59: 1690–7 Available from: https://pubmed.ncbi.nlm.nih.gov/19035419/. Cited 2020 Nov 20.
2. Del Rincón I, Williams K, Stern MP, Freeman GL, O'Leary DH, Escalantel A. Association between carotid atherosclerosis and markers of inflammation in rheumatoid arthritis patients and healthy subjects. Arthritis Rheum. 2003;48: 1833–40 Available from: https://pubmed.ncbi.nlm.nih.gov/12847676/. Cited 2020 Nov 20.
3. Roman MJ, Moeller E, Davis A, Paget SA, Crow MK, Lockshin MD, et al. Preclinical carotid atherosclerosis in patients with rheumatoid arthritis. Ann Intern Med. 2006;144:249–56 Available from: https://pubmed.ncbi.nlm.nih.gov/16490910/. American College of Physicians. Cited 2020 Nov 20.
4. Gonzalez-Juanatey C, Llorca J, Testa A, Revuelta J, Garcia-Porrua C, Gonzalez-Gay MA. Increased prevalence of severe subclinical atherosclerotic findings in long-term treated rheumatoid arthritis patients without clinically evident atherosclerotic disease. Medicine (Baltimore). 2003;82:407–13 Available from: https://pubmed.ncbi.nlm.nih.gov/14663290/. Cited 2020 Nov 20.
5. van Sijl AM, Peters MJ, Knol DK, de Vet HC, Gonzalez-Gay MA, Smulders YM, et al. Carotid intima media thickness in rheumatoid arthritis as compared to control subjects: a meta-analysis. Semin Arthritis Rheum. 2011;40:389–97 Available from: https://pubmed.ncbi.nlm.nih.gov/20889191/. Cited 2020 Nov 24.
6. Kao AH, Krishnaswami S, Cunningham A, Edmundowicz D, Morel PA, Kuller LH, et al. Subclinical coronary artery calcification and relationship to disease duration in women with rheumatoid arthritis. J Rheumatol. 2008;35:61–9 Available from: https://pubmed.ncbi.nlm.nih.gov/18050383/. Cited 2020 Nov 20.
7. Kao AH, Wasko MCM, Krishnaswami S, Wagner J, Edmundowicz D, Shaw P, et al. C-reactive protein and coronary artery calcium in asymptomatic women with systemic lupus erythematosus or rheumatoid arthritis. Am J Cardiol. 2008;102:755–60 Available from: https://pubmed.ncbi.nlm.nih.gov/18774002/. Cited 2020 Nov 20.
8. Chung CP, Oeser A, Raggi P, Gebretsadik T, Shintani AK, Sokka T, et al. Increased coronary-artery atherosclerosis in rheumatoid arthritis: relationship to disease duration and cardiovascular risk factors. Arthritis Rheum. 2005;52: 3045–53 Available from: https://pubmed.ncbi.nlm.nih.gov/16200609/. Cited 2020 Nov 20.
9. Arts EEA, Popa C, Den Broeder AA, Semb AG, Toms T, Kitas GD, et al. Performance of four current risk algorithms in predicting cardiovascular events in patients with early rheumatoid arthritis. Ann Rheum Dis. 2015;74: 668–74 Available from: https://pubmed.ncbi.nlm.nih.gov/24389293/. BMJ Publishing Group. Cited 2020 Nov 20.
10. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. European guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2016, 2016:2315–81 Available from: https://pubmed.ncbi.nlm.nih.gov/27222591/. Oxford University Press. Cited 2020 Nov 27.
11. Corrales A, Vegas-Revenga N, Rueda-Gotor J, Portilla V, Atienza-Mateo B, Blanco R, et al. Carotid plaques as predictors of cardiovascular events in patients with rheumatoid arthritis. Results from a 5-year-prospective follow-up study. Semin Arthritis Rheum. 2020; Available from: https://pubmed.ncbi.nlm.nih.gov/32416998/. W.B. Saunders. Cited 2020 Nov 24.
12. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010;62:2569–81 Available from: http://www.ncbi.nlm.nih.gov/pubmed/20872595. Cited 2018 Nov 10.
13. Prevoo ML, van't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum. 1995;38:44–8 Available from: http://www.ncbi.nlm.nih.gov/pubmed/7818570. Cited 2019 Jul 3.
14. Smolen JS, Breedveld FC, Schiff MH, Kalden JR, Emery P, Eberl G, et al. A simplified disease activity index for rheumatoid arthritis for use in clinical practice. Rheumatology (Oxford). 2003;42:244–57 Available from: http://www.ncbi.nlm.nih.gov/pubmed/12595618. Cited 2018 Nov 10.
15. Aletaha D, Smolen J. The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI): a review of their usefulness and validity in rheumatoid arthritis. Clin Exp Rheumatol. 23:S100–8 Available from: http://www.ncbi.nlm.nih.gov/pubmed/16273793. Cited 2019 Aug 19.
16. Aletaha D, Ward MM, Machold KP, Nell VPK, Stamm T, Smolen JS. Remission and active disease in rheumatoid arthritis: defining criteria for disease activity states. Arthritis Rheum. 2005;52:2625–36 Available from: http://doi.wiley.com/10.1002/art.21235. Cited 2019 Jul 17.
17. Pincus T, Yazici Y, Bergman MJ. RAPID3, an index to assess and monitor patients with rheumatoid arthritis, without formal joint counts: similar results to DAS28 and CDAI in clinical trials and clinical care. Rheum Dis Clin N Am. 2009:773–8 Available from: https://pubmed.ncbi.nlm.nih.gov/19962621/. Cited 2020 Nov 13.
18. Pincus T, Swearingen C, Wolfe F. Toward a multidimensional Health Assessment Questionnaire (MDHAQ): assessment of advanced activities of

daily living and psychological status in the patient-friendly health assessment questionnaire format. Arthritis Rheum. 1999;42:2220–30 Available from: http://doi.wiley.com/10.1002/1529-0131%28199910%2942%3A10%3C2220%3A%3AAID-ANR26%3E3.0.CO%3B2-5. Cited 2019 Jul 3.

19. Corrales A, González-Juanatey C, Peiró ME, Blanco R, Llorca J, González-Gay MA. Carotid ultrasound is useful for the cardiovascular risk stratification of patients with rheumatoid arthritis: results of a population-based study. Ann Rheum Dis. 2014;73:722–7 Available from: https://pubmed.ncbi.nlm.nih.gov/23505241/. BMJ Publishing Group. Cited 2020 Nov 20.

20. Touboul P-J, Hennerici MG, Meairs S, Adams H, Amarenco P, Bornstein N, et al. Mannheim carotid intima-media thickness consensus (2004-2006). An update on behalf of the Advisory Board of the 3rd and 4th Watching the Risk Symposium, 13th and 15th European Stroke Conferences, Mannheim, Germany, 2004, and Brussels, Belgium, 2006. Cerebrovasc Dis. 2007;23:75–80 Available from: https://www.karger.com/Article/FullText/97034. Cited 2019 Aug 2.

21. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics. 1988;44:837–45 Available from: http://www.ncbi.nlm.nih.gov/pubmed/3203132. Cited 2019 Jun 23.

22. Pencina MJ, D'Agostino RB, D'Agostino RB, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med. 2008;27:157–72 Available from: http://www.ncbi.nlm.nih.gov/pubmed/17569110. Cited 2019 Jun 23.

23. Tripepi G, Jager KJ, Dekker FW, Zoccali C. Statistical methods for the assessment of prognostic biomarkers(part II): calibration and re-classification. Nephrol Dial Transplant. 2010;25:1402–5 Available from: https://academic.oup.com/ndt/article-lookup/doi/10.1093/ndt/gfq046. Cited 2019 Jun 23.

24. Tripepi G, Jager KJ, Dekker FW, Zoccali C. Statistical methods for the assessment of prognostic biomarkers (part I): discrimination. Nephrol Dial Transplant. 2010;25:1399–401 Available from: https://academic.oup.com/ndt/article-lookup/doi/10.1093/ndt/gfq018. Cited 2019 Jun 23.

25. Rueda-Gotor J, Quevedo-Abeledo JC, Corrales A, Genre F, Hernández-Hernández V, Delgado-Frías E, et al. Reclassification into very-high cardiovascular risk after carotid ultrasound in patients with axial spondyloarthritis. Clin Exp Rheumatol. 2020;38:724–31 Available from: https://pubmed.ncbi.nlm.nih.gov/32083538/. Clinical and Experimental Rheumatology S.A.S. Cited 2020 Nov 21.

26. Palmou-Fontana N, Martínez-Lopez D, Corrales A, Rueda-Gotor J, Genre F, Armesto S, et al. Disease activity influences cardiovascular risk reclassification based on carotid ultrasound in patients with psoriatic arthritis. J Rheumatol. 2020;47:1344–53 Available from: https://pubmed.ncbi.nlm.nih.gov/31732555/. Cited 2020 Nov 21.

27. Quevedo-Abeledo JC, Rúa-Figueroa Í, Sánchez-Pérez H, Tejera-Segura B, De Vera-González A, González-Delgado A, et al. Disease damage influences cardiovascular risk reclassification based on carotid ultrasound in patients with systemic lupus erythematosus. J Rheumatol. 2019;46:483–91 Available from: https://pubmed.ncbi.nlm.nih.gov/30647175/. Cited 2020 Nov 21.

28. Liang KP, Kremers HM, Crowson CS, Snyder MR, Therneau TM, Roger VL, et al. Autoantibodies and the risk of cardiovascular events. J Rheumatol. 2009;36:2462–9 Available from: https://pubmed.ncbi.nlm.nih.gov/19833748/. Cited 2020 Nov 21.

29. Nicola PJ, Maradit-Kremers H, Roger VL, Jacobsen SJ, Crowson CS, Ballman KV, et al. The risk of congestive heart failure in rheumatoid arthritis: a population-based study over 46 years. Arthritis Rheum. 2005; 52:412–20 Available from: https://pubmed.ncbi.nlm.nih.gov/15692992/. Cited 2020 Nov 21.

30. Maradit-Kremers H, Nicola PJ, Crowson CS, Ballman KV, Gabriel SE. Cardiovascular death in rheumatoid arthritis: a population-based study. Arthritis Rheum. 2005;52:722–32 Available from: https://pubmed.ncbi.nlm.nih.gov/15751097/. Cited 2020 Nov 21.

31. Cambridge G, Acharya J, Cooper JA, Edwards JC, Humphries SE. Antibodies to citrullinated peptides and risk of coronary heart disease. Atherosclerosis. 2013;228:243–6 Available from: https://pubmed.ncbi.nlm.nih.gov/23474125/. Cited 2020 Nov 27.

32. Liao KP, Liu J, Lu B, Solomon DH, Kim SC. Association between lipid levels and major adverse cardiovascular events in rheumatoid arthritis compared to non-rheumatoid arthritis patients. Arthritis Rheumatol. 2015;67:2004–10 Available from: https://pubmed.ncbi.nlm.nih.gov/25917955/. John Wiley and Sons Inc. Cited 2021 Jan 19.

## Publisher's Note