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Disease activity predicts the development of cardiovascular events in patients with rheumatoid arthritis from the CARMA cohort

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ABSTRACT

Objective: To identify significant predictors of cardiovascular (CV) events in rheumatoid arthritis (RA) patients from the CARdiovascular in RheuMAtology (CARMA) project, followed prospectively for 10 years.
Methods: Between July 2010 and January 2012, 708 RA patients were recruited from 67 hospitals across Spain. The study focused on patients with no prior CV events at the time of recruitment. At the 10-year follow-up, data on the occurrence of CV events, patient-years of follow-up and linearized event rates were analyzed. Cox regression analyses were conducted, both crude and adjusted for PREVENT-CVD.
Results: Over 6608 patient-years, 114 patients (16.1%) experienced CV events, yielding a linearized event rate of 1.73 per 100 patient-years. Patients with CV events were older (70.7± 10.6 vs. 62.1±12.8 years, $p<0.001$), more frequently male (36.0% vs. 20.0%, $p<0.001$), and had higher rates of hypertension (46.5% vs. 23.4%, $p<0.001$), diabetes (14% vs. 4.9%, $p=0.001$), and dyslipidemia (37.7% vs. 27.4%, $p=0.03$). Higher baseline erythrocyte sedimentation rate (ESR) was also associated with future CV events. Those who developed CV events had a significantly higher predicted 10-year CV risk using the PREVENT-CVD score (18.0% vs. 10.3%, $p<0.001$). Cox regression analysis adjusted for PREVENT-CVD showed that although higher crude C-reactive protein and uric acid levels were associated with increased CV risk, after adjustment these associations weakened and became non-significant. However, higher disease activity (DAS28-ESR) was linked to greater CV risk, with moderate/high disease activity (DAS28-ESR>3.2) showing a significantly higher adjusted CV risk (HR 1.62; 95% CI: 1.06–22.47, $p=0.03$).
Conclusions: Disease activity is a key determinant of CV outcomes in RA patients. The PREVENT-CVD score is an effective tool for CV risk stratification in this population.

Introduction

Individuals with chronic inflammatory rheumatic diseases (CIRD), particularly those with rheumatoid arthritis (RA), exhibit a significantly elevated risk of cardiovascular (CV) complications, which are among the leading causes of death in this population. In this regard, the standardized mortality rate in patients with RA is higher than that of the general population (1.3-2.3) [1]. This increased CV risk is largely driven by persistent inflammation, which plays a key role in both the initiation and progression of cardiovascular disease (CVD) [1]. However, current evidence indicates that the risk of CV disease has decreased significantly in recent years. In this regard, much of the remaining excess risk appeared to be due to traditional CV risk factors, rather than inflammation alone. With respect to this, Crowson et al. showed that traditional risk factors explained 49% of CVD events, while RA-related characteristics explained 30% [2]. Interestingly, Raadsen *et al.* reported that traditional CV risk factors were significantly elevated in patients with RA compared with controls. The odds ratios (ORs) for CVD were increased in patients with RA compared with controls, 1.61 (95% confidence interval [CI]: 1.04 to 2.48) [3]. However, after adjusting for traditional risk factors, CV risk was not increased in RA patients (OR 0.95, 95% CI: 0.58 to 1.55) [3]. Nevertheless, it is important to note that this study assessed CVD cross-sectionally rather than prospectively; that is, prevalent rather than incident cases were examined. In addition to traditional risk factors and inflammation, genetic predisposition also contributes to the elevated CVD risk observed in RA patients [4].

A major concern in the management of patients with CIRD is the establishment of reliable tools to identify those at high CV risk. Therefore, the use of risk assessment scales that can accurately predict CV risk in this population is of great importance. We recently reported a strong correlation and high reliability among the Systematic Coronary Risk Evaluation (SCORE2), the Predicting Risk of Cardiovascular Disease Events (PREVENT-CVD), and the PREVENT-Atherosclerotic Cardiovascular Disease (ASCVD) tools in our cohort of patients with CIRD enrolled in the Spanish prospective CARdiovascular in RheuMAtology (CARMA) project and followed over a 10-year period [5]. These findings suggest that these risk assessment tools may be largely interchangeable for identifying high-risk CIRD patients [6]. Additionally, we evaluated the performance of SCORE2, PREVENT-CVD, and PREVENT-ASCVD in predicting CV risk among individuals with CIRD enrolled in the Spanish CARMA project. In patients with RA, QRISK3 was found to overestimate CV risk, whereas PREVENT-CVD was the only tool that consistently demonstrated reliable performance [7].

The PREVENT scale was introduced by the American Heart Association to estimate 10-year CV risk [8]. PREVENT model minimizes multicollinearity and over-adjustment by employing a single, validated composite score rather than multiple correlated variables. Consequently, associations between RA-specific predictors, such as systemic inflammation and disease activity, and CV outcomes may become more evident, as PREVENT accounts for traditional CV risk factors in a unified framework. Therefore, while originally developed for the general population, the PREVENT-CVD score can be applied in RA to adjust for conventional CV risk factors when assessing the influence of RA-specific variables.

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Table 1
Characteristics at recruitment of 708 rheumatoid arthritis patients included in this analysis*.

Variable	Category	Total	Event	No event	p
Age (years)		63.5 ±129	70.7 ±10.6	62.1 ±12.8	<0.001
Sex	**Men**	160 (22.6)	41 (36.0)	119 (20.0)	<0.001
	Women	548 (77.4)	73 (64.0)	475 (80.0)	
Disease duration (years)		8.9 ±7.8	10.0 ±8.9	8.6 ±7.5	0.07
Current smoking	**No**	524 (74.0)	88 (77.2)	436 (73.4)	0.40
	Yes	184 (26.0)	26 (22.8)	158 (26.6)	
Arterial hypertension	**No**	516 (72.9)	61 (53.5)	455 (76.6)	<0.001
	Yes	192 (27.1)	53 (46.5)	139 (23.4)	
Diabetes mellitus	**No**	663 (93.6)	98 (86.0)	565 (95.1)	0.001
	Yes	45 (6.4)	16 (14.0)	29 (4.9)	
History of dyslipidemia	**No**	502 (70.9)	71 (62.3)	431 (72.6)	0.03
	Yes	206 (29.1)	43 (37.7)	163 (27.4)	
Total cholesterol (mg/dL)		206.5 ±35.2	205.3 ±32.1	206.9 ±36.0	0.63
HDL-cholesterol (mg/dL)		62.0 ±17.3	59.3 ±16.1	62.5 ±17.4	0.07
LDL-cholesterol (mg/dL)		111.9 ±47.5	112.6 ±43.9	111.8 ±48.2	0.87
Triglycerides (mg/dL)		105.5 ±55.5	113.6 ±49.5	103.9 ±56.5	0.09
Abdominal perimeter (cm)		93.1 ±12.9	97.8 ±12.8	92.2 ±91.2	<0.001
BMI (kg/m^2)		26.7 ±4.7	27.2 ±4.2	26.6 ±4.8	0.23
ESR mm/1^{st} hour		21.2 ±16.1	24.5 ±17.6	20.5 ±15.8	0.02
CRP mg/l		7.7 ±13.0	7.9 ±11.4	7.6 ±13.3	0.84
DAS28-CRP		2.37 ±0.94	2.37 ±0.97	2.37 ±0.94	0.98
DAS28-ESR		2.73 ±1.06	2.80 ±1.03	2.71 ±1.07	0.38
Uric acid		4.3 ±1.4	4.8 ±1.3	4.3 ±1.4	0.001
HAQ		0.70 ±0.67	0.71 ±0.77	0.69 ±0.65	0.84
Rheumatoid factor	**Negative**	165 (23.3)	25 (21.9)	140 (23.6)	0.71
	Positive	543 (76.7)	89 (78.1)	454 (76.4)	
Anti-CCP	**Negative**	287 (40.5)	48 (42.1)	239 (40.2)	0.71
	Positive	421 (59.5)	66 (57.9)	355 (59.8)	
Treated with biologic therapies	**No**	426 (60.2)	76 (66.7)	350 (58.9)	0.12
	Yes	282 (39.8)	38 (33.3)	244 (41.1)	
Treated with glucocorticoids	**No**	393 (55.5)	56 (49.1)	337 (56.7)	0.13
	Yes	315 (44.5)	58 (50.9)	257 (43.3)	
PREVENT-CVD (% of CV risk in 10 years)		11.5 ±9.5	18.0 ±10.2	10.3 ±8.9	<0.001

* Data are expressed as mean ± standard deviation for continuous variables and number (percentage) for categorical variables.

In the present study, using PREVENT for risk adjustment, we aimed to identify the most significant predictors of CV events in the cohort of RA patients from the CARMA project, who were followed prospectively over a 10-year period.

Patients and methods

Study design

The CARMA project is a prospective cohort study designed to evaluate the CV risk profile in patients with CIRD over a 10-year period. The study included patients with ankylosing spondylitis, psoriatic arthritis, and RA, along with a comparison cohort of individuals without inflammatory diseases. Conducted between July 2010 and January 2012, the study recruited participants from 67 hospitals across Spain. This analysis specifically focuses on RA patients who had no prior CV events at the time of recruitment [5].

Baseline data collection was standardized across all participants. Data on CVD risk factors were gathered through personal interviews, clinical examinations, and medical record reviews, using methods such as blood pressure and body weight measurements, questionnaires, and laboratory tests. The assessment protocol was uniform across all participating centers, with a specific questionnaire used for interviews to ensure consistency. The collected data included demographic information, disease characteristics, activity levels, treatments, traditional CVD risk factors, medical history, and laboratory results. All patients with chronic inflammatory rheumatic diseases invited to participate in the prospective study were already being treated by the same hospital department at each center, which generally led to high participation rates.

This report specifically examines data related to CV events collected from RA patients 10 years after the start of the study.

At baseline, 773 patients with RA were recruited. As previously reported [5], since the CARMA project was designed before 2010, all participants were required to meet the 1987 American College of Rheumatology Classification Criteria for RA [9]. Patients with prior CV events before the period of recruitment (n = 65) were excluded from this analysis. Therefore, 708 patients were included in this analysis.

CV events recorded during the follow-up period included ischemic heart disease, heart failure, transient ischemic attacks, stroke, and peripheral arterial disease (e.g., limb claudication). These diagnoses were confirmed by physicians, and operational definitions for the study variables are provided in a separate report [5].

At the 10-year follow-up, information on the patients included in the initial cohort was assessed by consulting their medical records or by contacting patients or family members directly. When data were unavailable, information was sought from the National Mortality Index to determine survival status.

The study was conducted in accordance with the principles outlined in the Declaration of Helsinki, with a focus on ethical considerations. Full written informed consent was obtained from all participants prior to their inclusion in the project. The study was approved by the Clinical Research Ethics Committee of Lugo, Galicia (Spain) under protocol no. 2009/077. In parallel, approval was obtained from the Ethics Committee of each participating hospital.

Statistical analysis

Continuous variables are described as mean ± standard deviation. They are compared between patients with and without event with Student's t test. Categorical variables are described as number and percentages. They are compared with chi-squared test or Fisher exact test.

Event was defined as any CV event (angina, myocardial infarction, heart failure, transient ischemic accident, stroke, limb claudication) or death. Data on events were obtained from medical records and patient reporting. When an event was informed by the patient, it was confirmed

Table 2
Cox regression results adjusted for PREVENT-CVD.

Factor	Category	N (minimum-maximum)	Events	Crude HR (95% CI)	p	Adjusted HR (95% CI)*	p
ESR mm/1St hour	**First tertile**	234 (1, 11)	33	1 (ref.)	-	1 (ref.)	-
	Second tertile	239 (12, 25)	39	1.17 (0.73, 1.85)	0.52	1.19 (0.74, 1.90)	0.48
	Third tertile	219 (26, 98)	42	1.38 (0.87, 2.18)	0.17	1.35 (0.85, 2.13)	0.21
	Missing	16	0				
CRP mg/l	**First tertile**	233 (0.1, 1.8)	24	1 (ref.)	-	1 (ref.)	-
	Second tertile	239 (1.9, 6.0)	48	2.05 (1.25, 3.34)	0.004	1.61 (0.98, 2.65)	0.06
	Third tertile	230 (6.1, 90.5)	41	1.81 (1.09, 2.99)	0.02	1.46 (0.88, 2.44)	0.15
	Missing	6	1				
DAS28-CRP	**First tertile**	228 (0.97, 1.82)	35	1 (ref.)	-	1 (ref.)	-
	Second tertile	235 (1.83, 2.52)	40	1.13 (0.72, 1.77)	0.61	1.11 (0.71, 1.75)	0.65
	Third tertile	234 (2.52, 6.1)	38	1.06 (0.67, 1.68)	0.80	1.18 (0.74, 1.88)	0.58
	Missing	11	1				
DAS28-ESR	**First tertile**	230 (0.28, 2.27)	32	1 (ref.)	-	1 (ref.)	-
	Second tertile	226 (2.27, 3.00)	37	1.19 (0.74, 1.91)	0.47	1.15 (0.72, 1.86)	0.55
	Third tertile	231 (3.01, 6.52)	45	1.41 (0.90, 2.22)	0.14	1.57 (0.99, 2.49)	0.05
	Missing	21	0				
Uric acid mg/dl	**First tertile**	245 (1.6, 3.8)	25	1 (ref.)	-	1 (ref.)	-
	Second tertile	243 (3.8, 5.1)	44	1.83 (1.12, 2.99)	0.02	1.36 (0.82, 2.24)	0.24
	Third tertile	207 (5.2, 9.9)	43	2.19 (1.34, 3.59)	0.002	1.20 (0.71, 2.05)	0.50
	Missing	13	2				
HAQ	**First tertile**	263 (0, 0.25)	47	1 (ref.)	-	1 (ref.)	-
	Second tertile	233 (0.3, 1.0)	36	0.85 (0.55, 1.32)	0.48	0.83 (0.54, 1.29)	0.41
	Third tertile	201 (1.1, 3)	30	0.84 (0.53, 1.32)	0.44	0.78 (0.49, 1.25)	0.30
	Missing	11	1				
RF	**Negative**	165 (23.3)	25	1 (ref.)	-	1 (ref.)	-
	Positive	543 (76.7)	89	1.09 (0.70, 1.70)	0.70	1.04 (0.66, 1.62)	0.87
	Missing	0	0				
Anti-CCP	**Negative**	287 (40.5)	48	1 (ref.)	-	1 (ref.)	-
	Positive	421 (59.5)	66	0.95 (0.65, 1.37)	0.77	0.91 (0.62, 1.32)	0.61
	Missing	0	0				
Biologic	**No**	426 (60.2)	76	1 (ref.)	-	1 (ref.)	-
	Yes	282 (39.8)	38	0.74 (0.50, 1.09)	0.13	0.87 (0.59, 1.30)	0.50
	Missing	0	0				
Glucocorticoids	**No**	393 (55.5)	56	1 (ref.)	-	1 (ref.)	-
	Yes	315 (44.5)	58	1.32 (0.91, 1.90)	0.14	1.27 (0.88, 1.85)	0.20
	Missing	0	0				

by revising medical records. End of follow-up was the first date of the following: date of the first event, last contact with the hospital or administrative end of follow-up (i.e., ten years after recruitment). We report the number of patients with CV events in the follow-up, its percentage with 95% confidence interval (binomial approach), the number of patient-years of follow-up and the linearized event rate with its 95% CI. Then, Cox regression was carried out in two ways: crude and adjusted for PREVENT-CVD. As discussed previously, we have demonstrated its accuracy in predicting CV events in patients with RA [7]. PREVENT-CVD includes age, sex, systolic blood pressure, total cholesterol, HDL-cholesterol, diabetes, smoking, glomerular filtration rate, use of antihypertensive medication, and use of statins. Therefore, it provides a full adjustment for CV risk factors. To carry out Cox regression, continuous biomarkers and measures of disease activity were categorized into tertiles according to their distribution among our RA patients, with the first tertile used as the reference. Regarding dichotomous variables (rheumatoid factor, anti-CCP, or medication use), negative values were used as the reference. Results of the Cox regression are presented as hazard ratios with 95% CI. Missing data were not imputed. All statistical analyses were conducted using the Stata SE/18 package.

Results

The study included 708 patients with RA with 6608 patient-years of follow-up. During a 10-year prospective follow-up 114 patients experienced CV events (16.1%, 95% CI: 13.5, 19.0), with linearized event rate 1.73 per 100 patient-years (95% CI: 1.43, 2.07).

Regarding the 65 patients excluded from the analysis for having suffered a CV event before the recruitment period, in 10 years of follow-up, 51 new CV events occurred in these 65 patients (78.5%, 95% CI: 66.5, 87.7).

The main characteristics of 708 patients without CV events before the recruitment period with and without events during follow-up are shown in Table 1.

Patients who had a CV event were significantly older (70.7 ± 10.6 vs. 62.1 ± 12.8 years, $p< 0.001$), more often male (36.0% vs. 20.0%, $p< 0.001$), and more frequently hypertensive (46.5% vs. 23.4%, $p< 0.001$). Diabetes mellitus and dyslipidemia (14% vs. 4.9%, $p = 0.001$ and 37.7% vs. 27.4%, $p = 0.03$, respectively) were also more frequent in patients who had CV events.

Regarding baseline data on anthropometric measures, abdominal perimeter was significantly higher among patients who had CV events

Table 3
Cox regression results after DAS28-ESR categorizing using remission as reference.

Factor	Category	N (percent)	Events	Crude HR (95% CI)	p	Adjusted HR (95% CI)*	p*
DAS28-ESR	**<2.6**	344 (50.1)	53	1 (ref.)	-	1 (ref.)	-
	2-6-3.2	156 (22.7)	22	0.91 (0.55, 1.49)	0.70	0.92 (0.56, 1.51)	0.74
	≥3.2	187 (27.2)	39	1.37 (0.91, 2.07)	0.14	1.62 (1.06, 2.47)	0.03
	Missing	21	0				

* Adjusted for PREVENT-CVD

(97.8 cm vs. 92.2 cm, $p < 0.001$).

Higher erythrocyte sedimentation rate (ESR) ($p = 0.02$) and serum uric acid levels ($p = 0.001$) at baseline were also associated with future CV events. Importantly, patients who developed CV events had a significantly higher predicted 10-year CV risk using the PREVENT-CVD score (18.0% vs. 10.3%, $p< 0.001$).

The mean and standard deviations of 10-year CVD risk according to SCORE-2 (low-risk countries) were 7.2% ± 5.7.

Other baseline comparisons between RA patients who developed CV events during follow-up and those who did not are shown in Table 1.

In a second step we performed a Cox regression analysis adjusted for PREVENT-CVD (Table 2). Patients were categorized into tertiles according as described in Methods. This procedure disclosed that although higher crude C-reactive protein (CRP) levels were associated with increased CV risk (second tertile crude Hazard Ratio [HR] 2.05; 95% CI: 1.25–3.34; third tertile crude HR 1.81; 95% CI: 1.09–2.99), after adjustment these associations weakened and became non-significant. It was also the case for uric acid. In this regard, although crude associations suggested that higher uric acid was related to CV events, these associations were not significant after adjustment.

Health Assessment Questionnaire (HAQ), rheumatoid factor (RF), anticyclic citrullinated protein antibodies (anti-CCP) positivity, biologic therapy use, and glucocorticoid use were not independently associated with CV events after adjusting for PREVENT-CVD.

Interestingly, when disease activity measured by Disease Activity Score in 28 Joints (DAS28)- DAS28-ESR was assessed, we observed that there was a trend toward higher CV risk with greater disease activity. Patients in the highest tertile had an adjusted HR of 1.57 (95% CI: 0.99–2.49; $p = 0.05$) (Table 2).

Based on this observed trend, we conducted an additional analysis. In this regard, when patients were analyzed using three categories according to disease activity [10] we observed significant differences in DAS28-ESR scores. With respect to this, when using remission (<2.6) as the reference, patients with DAS28-ESR ≥ 3.2 (moderate/high disease activity) had a significantly higher adjusted CV risk (HR 1.62; 95% CI: 1.06–2.47; $p = 0.03$) (Table 3).

Discussion

In the 10-year prospective study of patients with RA included in the CARMA cohort, we found that traditional CV risk factors (age, sex, hypertension, diabetes and dyslipidemia) remain dominant predictors of future CV events, even in the context of a disease characterized by chronic inflammation. These findings validate the utility of the PREVENT-CVD risk score in adjusting for traditional risk factors in RA populations.

Taylor et al. showed that the DAS28-ESR discriminates satisfactorily between groups of patients with active and non-active RA, with no evidence of additional physician-specific factors explaining disease activity status [11]. Notably, in our cohort, moderate to high disease activity, as measured by DAS28-ESR (≥ 3.2), independently increased the risk of CV events by 62% after full adjustment. This highlights the critical role of inflammation in accelerating atherosclerosis among RA patients. The trend observed with higher ESR and CRP levels supports this hypothesis, although their independent associations diminished after controlling for established CV risk factors. These findings align with prior literature emphasizing that effective control of RA disease activity, achieving and maintaining remission, may protect against CV morbidity, beyond the management of traditional CV risk factors.

With respect to this, using a prospective longitudinal cohort study conducted within the CORRONA registry in the USA, Solomon et al. investigated whether the higher CV risk in patients with RA was explained more by traditional CV risk factors or by RA disease severity [12]. They found that both contribute, but markers of RA severity had a particularly strong association with CV events, suggesting that inflammation and RA disease activity are key drivers of CV risk in these patients [12]. Further studies have supported that higher disease activity in RA is associated with an increased risk of CV events. In this regard, Solomon et al. also showed that better control of RA disease activity may lower CV risk [13].

In line with these findings, Min et al. assessed the predictive role of time-averaged DAS28 and HAQ scores on CV events in patients with RA. They recruited 4,034 RA patients from 23 tertiary hospitals, with 826 patients in remission, 938 with low, 2,002 with moderate, and 268 with high time-averaged DAS28 scores [14]. The incidence rate ratio of CV events in the high time-averaged DAS28 group was 3.01 compared to the low time-averaged DAS28 group [14].

The results from the prospective assessment of the CARMA cohort are consistent with these data [12–14], showing that high disease activity is also associated with an increased risk of CV events in Spanish RA patients undergoing periodic follow-up at rheumatology outpatient clinics from referral centers. Of note, although Spain is classified among countries with low CV risk [15], Spanish RA patients still have higher CV risk than Spanish general population. For instance, results from the Spanish REGICOR registry reported 10-year CV risk of 4.5% in women and 8.2% in men [16]. Although the data from the REGICOR study coincide with the experience of some authors who highlight the male sex as having a higher risk of CV morbidity [17], the REGICOR figures contrast with our result of 16.1%. However, the REGICOR cohort was younger on average than the CARMA cohort, which limits the usefulness of this comparison.

Subclinical CVD is also more frequent in patients with RA [18]. In a six-year prospective follow-up study aimed at assessing the relationship between RA disease activity and carotid plaque development, a marker of subclinical atherosclerosis, among RA patients without classic CV risk factors at baseline, moderate to high RA disease activity was found to be a strong predictor of new carotid plaque formation [19]. Moreover, a study of 1,279 RA patients without previous CV events, diabetes, or chronic kidney disease showed that after carotid ultrasound assessments, 54% of the patients had carotid plaque and consequently fulfilled criteria for very high CV risk. In this study it was observed that disease activity was significantly associated with reclassification after full multivariable analysis [20]. A predictive model incorporating dyslipidemia, hypertension, age over 54 years, and a DAS28-ESR score ≥ 2.6 yielded the highest discrimination for reclassification [20]. Therefore, reclassification of RA patients as having high CV risk can be independently explained by disease activity [20].

Regarding other predictors of CVD in patients with RA, Chiou et al. examined the prevalence and impact of hyperuricemia and gout among patients with RA. Using data from the Veterans Affairs Rheumatoid Arthritis (VARA) registry, the researchers found that hyperuricemia and gout are relatively common in RA patients. Importantly, the coexistence of these conditions was associated with higher rates of comorbidities such as CVD and kidney disease, greater RA disease activity, and increased mortality risk [21]. However, in the CARMA cohort baseline serum uric acid levels, initially appearing predictive, lost significance after adjustment, suggesting that hyperuricemia may be more of a marker of overall CV risk rather than an independent contributor.

With respect to autoantibody status, RF and anti-CCP did not independently predict CV outcomes in the CARMA cohort. It was also the case for functional disability, as well as the use of biologics or glucocorticoids. However, when assessing patients from an international observational cohort that included 3,982 patients with RA, Karpouzas et al. showed that the relationship between BMI and CV risk is not uniform across all RA patients. In particular, ACPA-positive patients and those using biologic treatments demonstrated different patterns of BMI's impact on CV outcomes compared to ACPA-negative or non-biologic-treated individuals. These findings suggest that personalized CV risk assessment and management in RA should consider both immune profile (ACPA status) and treatment type (biologics) [22]. Moreover, an evaluation of 4,362 patients with RA from the same international cohort [22] suggested that methotrexate use may be associated with a CV

benefit in males but not in females with RA, and this effect was independent of inflammation [23]. Moreover, CORRONA investigators found that patients treated with tumor necrosis factor (TNF) inhibitors had a significantly lower risk of CV events compared to those not treated with these biologic agents. The findings suggest that, beyond controlling RA disease activity, TNF antagonists may confer important CV protective effects in RA patients [24]. The absence of an association in the CARMA cohort of patients followed at rheumatology outpatient clinics from referral centers could be due to the number of patients included in this registry, which might reduce the relevance of the therapy in the CV outcomes of these patients.

This study has several potential clinical implications for CV risk management in patients with RA. First, it reinforces the idea that traditional CV risk factors are closely linked to CV events in patients with RA. Whenever possible, physicians should address these factors aggressively alongside RA management. Furthermore, the present results highlight the need to incorporate disease activity into CV risk assessment. According to the data, moderate to high RA activity (DAS28-ESR $\geq$3.2) is an independent risk factor for CV events. This suggests that controlling RA activity is crucial for preventing CVD complications. This justifies the adoption of practical measures, such as adopting a "treat to target" strategy to achieve sustained remission or low disease activity. This strategy benefits both joint and CV health. According to that, it is critical to communicate to patients that controlling their RA is fundamental to managing their CV health. In this regard, although some markers (such as CRP and uric acid) were not independently associated with CV events after adjustment in this cohort of RA patients, the study highlights the importance of a more comprehensive assessment of CV risk. Furthermore, it supports the use of multiparametric risk scores such as PREVENT-CVD for a more personalized and accurate assessment of CV risk.

The results found in the 10-year prospective follow-up of RA patients included in the CARMA cohort also present limitations derived from the multicenter evaluation and the number of patients involved in the recruitment. In this regard, while the purpose of the present study was to assess disease activity in the CARMA cohort of RA patients rather than comparing the cohort with a control population, the absence of a control population may be considered another potential limitation of the study. Furthermore, the ratio of the number of hospitals (n=67) to the number of RA patients assessed (n=708) might seem low. However, the CARMA study was designed to evaluate CV risk not only in patients with RA, but also in patients with psoriatic arthritis and ankylosing spondylitis. Therefore, recruitment was designed to reach prespecified levels for each disease. This fact reinforces the external validity of the study. Moreover, our results highlight the importance of disease activity in the CV outcomes of patients with RA. Thus, close monitoring and aggressive treatment of RA disease activity are warranted not only for joint outcomes but also for long-term CV health. Moreover, the results from the CARMA cohort indicate that PREVENT-CVD is a useful tool for risk stratification in RA patients. The incorporation of inflammation control into CV risk management strategies may help reduce the burden of CV disease in RA populations.

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CRediT authorship contribution statement

Javier Llorca: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. **Iván Ferraz-Amaro:** Formal analysis, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. **Santos Castañeda:** Conceptualization, Writing – original draft, Data curation, Formal analysis, Investigation. **Zulema Plaza:** Data curation, Formal analysis, Writing – review & editing. **Fernando Sánchez-Alonso:** Data curation, Formal analysis, Writing – review & editing. **Carmen García-Gómez:** Conceptualization, Writing – original draft, Data curation, Formal analysis, Investigation. **Carlos González-Juanatey:** Conceptualization, Writing – original draft, Data curation, Formal analysis, Investigation. **Miguel Ángel González-Gay:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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