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Incidence of first cardiovascular event in Spanish patients with inflammatory rheumatic diseases: prospective data from the CARMA Project

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Abstract

Objective

To determine the incidence and risk factors of first cardiovascular event (CVE) in patients with chronic inflammatory rheumatic diseases (CIRD).

Methods

Analysis of data after 2.5 years of follow-up from the prospective study CARMA project, that includes patients with CIRD [rheumatoid arthritis (RA), ankylosing spondylitis (AS), and psoriatic arthritis (PsA)] and matched individuals without CIRD from 67 hospitals in Spain. CVE cumulative incidence per 1000 patients was calculated after 2.5 years from the start of the project. Weibull proportional hazard model was used to calculate hazard ratio (HR) and 95% confidence interval (95% CI) of the risk factors.

Results

2595 (89.1%) patients completed the 2.5 years of follow-up visit. Cumulative incidence of CVE in patients with CIRD was 15.30 cases per 1000 patients (95% CI: 12.93–17.67), being higher in the subgroup with AS; 22.03 (95% CI: 11.01–33.04). Patients with AS (HR: 4.11; 95% CI: 1.07–15.79), those with older age (HR: 1.09; 95% CI: 1.05–1.13), systolic hypertension (HR: 1.02; 95% CI: 1.00–1.04) and long duration of the disease (HR: 1.07; 95% CI: 1.03-1.12) were at higher risk of first CVE during the 2.5 years of follow-up. In contrast, female gender was a protective factor (HR: 0.43; 95% CI: 0.18–1.00).

Conclusion

Among CIRD patients prospectively followed-up at rheumatology outpatient clinics, those with AS show higher risk of first CVE. Besides cardiovascular risk factors, such as hypertension, being a man and older as well as having a long disease duration increase the risk of CVE in patients with CIRD.

Key words

incidence, cardiovascular diseases, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, cohort study, CARMA project

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Introduction

Cardiovascular (CV) disease (CVD) is more common in patients with chronic inflammatory rheumatic diseases (CIRD) than in the general population (1). This increased CVD risk results from the effect of traditional CV risk factors (CVRFs) along with chronic inflammation and a genetic component (2-4), leading to a process of accelerated atherogenesis (5, 6). Different reports highlight the complex interaction of classic CVRFs with chronic inflammation and certain genetic components (7-10).

In patients with rheumatoid arthritis (RA), the incidence of CV events (CVE) is augmented by almost 50% compared to the general population, while the risk of myocardial infarction (MI) and stroke is increased by about 68% and 41%%, respectively (1, 4). As observed in patients with type 2 diabetes, different studies have shown a higher incidence of CV mortality in RA patients compared to people of the same age and sex (11-13). In general, patients with RA have a 2 to 3-fold increased risk of MI, even in the absence of traditional CVRFs (8, 14-16). An increased prevalence of ischaemic heart disease (IHD) in patients with RA was found in a recent study that included 11,782 patients with RA and 57,973 age and sex matched controls, (16.6% versus 12.8% respectively, $p<0.001$) (17). Spondyloarthropathies (SpA) constitute another group of CIRD associated with a higher CVD risk than the general population (18, 19). In this regard, CVE and CV mortality are more common in patients with psoriatic arthritis (PsA) than in the general population regardless of the presence of classic CVRFs (20-22). The presence of severe psoriasis was found to be an important predictor for the development of CVE in these patients (21, 22). PsA patients without traditional CVD risk factors also have higher frequency of subclinical atherosclerosis than matched controls (23, 24). Therefore, although the role of classic CVRFs cannot be ruled out (20), the disease itself appears to be a good predictor of CVE. Ankylosing spondylitis (AS) has also been associated with a mortality rate 1.5 to 2.0 times greater than the general population, which is largely due to CVD complications (18, 25, 26).

Despite these evidences, most epidemiological studies on CVD in CIRD have methodological limitations, mainly due to their retrospective nature. Because of that, we analysed the incidence of CVE in patients from the prospective CARdiovascular in rheuMAtology (CARMA) project that included patients with CIRD attending Spanish rheumatology clinics after a first assessment performed at 2.5 years of follow-up.

Patients and methods

Study design

The CARMA project is a prospective cohort study aimed to identify the CVD risk profile in patients with CIRD after 10 years of follow-up. It includes patients with RA, AS and PsA as well as a cohort of patients without inflammatory disease, who have been recruited in 67 Spanish hospitals (27). In this report, we describe the results at 2.5 years of follow-up.

Study population

As previously reported (27), patients with CIRD and individuals without CIRD attending outpatient rheumatology clinics from the participating hospitals were invited to take part in the study. The period of recruitment was July 2010 to January 2012.

A probabilistic cluster sampling that ensured that the different Rheumatology Units (RU) in Spain had equal probabilities of being chosen was performed. We randomly selected 67 Spanish centres with RU from the database of the Spanish Society of Rheumatology (SSR). Recruitment was done by the inclusion of consecutive patients with any of the three aforementioned conditions, regardless of disease severity or duration. The recruited patients fulfilled one of the following inclusion criteria: the 1987 American College of Rheumatology (ACR) Classification Criteria for RA (28), the modified New York Criteria for Definite AS (29), or the Moll and Wright Criteria for PsA (30). The selection of the controls was performed at the rheumatology outpatient's clin-

ics where the patients with inflammatory arthritis, RA, AS and PsA, were recruited. Controls were selected during the same period of recruitment as patients did. The criteria for the selection of controls were the following: individuals aged 18 years and older attending rheumatology outpatient's clinics for conditions different from inflammatory arthritis, connective tissue diseases or systemic vasculitis. Because of that, individuals with osteoarthritis, osteoporosis and those with mechanic low back pain and soft tissue rheumatisms (*e.g.* epicondylitis, trochanteric bursitis, anserine bursitis) were included as controls. However, subjects with erosive (inflammatory) osteoarthritis of the hands or with microcrystalline arthropathies were not eligible as controls. Patients and controls were matched by age (±5 years) and sex at ratio of 1:1. Moreover, we performed a multivariate statistical analysis to control the possible bias that could have occurred as the result of the heterogeneous distribution of potential confounding factors in both cohorts. The recruitment of all the subjects included in this study, both individuals with inflammatory arthritis (RA, AS and PsA) and controls was performed following the date in which they attended the rheumatology outpatient clinic of each centre, regardless of their severity or the duration of their disease. At the end of the recruitment period, 2986 patients who had met the inclusion criteria were invited to participate. Of them, 75 declined to take part in the study. The statistical power was estimated using the remaining 2911 patients (775 RA, 738 AS, 721 PsA, and 677 non-CIRD individuals). The percentage of individuals with high or very high CV risk according the European Systematic COronary Risk Evaluation (SCORE) risk charts, which identify these patients if values are ≥5%, was 6% in the controls and 12% in the RA cohort (31, 32). Based on this assumption, the power of the sample numbering 2911 individuals to detect a statistically significant risk difference of 6% between the cohorts was 0.98. From the initial series of 2911, 2595 of them (89.1%) accomplished the 2.5 years follow-up visit.

Follow-up

Patients included in the study were actively followed-up by their rheumatologists in an attempt to identify the occurrence of the first CVE. The follow-up was considered successful if the patient fulfilled the 2.5-year follow-up visit, had suffered his/her first CVE within the 2.5 years follow-up period or had died by CV cause. Otherwise, the patient was considered lost to follow-up. When a patient was lost to follow-up, researchers in the participant hospitals looked for a possible cause of death at the hospital and primary care centre medical records. They also searched for information on fatal or a non-fatal CV disease events from other centres of the Spanish National Health system. In the cases lost to follow-up in whom this information was not available, data provided by the Spanish Statistical Office was assessed to determine if the patient was alive or dead and, in this case, the cause of the death.

Variables and operative definitions

The main variable analysed was the presence of a first CVE (IHD, cerebrovascular accidents [CVA], peripheral arterial disease [PAD], heart failure [HF] and mortality from these causes) from the time of the inclusion in the study to the 2.5 years follow-up visit in patients without previous history of CVD. Secondary variables were as follows: (1) traditional (classic) CVRFs (hypertension, dyslipidaemia, obesity, smoking, and diabetes); (2) parameters of inflammation and disease activity; (3) sociodemographic variables (age and sex), comorbidities and laboratory parameters; and (4) potential confounding factors (disease severity, duration of disease, and therapies). Operative definitions of the principal and secondary variables can be found in the Supplementary material of the article published by Castañeda *et al*. (27). The CVE risk was calculated for people without CVE at the beginning of the CARMA project.

Statistical analysis

Numerical variables with normal distribution were expressed as mean and standard deviations (SD). Variables not normally distributed were expressed as median and interquartile ranges (IQR p25–p75). Absolute and relative frequencies were calculated for qualitative variables.

A descriptive analysis of losses to follow-up was carried out. Comparison with patients who attended the 2.5 years visit was performed using parametric and nonparametric tests according to the distribution of each variable. Numerical variables were assessed using the Student *t*-test or the Mann-Whitney U-test. Qualitative variables were assessed by a Chi-squared test (with or without Yates correction), or Fisher's exact test in 2x2 tables. Cumulative incidence of the first CVE per 1000 patients along with 95% confidence interval (CI) for the total number of patients and also for each group of conditions was also calculated. Bivariate analysis of the patients who completed the 2.5 years follow-up visit was conducted. Later, a multivariate proportional hazard Weibull model was carried out. Development of first CVE from the entry of the study up to the 2.5 years follow-up visit was the dependent variable. Results were presented as hazard ratio (HR) and 95% CI.

The selection of independent variables in the multivariate models was based on clinical judgments and those with $p<0.20$ in the bivariate analysis were included. All analyses were performed using the SPSS 21.0 statistical programme.

This study was performed following the principles outlined in the Helsinki Declaration, and the study protocol was approved by the Ethics Committee for Clinical Research of Galicia, Spain (approval number: 2009/077). All patients had written informed consent to participate in the study and to publish the data obtained.

Results

Two thousand nine hundred eleven patients were included in the study: 775 patients with RA, 738 with AS, 721 with PsA, and 677 individuals attending rheumatology outpatient clinics without CIRD or autoimmune diseases. Of them, 89.1% (2595: 706 RA, 657 AS, 661 PsA and 571 controls) performed the 2.5 years follow-up visit. Among the patients who attended the 2.5 years

Table I. Baseline sociodemographic, traditional cardiovascular risk factors and clinical characteristics of the population included in the study.

Variables	Rheumatoid arthritis (n=775)	Ankylosing spondylitis (n=738)	Psoriatic arthritis (n=721)	Matched cohort (n=677)	*p*-value
Sociodemographic features					
Age at inclusion, years, mean (SD)	57.1 (12.3)	48.1 (11.7)	51.8 (12.0)	54.0 (12.4)	<0.001
Age at the beginning of disease, years, mean (SD)	45.8 (13.4)	29.7 (11.8)	39.5 (13.3)	48.5 (12.4)	<0.001
Sex, female, n (%)	581 (75.0)	200 (27.1)	327 (45.4)	437 (64.5)	<0.001
Educational level, n (%)					
- Elementary	467 (60.9)	318 (43.3)	331 (46.3)	229 (34.1)	
- Secondary /University	300 (39.1)	416 (56.7)	383 (53.7)	443 (65.9)	<0.001
Traditional CVRF					
BMI, kg/m^2, mean (SD)	26.9 (4.8)	27.4 (4.4)	28.2 (4.7)	26.7 (4.4)	<0.001
Abdominal perimeter (cm), mean (SD)	93.7 (7.0)	96.3 (12.9)	97.6 (13.0)	93.5 (12.9)	<0.001
Hypertension, n (%)	236 (30.5)	190 (25.7)	213 (29.5)	158 (23.3)	0.008
Hypercholesterolaemia, n (%)	238 (30.7)	199 (27.0)	257 (35.6)	224 (33.1)	0.003
Total cholesterol (mg/dL)	204.2 (35.6)	196.6 (37.0)	202.1 (36.1)	208.7 (39.9)	<0.001
Triglycerides (mg/dL)	107.2 (55.2)	113.2 (71.6)	121.5 (76.8)	110.2 (70.2)	0.001
LDL-c (mg/dL), mean (SD)	122.8 (32.9)	123.6 (32.3)	124.2 (32.0)	128.0 (36.9)	0.023
HDL-C (mg/dL), mean (SD)	61.3 (17.2)	52.8 (13.9)	54.4 (14.9)	59.9 (16.8)	<0.001
Atherogenic index, mean (SD)	3.6 (1.3)	4.0 (1.2)	3.9 (1.1)	3.7 (1.1)	<0.001
Diabetes mellitus, n (%)	60 (7.8)	56 (7.6)	66 (9.2)	34 (5.0)	0.030
Obesity (BMI ≥30), n (%)	180 (23.2)	186 (25.2)	209 (29.1)	147 (21.8)	0.010
Smoking status, n (%)					
- Current smokers	189 (24.4)	254 (34.4)	157 (21.8)	143 (21.2)	
- Past smokers	202 (26.1)	240 (32.5)	227 (31.5)	176 (26.0)	<0.001
- Never smoking	384 (49.5)	244 (33.1)	337 (46.7)	357 (52.8)	
Clinical characteristics					
Disease duration, years	8.0 [3.0-14.0]	15.0 [8.0-26.0]	9.0 [4.0-16.0]	2.0 [0.0-6.0]	<0.001
DAS28-ESR	3.1 [2.3-4.0]	--	2.9 [2.0-3.8]	--	0.002
HAQ (0-3)	0.5 [0.1-1.1]	--	0.4 [0.0-0.9]	--	<0.001
BASDAI, mm (0-10)	--	3.5 [1.7-5.3]	--	--	--
BASFI, mm (0-10)	--	3.1 [1.3–5.2]	--	--	--
ESR, mm/1st hour	17.0 [9.0-29.0]	10.0 [6.0-21.0]	12.0 [6.0-21.0]	10.0 [5.0-18]	<0.001
CRP, mg/L	3.1 [1.2-8.0]	3.6 [1.6-8.9]	2.9 [1.4-6.1]	1.9 [1.3-3.3]	<0.001
RF positive, n (%)	528 (68.1)	--	--	--	--
ACPA positive, n (%)	482 (62.2)	--	--	--	--
HLA-B27, n (%)	--	561 (76)	--	--	--
Erosions (RA), n (%)	352 (45.4)				--
Biologic DMARDs, n (%)	313 (40.4)	349 (47.4)	300 (41.7)	--	<0.001
Synthetic DMARDs, n (%)	674 (87.0)	239 (32.4)	536 (74.5)	--	<0.001
NSAID, n (%)	309 (39.9)	431 (58.5)	329 (45.9)	142 (21.0)	<0.001
GC, n (% ever treated)	357 (46.1)	59 (8.0)	129 (17.9)	--	<0.001
Statins, n (%)	161 (20.8)	119 (16.1)	156 (21.6)	136 (20.1)	0.04

All variables are recorded at the time of inclusion in the study.
Data expressed as median [IQR] unless specified. Categorical variables are expressed as number (n) and percentages (%); SD: standard deviation. ACPA: anti-cyclic citrullinated peptide antibodies; BASDAI (0-10): Bath Ankylosing Spondylitis (AS) Disease Activity Score; BASFI (0-10): Bath AS Functional Index; BMI: body mass index; CRP: C-reactive protein; CV: cardiovascular; CVRF: cardiovascular risk factors; DAS28-ESR: Disease Activity Score using 28 joints-erythrocyte sedimentation rate; DMARD: Disease-modifying anti-rheumatic drugs; GC: glucocorticoids; HAQ (0-3): Health Assessment Questionnaire; HLA-B27: histocompatibility antigen HLA-B27; NSAID: non-steroidal anti-inflammatory drugs; RA: rheumatoid arthritis; RF: rheumatoid factor.

follow-up visit, 52.9% were women. The mean age (SD) at the onset of the study was 52.3 (12.6) years. The main baseline sociodemographic and clinical characteristics of the patients included in the study are shown in Table I.

Losses to follow-up and their causes

The group of patients that showed the highest loss to follow-up was the group of controls without CIRD patients (15.9%), followed by patients with AS (11.1%), RA (9.2%) and those with PsA (8.6%). The outcome of the patients at 2.5 years of follow-up visit is shown in Supplementary Table S1. There were no significant differences between the group of patients who were lost to follow-up and those who completed the 2.5 years visit, except for hypertension, which was more prevalent in the loss to follow-up patient group (33% *vs*. 26.7%, p=0.03) and smoking habit. Also, the frequency of high CVD risk according to the SCORE at the onset of the study was higher among those who were lost to follow-up (16.4% *vs*. 12.9, p<0.05). The main sociodemographic factors and clinical characteristics of the patients who were lost to follow-up are described in Supplementary Table S2.

Cumulative incidence of CVE

During the 2.5 years follow-up time, 51 CIRD patients experienced a first CVE (Table II). Twenty-three of them were due to IHD, 16 CVA, 7 PAD and 5 HF episodes.

At 2.5 years from the onset of the prospective assessment the cumulative incidence of CVE in the individuals without CVE at the time of recruitment was

Table II. Cardiovascular events and cumulative incidence of cardiovascular events in our cohort at the 2.5 years follow-up visit*.

	Total	RA	AS	PsA	Matched controls	*p*-value
CVE, n	51	11	16	13	11	0.04
CVE Cumulative incidence [95% CI]	15.3 [12.9-17.7]	11.5 [3.1-19.5]	22.03 [11.0-33.0]	16.5 [6.8-26.1]	11.04 [2.9-19.2]	<0.05

RA: rheumatoid arthritis; AS: ankylosing spondylitis; PsA: psoriatic arthritis; CVE: cardiovascular events; n: number; CI: [confidence interval].
*The comparative analysis between the different groups in pairs did not yield statistical differences, showing the following data: RA *vs*. controls (*p*-value=0.465), AS *vs*. controls (*p*=0.06), PsA *vs*. control group (*p*=0.200), RA *vs*. AS (*p*=0.064), RA *vs*. PsA (*p*=0.219), and AS *vs*. PsA (*p*=0.228).

15.3 cases per 1000 patients (95% CI: 12.9–17.7). Patients with AS exhibited the highest cumulative incidence of first CV event (22.03; 95% CI: 11.01–33.04). CVE cumulative incidence in RA, PsA and controls is shown in Table II.

Cardiovascular mortality

Overall, only seven patients had died due to CVE and 30 because of non-CVE between the basal visit and the 2.5 years follow-up time.

Risk factors to develop the first CVE

After excluding those with CVD prior to inclusion in the study, the total number of patients who completed the 2.5 years follow-up visit was 2402 patients. The mean age at the onset of the study of the patients who developed a first CVE was 62.9 (12.02) years and 68.3% were men. Table III shows the main characteristics of the patients who developed a first CVE throughout the 2.5 years of follow-up.

The highest risk of developing a first CVE during the 2.5 years of follow-up was found in those with AS (HR: 4.11; 95% CI: 1.07–15.79, *p*=0.04), patients with older age (HR: 1.09; 95% CI: 1.05–1.13, *p*<0.001), higher systolic blood pressure (HR: 1.02; 95% CI: 1.00–1.04, *p*=0.01) and longer duration of the rheumatic disease (HR: 1.07; 95% CI: 1.03–1.12, *p*<0.01). In contrast, female gender was a protective factor (HR: 0.43; 95% CI: 0.18–1.00, *p*=0.05) (Table IV).

Impact of the biologic therapy on CVE

We also aimed to assess the potential impact of receiving biologic drugs (the exposure) on the outcome data. For this purpose, we recalculated the crude and adjusted HR of the effect of biologic therapy, stratifying each one the CIRD included in our cohort separately (RA, AS and PsA) (Table S3). We could not find a significant effect of the biologic therapy on CVE in any of the groups, although the point estimates of HR suggests a protective effect of the biologic therapy reducing the risk of CVE in patients with RA and AS. However, the width of the confidence intervals did not allow us to perform further analyses. Nevertheless, we feel that the relationship between the use of biologic therapy and the development of CVE may be altered by a potential confounding-by-indication bias, as patients with higher disease activity were expected to be treated with biologic DMARDs more commonly and to have higher risk of suffering CVE due to disease severity as well (Table S3).

Table III. Baseline features of the patients who developed a first CVE from the inclusion in the study to the 2.5 years follow-up visit.

Variables	Patients who completed the first follow-up visit (2.5 years) (n=2402)§		
	With first CVE (n=51)	Without first CVE (n=2351)	*p*-value
Age, mean (SD)	62.9 (12.02)	52.0 (12.47)	<0.001
Disease duration (years), median [p25-p75]	11.5 [2.7-23.2]	8 [3-16]	0.07
Sex (women), (%)	31.7	54.4	<0.01
Smoking status, (%)			
Current smokers	34.1	46.1	0.14
Past smokers	41.5	28	
Never smoking	24.4	25.9	
SCORE, (%)			
Low	17.1	54.5	<0.001
Moderate	36.6	34.9	
High	46.3	10.6	
Family history of IHD,	4.9	12.4	0.14
Hypercholesterolaemia, (%)	58.8	22.3	<0.001
Hypertension, (%)	41.5	28.8	0.07
Obesity (BMI ≥ 30), (%)	22.5	24.2	0.81
Diabetes mellitus, (%)	4.9	1.3	0.05
Total cholesterol (mg/dl), mean (SD)	206 (38.7)	204.7 (36.3)	0.81
Systolic blood pressure (mmHg), mean (SD)	142.2 (19.8)	129.6 (18)	<0.001
ESR (mm/1st h), median [p25-p75]	16 [17-27]	12.2 [6-12]	0.14
CRP (mg/l), median [p25-p75]	4.5 [2-9.5]	2.9 [1.1-6.1]	0.03

§After excluding those with CVE prior to inclusion in the study. All variables are recorded at the time of inclusion in the study. SD: standard deviation; SCORE: Systematic Coronary Risk Evaluation; CVE: cardiovascular event; IHD: ischaemic heart disease; BMI: body mass index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

Discussion

The present prospective study confirms the claim that CVE are increased in unselected patients with CIRD. In our series, it was mainly due to individuals with AS. A predominance of men and a longer disease duration may have accounted for a higher incidence of CVE in the subgroup of AS than in other CIRD patients. Also, CVRFs, such as hypertension, increased the risk of CVE. In the CARMA study the frequency of hypertension was higher in the subgroup of patients with RA (30.5%). Hypertension was also common in the

Table IV. Risk factors to experience first CVE from the inclusion in the study to the 2.5 years follow-up visit.

Variables	HR (95% CI) Crude	HR (95% CI) Adjusted	*p*-value
Type of CIRD (ref. patients without CIRD)			
RA	1.01 (0.37-2.78)	1.02 (0.29-3.65)	0.97
AS	1.92 (0.78-4.71)	4.11 (1.07-15.79)	0.04
PsA	1.33 (0.51-3.49)	1.39 (0.38-5.05)	0.61
Age at the onset of the study	1.04 (1.02-1.06)	1.09 (1.05-1.13)	<0.001
Sex (ref. men)	0.41 (0.21-0.79)	0.43 (0.18-1.00)	0.05
Smoking (ref. never smoking)			
Current smokers	1.25 (0.56-2.81)	1.17 (0.45-3.01)	0.75
Past smokers	1.94 (0.95-3.98)	0.93 (0.39-2.19)	0.87
Family history of IHD (ref. no)	0.38 (0.09-1.58)	0.29 (0.04-2.16)	0.23
Diabetes mellitus (ref. no)	3.78 (0.91 - 15.66)	1.64 (0.21-12.94)	0.64
Systolic blood pressure, (mmHg)	1.03 (1.02 – 1.05)	1.02 (1.00-1.04)	0.01
Hypercholesterolaemia (ref. no)	1.68 (0.89 - 3.16)	0.83 (0.39-1.80)	0.64
Disease duration (years)	1.03 (1.00 - 1.05)	1.07 (1.03-1.12)	<0.01
ESR (mm/1st h)	1.02 (1.00 - 1.03)	1.00 (0.98-1.03)	0.7

All variables are recorded at the time of inclusion in the study.
HR: hazard ratio; CIRD: chronic inflammatory rheumatic diseases; RA: rheumatoid arthritis; AS: ankylosing spondylitis; PsA: psoriatic arthritis; IHD: ischaemic heart disease; ESR: erythrocyte sedimentation rate. HR adjusted for all variables included in the multivariate model.

COMOrbidities in Rheumatoid Arthritis (COMORA) study (33). In this international, cross-sectional study, which included 3920 patients with RA from 17 participating countries on five different continents, the frequency of hypertension was 40.4%. However, the prevalence of CVD in RA patients from the COMORA study was lower than that observed in the patients with RA from the CARMA study at the baseline visit (6.6% *vs*. 10.5%) (27, 33). A possible explanation for this discrepancy may be the different definitions for CVD used in these studies. In this regard, in the COMORA study only myocardial infarction and stroke were included in this category whereas in the CARMA study CVD was defined by the presence of IHD (angina and myocardial infarction), CVA, HF of ischaemic origin and peripheral arteriopathy.

Our results are in keeping with data published by other authors (34,35). With respect to this, in a meta-analysis that encompassed seven longitudinal studies, Mathieu *et al*. described an increased risk of acute myocardial infarction (odds ratio [OR]: 1.60; 95% CI: 1.32–1.93) and CVA (OR: 1.50; 95% CI: 1.39–1.62) in AS when compared to the general population without inflammatory diseases (36). Also, Vinker *et al*. have recently reported a higher risk of CVE in patients with AS than in the control group (14.1% *vs*. 6.36%, respectively, $p<0.01$) (37).

In a meta-analysis of observational studies reported by Avina-Zubieta *et al*. (1), patients with RA had higher risk of developing acute myocardial infarction (68%) and CVA (41%) than the general population. However, in contrast to what might be expected, RA patients from our series did not show a higher increase in the risk of developing CVE after 2.5 years of follow-up when compared to controls without CIRD. Since the EULAR recommendations for CVD risk management in patients with RA have been actively discussed by the members of the Spanish Society of Rheumatology (38, 39), it is possible that the impact of these recommendations along with further recommendations proposed by members of the Spanish Society of Rheumatology (38, 40), including the search for patients with RA at high risk of CVD using non-invasive tools (41-43), may have had a positive influence on the results found in our prospective follow-up study.

RA patients with worse control of disease activity have an increased risk of type 2 diabetes (44). The close association between uncontrolled disease activity in patients with inflammatory arthritis and cardiometabolic comorbidities was supported by Ruscitti *et al*. (44). Also, Crepaldi *et al*. (45) have reported that diabetes was associated with higher disease activity. Although patients with chronic inflammatory rheumatic diseases (RA, AS and PsA) from the CARMA study had an acceptable control of the disease, they also had a higher frequency of diabetes than controls. However, in the adjusted multivariate model the difference did not reach statistical significance.

As discussed before, besides classic CVRFs, the duration of disease seems to influence the development of accelerated atherogenesis in CIRD patients (36, 46, 47). Also, the magnitude and chronicity of the inflammatory burden was found to correlate directly with the presence of subclinical atherosclerosis in patients with RA (48). In the present study, a longer duration of the disease was related independently with an increased risk of developing CVE at 2.5 years of the study. Also, baseline ESR and CRP levels we higher in the subgroup of CIRD patients who experienced CVE over the 2.5 follow-up period, although they did not reach statistical significance in the multivariate analysis. Interestingly, in a sample of 1222 patients that was randomly selected from the register of a rheumatology outpatient clinic in Amsterdam (49), the ESR was considered as a predictive factor of CVD mortality in patients with RA. This study also showed that patients with RA had a higher risk of CVD mortality than the general population. This finding was maintained throughout the 15 years of the study.

Our study has a number of strengths and limitations. In this regard, it included a large cohort of patients that encompassed 3 of the most representative chronic inflammatory rheumatic diseases (RA, AS and PsA). This fact allowed us to establish comparisons between the different subtypes of inflammatory arthritis, since we used a common methodology for data collection and patient follow-up. Another strength of the study was the low rate of loss of subjects after 2.5 years of follow-up. Moreover, the prospective design of the study allowed us to verify hypothesis of causality. However, the main limitation

of our study is that the follow-up period of 2.5 years is still short to reach definitive conclusions. Moreover, our study included a population of individuals periodically assessed at rheumatology units. Tight control of these patients may underestimate the actual prevalence of CVD in patients with CIRD.

In summary, despite efforts to improve the management of patients with CIRD, the results from the present study indicate that patients with AS followed-up prospectively in rheumatology outpatient clinics have an increased risk of CVE. Male gender, age, systolic hypertension, and a longer duration of disease, are associated with CVE in patients with CIRD attending rheumatology outpatient's clinics

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