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


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
First CV event in inflammatory arthritis / M.A. Martín-Martínez et al.

Maria A. Martín-Martínez, MD
Santos Castañeda, MD, PhD
Carlos González-Juanteay, MD, PhD
Fernando Sánchez-Alonso, MD
Carmen García-Gómez, MD, PhD
Ruth López-González, MD, PhD
Jesús Babío-Herraez, MD
Antonio Juan-Mas, MD, PhD
Maria P. Moreno-Gil, MD
Carmen O. Sánchez-González, MD
Montserrat Romera-Baurés, MD, PhD
José A. Pinto-Tasende, MD, PhD
Jesús Torrente-Molina, MD, PhD
Dolores Fábregas-Canales, MD
Javier Llorca, MD, PhD
Miguel A. González-Gay, MD, PhD

The members of the CARMA Project Collaborative Group are listed on page 737.

Please address correspondence to:
Prof. Miguel A. González-Gay,
Rheumatology Division, Hospital Universitario Marqués de Valdecilla,
IDIVAL, Avenida de Valdecilla, s/n, 39008 Santander, Spain.
E-mail: miguelaggay@hotmail.com
Received on August 1, 2018; accepted in revised form on November 5, 2018.
© Copyright CLINICAL AND EXPERIMENTAL RHEUMATOLOGY 2019.

Funding: this project was supported by an unrestricted grant from Abbvie, Spain.
However, the design, analysis, interpretation of results and preparation of the manuscript was made independently of Abbvie.
Prof. González-Gay’s research was supported by grants from “Fondo de Investigación Sanitaria” (grants PI060024, PS09/0074, PI12/00660 and PI15/00525) from ‘Instituto de Salud Carlos III’ (ISCIII, Health Ministry, Spain) and by RETICS Programs RD12/0009 and RD16/0012 (RIER) from ‘Instituto de Salud Carlos III’ (ISCIII, Health Ministry, Spain).
Competing interests: S. Castañeda received consultation fees/participation in company sponsored speaker’s bureau from Abbott, BMS, Lilly, MSD, Pfizer, Roche and Sobi; M.A. González-Gay received grants/research support from Abbott, MSD, Janssen and Roche, and had consultation fees/participation in company sponsored speaker’s bureau from Abbott, Lilly, MSD, Novartis, Pfizer, Roche, Sanofi and Sobi; the other authors have declared no competing interests.

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). Spondyloarthopathies (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 participating 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 2×2 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
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.

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

Clinical and Experimental Rheumatology 2019

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

<table>
<thead>
<tr>
<th>Variables</th>
<th>Rheumatoid arthritis (n=775)</th>
<th>Ankylosing spondylitis (n=738)</th>
<th>Psoriatic arthritis (n=721)</th>
<th>Matched cohort (n=677)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sociodemographic features</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at inclusion, years, mean (SD)</td>
<td>57.1 (12.3)</td>
<td>48.1 (11.7)</td>
<td>51.8 (12.0)</td>
<td>54.0 (12.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age at the beginning of disease, years, mean (SD)</td>
<td>45.8 (13.4)</td>
<td>29.7 (11.8)</td>
<td>39.5 (13.3)</td>
<td>48.5 (12.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex, female, n (%)</td>
<td>581 (75.0)</td>
<td>200 (27.1)</td>
<td>327 (45.4)</td>
<td>437 (64.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Educational level, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Elementary</td>
<td>467 (60.9)</td>
<td>318 (43.3)</td>
<td>331 (46.3)</td>
<td>229 (34.1)</td>
<td></td>
</tr>
<tr>
<td>- Secondary /University</td>
<td>300 (39.1)</td>
<td>416 (56.7)</td>
<td>383 (53.7)</td>
<td>443 (65.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Traditional CVRF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m², mean (SD)</td>
<td>26.9 (4.8)</td>
<td>27.4 (4.4)</td>
<td>28.2 (4.7)</td>
<td>26.7 (4.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Abdominal perimeter (cm), mean (SD)</td>
<td>93.7 (7.0)</td>
<td>96.3 (12.9)</td>
<td>97.6 (13.0)</td>
<td>93.5 (12.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>236 (30.5)</td>
<td>190 (25.7)</td>
<td>213 (29.5)</td>
<td>158 (23.3)</td>
<td>0.008</td>
</tr>
<tr>
<td>Hypercholesterolaemia, n (%)</td>
<td>238 (30.7)</td>
<td>199 (27.0)</td>
<td>257 (35.6)</td>
<td>224 (33.1)</td>
<td>0.003</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>204.2 (35.6)</td>
<td>196.6 (37.0)</td>
<td>202.1 (36.1)</td>
<td>208.7 (39.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>107.2 (55.2)</td>
<td>113.2 (71.6)</td>
<td>121.5 (76.8)</td>
<td>110.2 (70.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>LDL-C (mg/dL), mean (SD)</td>
<td>122.8 (32.9)</td>
<td>123.8 (32.3)</td>
<td>124.2 (32.0)</td>
<td>128.0 (36.9)</td>
<td>0.023</td>
</tr>
<tr>
<td>HDL-C (mg/dL), mean (SD)</td>
<td>61.3 (17.1)</td>
<td>52.8 (13.9)</td>
<td>54.4 (14.9)</td>
<td>59.9 (16.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atherogenic index, mean (SD)</td>
<td>3.6 (1.5)</td>
<td>4.0 (1.2)</td>
<td>3.9 (1.1)</td>
<td>3.7 (1.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>60 (7.8)</td>
<td>56 (7.6)</td>
<td>66 (9.2)</td>
<td>34 (5.0)</td>
<td>0.030</td>
</tr>
<tr>
<td>Obesity (BMI ≥30), n (%)</td>
<td>180 (23.2)</td>
<td>186 (25.2)</td>
<td>209 (29.1)</td>
<td>147 (21.8)</td>
<td>0.010</td>
</tr>
<tr>
<td>Smoking status, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Current smokers</td>
<td>189 (24.4)</td>
<td>254 (34.4)</td>
<td>157 (21.8)</td>
<td>143 (21.2)</td>
<td></td>
</tr>
<tr>
<td>- Past smokers</td>
<td>202 (26.1)</td>
<td>240 (32.5)</td>
<td>227 (31.5)</td>
<td>176 (26.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- Never smoking</td>
<td>384 (49.5)</td>
<td>244 (33.1)</td>
<td>337 (46.7)</td>
<td>357 (52.8)</td>
<td></td>
</tr>
<tr>
<td>Clinical characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease duration, years</td>
<td>8.0 [3.0-14.0]</td>
<td>15.0 [8.0-26.0]</td>
<td>9.0 [4.0-16.0]</td>
<td>2.0 [0.0-6.0]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DAS28-ESR</td>
<td>3.1 [2.3-4.0]</td>
<td>--</td>
<td>2.9 [2.0-3.8]</td>
<td>--</td>
<td>0.002</td>
</tr>
<tr>
<td>HAQ (0-3)</td>
<td>0.5 [0.1-1.1]</td>
<td>--</td>
<td>0.4 [0.0-0.9]</td>
<td>--</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BASDAI, mm (0-10)</td>
<td>--</td>
<td>3.5 [1.7-5.3]</td>
<td>--</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>BASFI, mm (0-10)</td>
<td>--</td>
<td>3.1 [1.3-5.2]</td>
<td>--</td>
<td>--</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ESR, mm/hour</td>
<td>17.0 [9.0-29.0]</td>
<td>10.0 [6.0-21.0]</td>
<td>12.0 [6.0-21.0]</td>
<td>10.0 [5.0-18]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>3.1 [1.2-8.0]</td>
<td>3.6 [1.6-8.9]</td>
<td>2.9 [1.4-6.1]</td>
<td>1.9 [1.3-3.3]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RF positive, n (%)</td>
<td>528 (68.1)</td>
<td>--</td>
<td>93 (68.1)</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>ACPO positive, n (%)</td>
<td>482 (62.2)</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>HLA-B27, n (%)</td>
<td>--</td>
<td>561 (76)</td>
<td>--</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Erosions (RA), n (%)</td>
<td>352 (45.4)</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Biologic DMARDs, n (%)</td>
<td>313 (40.4)</td>
<td>349 (47.4)</td>
<td>300 (41.7)</td>
<td>--</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Synthetic DMARDs, n (%)</td>
<td>674 (87.0)</td>
<td>239 (32.4)</td>
<td>536 (74.5)</td>
<td>--</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NSAID, n (%)</td>
<td>309 (39.9)</td>
<td>431 (58.5)</td>
<td>329 (45.9)</td>
<td>142 (21.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GC, n (ever treated)</td>
<td>357 (46.1)</td>
<td>59 (8.0)</td>
<td>129 (17.9)</td>
<td>--</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Statins, n (%)</td>
<td>161 (20.8)</td>
<td>119 (16.1)</td>
<td>156 (21.6)</td>
<td>136 (20.1)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

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. ACPO: anti-cyclical citrullinated peptide antibodies; BASDAI: Bath Ankylosing Spondylitis (AS) Disease Activity Score; BASFI: 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.
15.3 cases per 1000 patients (95% CI: 12.9–17.7). Patients with AS exhibited the highest cumulative incidence of first CVE 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: 12.9–17.7). Patients with AS exhibited the highest cumulative incidence of first CVE event (22.03; 95% CI: 11.01–33.04). CVE cumulative incidence in RA, PsA and controls is shown in Table II.

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 suggest 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).

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
First CV event in inflammatory arthritis / M.A. Martín-Martínez et al.

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

<table>
<thead>
<tr>
<th>Variables</th>
<th>HR (95% CI)</th>
<th>Adjusted HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of CIRD (ref. patients without CIRD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA</td>
<td>1.01 (0.37-2.78)</td>
<td>1.02 (0.29-3.65)</td>
<td>0.97</td>
</tr>
<tr>
<td>AS</td>
<td>1.92 (0.78-4.71)</td>
<td>4.11 (1.07-15.79)</td>
<td>0.04</td>
</tr>
<tr>
<td>PsA</td>
<td>1.33 (0.51-3.49)</td>
<td>1.39 (0.38-5.05)</td>
<td>0.61</td>
</tr>
<tr>
<td>Age at the onset of the study</td>
<td>1.04 (1.02-1.06)</td>
<td>1.09 (1.05-1.13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex (ref. men)</td>
<td>0.41 (0.21-0.79)</td>
<td>0.43 (0.18-1.00)</td>
<td>0.05</td>
</tr>
<tr>
<td>Smoking (ref. never smoking)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smokers</td>
<td>1.25 (0.56-2.81)</td>
<td>1.17 (0.45-3.01)</td>
<td>0.75</td>
</tr>
<tr>
<td>Past smokers</td>
<td>1.94 (0.95-3.98)</td>
<td>0.93 (0.39-2.19)</td>
<td>0.87</td>
</tr>
<tr>
<td>Family history of IHD (ref. no)</td>
<td>0.38 (0.09-1.58)</td>
<td>0.29 (0.04-2.16)</td>
<td>0.23</td>
</tr>
<tr>
<td>Diabetes mellitus (ref. no)</td>
<td>3.78 (0.91-15.66)</td>
<td>1.64 (0.21-12.94)</td>
<td>0.64</td>
</tr>
<tr>
<td>Systolic blood pressure, (mmHg)</td>
<td>1.03 (1.02-1.05)</td>
<td>1.02 (1.00-1.04)</td>
<td>0.01</td>
</tr>
<tr>
<td>Hypercholesterolaemia (ref. no)</td>
<td>1.68 (0.89-3.16)</td>
<td>0.83 (0.39-1.80)</td>
<td>0.64</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>1.03 (1.00-1.05)</td>
<td>1.07 (1.03-1.12)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ESR (mm¹/h)</td>
<td>1.02 (1.00-1.03)</td>
<td>1.00 (0.98-1.03)</td>
<td>0.7</td>
</tr>
</tbody>
</table>

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 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 athrogenesis 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 were 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

Clinical and Experimental Rheumatology 2019

736
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 CVD. Male gender, age, systolic hypertension, and a longer duration of disease, are associated with CVE in patients with CIRD attending rheumatology outpatient’s clinics

**CARMA Project Collaborative Group**

The members of the CARdiovascular in rheuMAtology Project Collaborative Group include: Eugenia González de Rabago, Elena Alonso Blanco Morales, J. Carlos Fernández Lopez, Natividad Oreiro Villar, Antonio Atanes Sandoval, Francisco J. Blanco García (Complejo Hospitalario A Coruña, Xubias de Arriba, A Coruña); Cayetano Alegre De Miquel, María J. González Fernández, Ramón Huguet Codina, Beatriz Yoldi, Mercedes Ramontol (Instituto Dexeus, Barcelona); Gabriela Ávila, Sara Marsal Barril, Estefanía Quesada (Hospital Universitari Vall d’Hebron, Barcelona); Martina Steiner, Santiago Muñoz, Tatiana Cobo (Hospital Infantia Sofía, Madrid); Fernando Gamero, José García Torón, (Hospital S. Pedro de Alcántara, Cáceres); Pilar Espino, Inmaculada Ros, Mónica Ibáñez, and Claudia Murillo (Hospital Son Llatzer, Palma de Mallorca); Raïmon Sanmartí, Horacio Bertran, Sonia Cabrera, and Virginia Ruiz Rodríguez (Hospital Clinic i Provincial, Barcelona); Beatriz González Álvarez, Santiago Muñoz, Tatiana Cobo (Hospital Infanta Sofía, Madrid); Marta Peiser, Inmaculada Ros, and Natalia Palmou (Hospital General Universitario de Elda, Alicante); Celia Erazquin, Soledad Ojeda, Juan Carlos Quevedo, Félix Francisco, Carlos Rodríguez Lozano (Hospital Dr. Negrín, Las Palmas de Gran Canaria); Francisco J. López Longo, Delia Gerona, Carlos González Fernández, Indalecio Montero, Manuel Riella (Hospital Gregorio Marañón, Madrid); Javier del Pino, María Dolores Sánchez González (Hospital Un. de Salamanca); Alfonso Corrales, María Enriqueta Peiró (Hospital Un. Marqués de Valdecilla, Santander); José M. Senabre, José C. Rosas (Hospital de la Marina Baixa, Alicante); Isabel Rotés, Estefanía Moreno, Alba Erra, Dolors Grado (Hospital de San Rafael, Barcelona); Javier Calvo, Amelia Rueda (Hospital General Universitario, Valencia); Ingrid Moller, Isabel Rodríguez (Instituto Poal, Barcelona); Carmen Barbadillo (Hospital Universitario Puerta de Hierro, Madrid); Enric Raya, Pilar Morales, Ana Nieto, Inmaculada Jiménez, Cesar Magro (Hospital Clínico Un. San Cecilio, Granada); Ana Ruibal Escrivan (Hospital Santiago Apóstol, Vitoria-Gasteiz); Sergio Ros Expósito (Hospital de Viladecans, Barcelona); Ginés Sánchez Nieves, Enrique Júdez Navarro, Manuela Sianes Fernández, María A. García Morales, Isabel Labiano Bastero, Gloria García Consuegra, and Natalia Palmou (Hospital General de Albacete); Silvia Martínez Pardo, Manel Pujol, Elena Riera Alonso, Georgiina Salvador (Hospital Mutua Terrassa, Terrassa); Beatriz González Álvarez, Alberto Cantabranos (Hospital Ntra. Sra. de Candelaria, Santa Cruz de Tenerife); Sagrario Bustabad, Esmeralda Delgado (Hospital Un. de Canarias, La Laguna, Tenerife); Alejandro Muñoz, Sergio Rodríguez Montero, Luis M. Jiménez (Hospital Univ. de Valme, Sevilla); Javier Rivera Redondo, Teresa González Hernández (Instituto Provincial de Rehabilitación, Madrid); Francisco J. González. Polo (Hospital de Cantoblanco, Madrid); Raúl Menor Almagro (Hospital de Jerez de la Frontera, Jerez de la Frontera, Cádiz); José M. Moreno, Emilio Giner Serret, Carla Lannuzzelli Barroso (Hospital Obispo Polanco, Teruel); Laura Cebrián Méndez, María T. Navío (Hospital Infanta Leonor, Madrid); Cristina Fernández Carballido (Hospital General de Elda, Alicante); Encarnación Pagán, Pablo Mesa del Castillo (Hospital Los Arcos, Murcia); Esperanza Naredo, Ana Cruz (Hospital Severo Ochoa, Madrid); Ana Turrión (Hospital Príncipe de Asturias, Madrid); Julio Sánchez, María Galindo, Javier García González (Hospital Univ. 12 de Octubre, Madrid); Eduardo Collantes, Desireé Ruiz, Pilar Font (Hospital Univ. Reina Sofía, Córdoba); Gema Bonilla (Hospital Univ. La Paz, Madrid); Antonio López Meseguer (Hospital Gutiérrez Ortega, Valdepeñas, Ciudad Real); Manuel J. Moreno, María José Moreno Martínez; María D. Beteta Fernández, Luis F. Linares (Hospital Virgen de la Arrixaca, Murcia); Mercedes Morcillo, María L. González Gómez (Hospital del Escorial, Madrid); Natalia A. Rivera, Olaia Fernández Berrizbeitia, María L. García Vivar (Hospital de Basurto, Bilbao); Manel Riera, Yolanda María León (Hospital Dos de Maig, Barcelona); Joan Maymó, Miriam Amiral, Silvia Iniesta Escolano, Silvia Sánchez Serrano, María P. Lís Bona (Hospital del Mar, Barcelona); Jordi Fiter, Julia Fernández Melón, Luis Espadaler (Hospital Universitario Son Espases, Palma de Mallorca); Olga Maiz, Joaquín Belunegui, Inmaculada Banegil (Hospital del Prat, Donostia); César Díez (Hospital de la Santa Creu i Sant Pau, Barcelona); Ramón Valls (Hospital de Palamós, Gerona); Iván Castellvi, María Bonet, Estefanía Moreno Ruaza (Hospital Comarcal de L’Ait Penedés, Vilafranca del Penedés, Barcelona); Jaime Calvo Alen (Hospital Sierra Rallana, Torrelavega); Trinidad Pérez Sandoval (Complejo Asistencial de León); Eva Revuelta Evrad (Hospital General de
Ciudad Real); Javier R. Godo, Cruz Fernández Espartaro (Hospital General de Móstoles, Madrid); Francisco J. Navarro Blasco, José A. González (Hospital General Universitario de Elche, Alicante); José A. Miranda-Filloy (Hospital Xeral Calde, Lugo).

References
32. LOZA E, LAJAS C, ANDREU JL et al.: Consensus statement on a framework for the


