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Cardiovascular risk factors' behavior during the early stages of the disease, in Hispanic rheumatoid arthritis patients: a cohort study

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Abstract

Rheumatoid arthritis (RA) patients from Latin America present distinctive characteristics relevant when assessing their cardiovascular (CV) risk. The objective was to monitor CV risk factor behavior in the early stages of the disease and to identify predictors of major CV outcomes (MACE). A recent-onset RA cohort was initiated in 2004; data from 185 patients with ≥ 1 year of follow-up were analyzed. Patients underwent prospective assessments of CV risk factors. Incident MACE were confirmed according to standardized definitions. Appropriated statics was used based on the distribution of the variables. At baseline, patients were primarily middle-aged females (87.6%), with active disease (69.7%). Most prevalent CV risk factors were C-reactive-protein > 1 mg/L (90.3%), Castelli ratio > 3 (83.8%), and low–high-density lipoprotein levels (73.5%). The number of patients with an incident CV risk factor after 1 year was higher for a Castelli ratio > 3 (23%), low–high-density lipoprotein serum cholesterol (16.3%), high total serum cholesterol (10.6%), and BMI ≥ 30 kg/m^2 (10%). A minority of patients met the age-range criteria for the application of ACC/AHA 2013 criteria and Reynolds Risk Score (45.8% and 34.1%, respectively). Fifteen patients were classified with high-CV risk during the first year of follow-up, according to ACC/AHA 2013 criteria. Until June 2018, the cohort underwent 1358 patient/years follow-up; six patients developed incidental MACE; high-CV risk at baseline failed to predict MACE. Recent-onset RA Hispanic patients present a distinctive pattern and first-year behavior of CV risk factors. During follow-up, few patients developed incidental MACE.

Keywords Cardiovascular diseases · Risk factors · Rheumatoid arthritis

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Introduction

Rheumatoid arthritis (RA) patients present an increased risk of cardiovascular (CV) morbidity and mortality compared with the general population, which has been related to different factors [1–5]; the increased risk is present in patients with early disease [4]. The updated 2015/2016 European League Against Rheumatism recommendations for CV disease risk management in patients with RA recommend a CV risk assessment for all patients with RA at least once every 5 years and its reconsideration following major changes in anti-rheumatic therapy; recommendations include the achievement of specific goals, CV risk estimation according to local guidelines, lifestyle changes, lipid measurements, anti-hypertensive agent and/or statin use as in the general population, and, finally, a careful review of the non-steroidal anti-inflammatory drugs and corticosteroid indication [6].

RA patients from Latin America present distinct epidemiological, serological, and clinical disease features, some

of which are relevant when assessing CV risk. The literature highlights a female preponderance, a younger age at presentation, and a less severe clinical expression in this population compared to Caucasians [7, 8]. In addition, dyslipidemia is the most frequent cardiovascular risk factor in Mexican adults [9, 10]; notably, hypoalphalipoproteinemia has been found to affect close to 60% of this particular population. In the clinical context of early RA, we demonstrated that dyslipidemia was present in 75% of Hispanic patients at their baseline evaluation, which was characterized by high disease activity [11]. Also, the most recent Mexican National Health and Nutrition Survey highlights that up to 39% of adult Mexican females have some degree of obesity, while 37% are overweight [12]; this percentage could be even higher if the BMI cut-off points to define overweight and obesity are reduced by 2 kg/m^2, as recommended in RA patients [13]. There are limited data concerning CV disease in RA patients from Latin America region [14, 15], and recognition of the most prevalent CV risk factors in Hispanic patients is relevant to improve knowledge regarding CV risk in the clinical context of RA. Moreover, to determine the real impact on RA patient CV morbidity and mortality, control/modification of as many as possible (reversible) CV risk factors must be achieved, some of which, such as disease activity control, may be more easily targeted in a substantial proportion of patients with early disease [16, 17]. Concurrently, others have been recognized as under-diagnosed and under-treated among Caucasian patients with RA [18, 19].

Cohorts are exceptional tools in clinical research, because they allow the prospective evaluation of relevant long-term outcomes [20, 21]. In 2004, we initiated an early RA cohort at a referral center for rheumatic diseases in Mexico City. Consecutive Hispanic patients entering the cohort presented recent-onset RA. Up to June 2018, the cohort comprised 199 patients with prospective assessments of CV risk factors. The objective of this study was to monitor CV risk factor behavior in the early stages of the disease, and to identify predictors of major CV outcomes (MACE) in our population. Early stages of the disease was selected, during which a more intensive search, identification, and treatment of comorbidities/risk factors has been described [22].

Methods

Ethics

The study received approval from Institution's internal review board "Comité de Ética en Investigación del Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (Reference number: IRE 274-10-11-1). Written informed consent was obtained from all the patients entering the cohort, who additionally consent to have their charts reviewed and data presented in scientific forums or published. Most recent local IRB re-approval was obtained on February 2019 (valid up to February 2020).

Setting and study population

Patients entering the cohort had symptom's duration of less than 1 year and nonspecific rheumatic diagnosis but with RA; up to June 2018, the cohort comprised 185 patients with confirmed RA, and who additionally had at least 1 year of follow-up in the cohort, which was required to achieve the described objective.

Once enrolled, patients underwent a complete medical history and collection of socio-demographic characteristics; serum titer of disease specific autoantibodies was determined. Rheumatic assessments were scheduled at regular intervals, at least 6 months apart as previously described [8]. Clinical evaluations included at least height, weight, and blood pressure measurements, extended joint counts, physician and patient-reported outcomes, disease activity score evaluated in 28 joints (DAS28), adverse events, comorbidity, and treatment assessments; the erythrocyte sedimentation rate (ESR in mm/H) and the C-reactive protein (CRP in mg/L) were performed. During follow-up, patients received treat-to-target oriented treatment, primarily with traditional disease-modifying anti-rheumatic drugs (DMARDs) with/without corticosteroids [8].

Prospective CV risk factor assessments

CV risk factor assessments performed at baseline were age, gender, ethnicity, physical activity, and history of first-degree relatives with premature heart disease.

CV risk factor assessments scheduled at baseline and at least 6 months apart during the entire follow-up were blood pressure, serum total cholesterol (CHO) and high-density lipoprotein (HDL) cholesterol (the Castelli ratio CHO/HDL was derived), serum glucose level (GLU, in mg/dL), body mass index (BMI), CRP levels (in mg/L), and (at least) the following comorbidities: hypertension (HT and HT treatment), diabetes mellitus (DM), advanced chronic kidney failure (CKF), and atrial fibrillation (AF, EKG was performed in all patients upon entering the cohort).

Finally, smoking status was assessed at baseline and at the last follow-up.

MACE

Incident MACE were defined from the 4-month follow-up evaluation to the last follow-up, or death. Patients who had MACE recorded on their charts, from the baseline evaluation up to the first 4 months of follow-up, were considered to

have prevalent MACE (there was no patient with prevalent MACE).

The considered MACE were as follows: CV mortality (including coronary, cerebrovascular, cardiac, and non-cardiac vascular events) and non-fatal CV events (including myocardial infarction and cerebrovascular events, congestive heart failure, new cardiac arrhythmia and angina). In addition, the following CV outcomes were included as MACE: peripheral arterial vascular disease, abdominal aneurysm, hypertensive emergency, pulmonary embolism, and deep venous thrombosis [23].

Variables and definitions

BMI was calculated as weight (kg)/height (m^2). Weight and height were determined by a trained nurse, usually with the same equipment.

Smoking status was self-reported and categorized as never smoker, former smoker (at least one cigarette per day for at least 3 months during their lifetime but do not currently smoke), or current smoker (at least one cigarette per day for at least 3 months).

Fasting GLU, CHO, and HDL were measured in serum and reported in milligrams (mg) per deciliter (dL). Low HDL levels and high CHO levels were defined according to standard definition [9, 10].

HT was defined if recorded on the charts, or anti-hypertensive medication was used, or a diastolic blood pressure ≥ 90 mmHg was detected, or a systolic blood pressure ≥ 140 mmHg was detected.

DM was defined if a physician diagnosis was recorded on the charts, if anti-diabetic medication was recorded, or if a fasting serum GLU level ≥ 126 mg/dL was detected.

RA statuses (remission, low disease activity, moderate disease activity, and high disease activity) were defined according to DAS28 cut-offs [24].

MACE definitions are summarized in Supplementary Material (Table) [23]. Confirmed MACE were established if standard definitions were met after the charts were reviewed by an independent observer. If not, or if the data were incomplete, suspicion of MACE was established.

CV risk assessment

We used two different CV risk calculators, to assign a group average risk to each individual patient, in the form of a percentage risk of having an event over the next 10 years: the Reynolds Risk Score (RRS) and the algorithm developed by the American College of Cardiology and the American Heart Association in 2013 (ACC/AHA 2013). Both had been used in Mexican patients [15]. A multiplication factor for 1.5 was applied to the predicted CV risk as both algorithms do not include RA diagnosis as a variable, in accordance to the EULAR 2015/2016 update on evidence-based recommendations for CV risk management in RA patients. Patients were classified into risk categories and specific thresholds for each calculator were used; using ACC/AHA 2013 algorithm, high-risk category was defined as a 10-year CV risk above 7.5% and using the RRS, above 20%.

Statistical analysis

Descriptive statistics included, frequencies and percentages, mean (± SD) for normally distributed variables and median (interquartile range [IQR]) for non-normally distributed variables. χ^2 test, Student's t test, and the Mann–Whitney U test were used to compare normally and non-normally distributed variables, respectively. Linear trends for the proportions of patients achieving each CV risk factor were performed by basic χ^2 test.

Cox regression analysis was used to investigate if high-CV risk at baseline (independent variable) predicted incidental MACE (dependent variable); due to the limited number of incidental MACE, no further variables were included.

Follow-up missing data varied from 3% (for BMI) to 20% (for serum GLU levels). Imputation was calculated for the linear regression method, considering an arbitrary pattern of missing values.

All statistical tests were two-sided and evaluated at the 0.05 significance level. The statistical analysis was performed using the SPSS/PC program (v.17.0; Chicago IL).

Results

Characteristics of the patients at the baseline evaluation

The 185 patients for whom data were analyzed were primarily middle-aged (median [25th–75th (IQR)]: 38.2 years [26.7–48.2]) females (162 patients [87.6%]), had a medium–low socioeconomic level (165 [89.2%]), and a median (25th–75th IQR) of 12 years of formal education (9–14) and 5.3 months (3.3–7.1) of disease duration. The majority of the patients had rheumatoid factor (RF) (154 patients [83.2%]) and antibodies to cyclic citrullinated peptides (ACCP) (155 [83.8%], one missing data), while a few had erosive disease (17 patients [9.2%]). As expected, the majority of the patients had active disease at the time of cohort entry: 129 patients (69.7%) had high disease activity, 48 (25.9%) had moderate disease activity, 6 (3.2%) had low disease activity, and 2 (1.1%) were in remission according to DAS28-ESR.

Prevalence of CV risk factors and their behavior during the first year of follow-up

Table 1 summarizes the prevalence of individual CV risk factors at baseline and at 6 and 12 months of follow-up. All the patients were classified as Hispanic and a minority (10 patients [10.8%]) was male. At baseline, almost the totality of the patients had (high) disease activity according to DAS28; in addition, the most prevalent CV risk factors were CRP > 1 mg/L, Castelli ratio > 3, and low HDL levels (Table 1). During the first year of follow-up, the prevalence of (a priori reversible) CV risk factors showed significant variations; smoking status, systolic blood pressure ≥ 140 mmHg (and ≥ 130 mmHg), diastolic blood pressure ≥ 90 mm Hg (and ≥ 85 mmHg), low serum HDL levels, Castelli ratio > 3, high serum levels of CRP (either > 5 mg/L or > 1 mg/L), and patients with active disease progressively decreased; concomitantly, the opposite profile was observed for BMI ≥ 30 kg/m^2 and the prevalence of patients on corticosteroids (Table 1).

There was a linear trend for the proportion of patients achieving systolic blood pressure ≥ 140 mmHg, low serum HDL, CRP > 1 mg/L, Castelli ratio > 3, and DAS28 > 2.6, as summarized in Table 1.

In addition to the prevalence of individual CV risk factors at baseline, patients who maintained each CV risk factor at 12 months were recorded. The results are summarized in Figs. 1 and 2. Use of anti-hypertensive drugs and corticosteroids, DM and advanced chronic kidney failure diagnosis, and age ≥ 45 years were all maintained in the few patients with each CV risk factor present at the baseline evaluation. The CRP > 1 mg/L, Castelli ratio > 3, low HDL serum levels, high (total) CHO serum levels, BMI > 30 kg/m^2, and current smoking status were maintained in the majority of the patients (53–88%); concomitantly, the opposite profile was observed for patients who maintained disease activity (29.5%) and either high systolic blood pressure and high diastolic blood pressure (25% and 39%, respectively).

Finally, during the first year of follow-up, the number of patients with an incident CV risk factor was higher for Castelli ratio > 3 (23%), low HDL serum cholesterol (16.3%), high total serum CHO (10.6%), BMI ≥ 30 kg/m^2 (10%), CRP > 1 mg/L (7.5%), and age ≥ 45 years (3.3%). No patient acquired the smoking habit or reported first-degree relatives with premature heart disease, or developed neither DM nor advanced chronic kidney failure (Figs. 1, 2).

CV risk score

During the first year of follow-up, only 84 patients (45.8%) had an age between 40 and 79 years, which was required for the application of the ACC/AHA 2013 criteria. Table 2 summarizes CV risk at 3 time-points and shows that only a minority of the patients had high-CV risk. There were

Table 1 Prevalence of CV-RF during the first year of follow-up

CV-RF	At baseline[a]	At 6 months of follow-up[a]	At 12 months of follow-up[a]	*p* value[d]
Age > 45 years	63 (24.1)	65 (35.1)	67 (36.2)	0.663
Smoking status	31 (16.8)	23 (12.4)[b]	21 (11.4)[c]	0.067
Systolic blood pressure ≥ 140 mmHg	20 (10.8)	14 (7.6)	8 (4.3)[c]	0.018
Diastolic blood pressure ≥ 90 mmHg	18 (9.7)	11 (5.9)	12 (6.5)	0.233
Increased serum CHO	34 (18.4)	36 (19.5)	34 (18.4)	0.807
Low serum HDL	136 (73.5)	109 (58.9)[b]	105 (56.8)[c]	0.001
Use of anti-hypertensive drugs	15 (8.1)	15 (8.1)	15 (8.1)	1
Diabetes mellitus diagnosis	11 (5.9)	11 (5.9)	11 (5.9)	0.829
BMI > 30 kg/m^2	34 (18.4)	41 (22.2)	45 (24.3)[c]	0.165
First-degree relatives with premature heart disease	0	0	0	NA
Advanced chronic kidney failure	2 (1.1)	2 (1.1)	2 (1.1)	1
CRP > 1 mg/L	167 (90.3)	145 (78.4)[b]	146 (78.9)[c]	0.004
Castelli ratio > 3	155 (83.8)	138 (74.6)[b]	132 (71.4)[c]	< 0.0001
DAS28 > 2.6	183 (98.9)	86 (46.5)[b]	54 (29.2)[c]	< 0.0001
Corticosteroid use	85 (45.9)	95 (51.4)[b]	98 (53)[c]	0.177

CV-RF cardiovascular risk factor, *CHO* serum total cholesterol, *HDL* high-density lipoprotein, *BMI* body mass index, *CRP* C-reactive protein, *DAS28* disease activity score (28 joints evaluated). *NA* not applicable

[a]*No* (%) of patients

[b]$p \leq 0.01$ vs. baseline

[c]$p \leq 0.05$ vs. baseline

[d]*p* value for analysis of trends in proportions

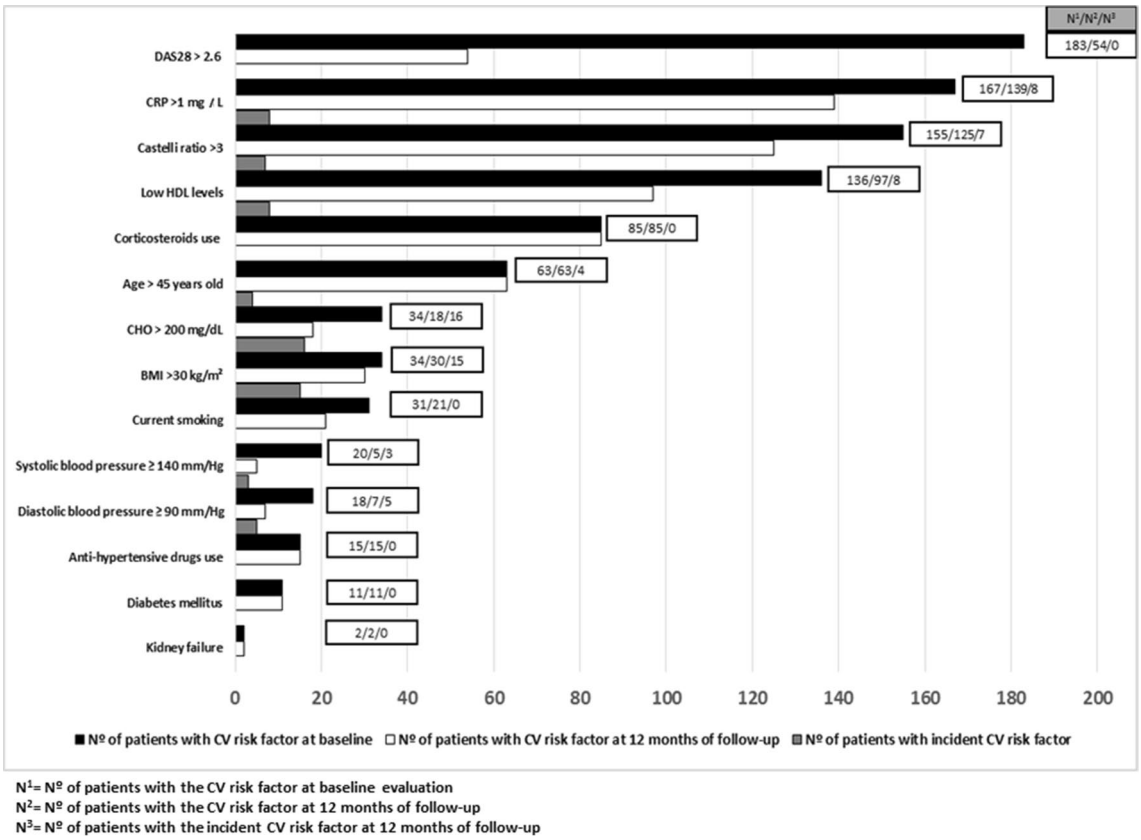

Fig. 1 Individual CV-RF behavior during the first year of follow-up. Black bars represent patients with prevalent CV-RF at baseline, white bars represent patients who maintained CV-RF after 1 year of follow-up, and gray bars patients with incident CV-RF at 1 year of follow-up

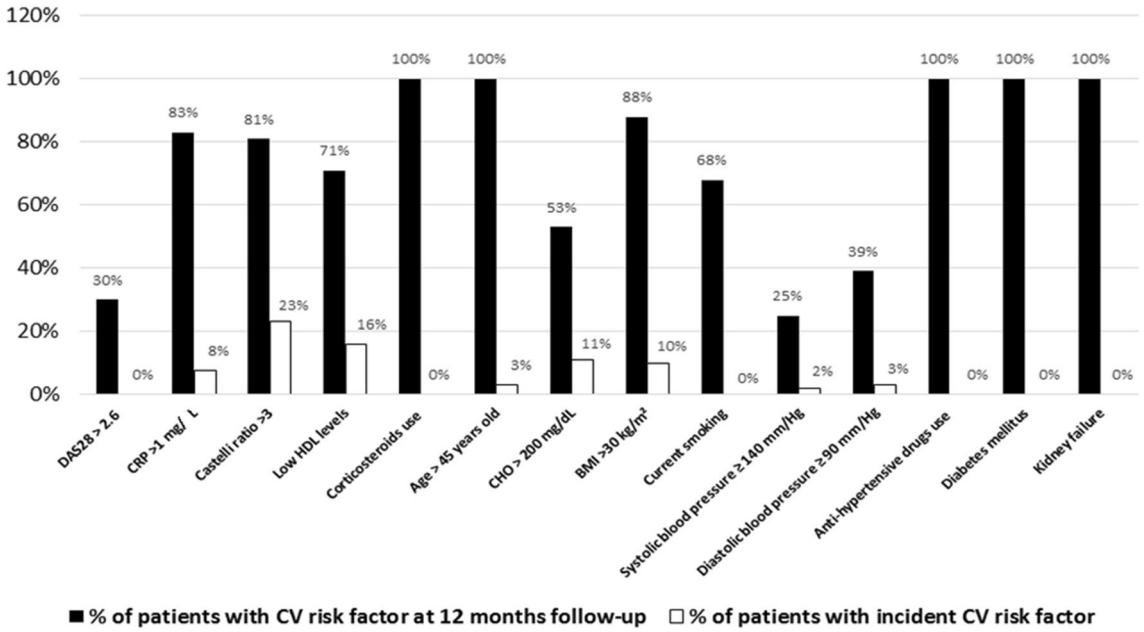

Fig. 2 Prevalent and incident CV risk factors at the end of the first year of follow-up. Black bars represent the percentage of patients with a particular CV-RF at 1 year follow-up; meanwhile, white bars represent the percentage of patients with incident CV-RF at the same follow-up

Table 2 High-CV risk and disease activity behavior at 3 time-points

	At baseline	At 6 months of follow-up	At 1 year of follow-up
Patients with high-CV risk according to ACC/AHA 2013 criteria[a]	14 (16.7)	12 (14.5)	13 (15.5)
Patients with high-CV risk according to RRS[a]	3 (4.8)	1 (1.6)	0
Median (25th–75th IQR) DAS28	5.8 (4.9–6.8)	2.8 (1.8–3.6)	2 (1.3–2.9)
DAS28 remission (< 2.6)[a]	1 (1.2)	36 (42.9)	54 (64.7)

CV cardiovascular, *IQR* interquartile range, *DAS28* disease activity score (28 joints evaluated)

[a]No (%) of patients

15 patients who were classified with high-CV risk at some time-point during the first year of follow-up; 11 (73.3%) had consistently high-CV risk at baseline and at 6 and 12 months of follow-up. Disease activity progressively decreased during the first year of follow-up (Table 2). Similar results were obtained regarding RRS (data not shown), although only 3 patients had high-CV risk at the baseline evaluation.

Incidental MACE and associated baseline factors

Up to June 2018, the cohort had 1358 patient/years follow-up. Up to last follow-up, 16 patients were lost to follow-up; their baseline characteristics and CV risk factors did not differ from those who complete last follow-up evaluation (data not shown). In addition, 6 patients had incidental MACE; 4 of them were ascertained as definite, while 2 sudden deaths were classified as likely related to acute myocardial infarction. Table 3 summarizes the description of patients who developed incidental MACE, which were diagnosed after (median, interquartile range) 6.5 years of follow-up (3.3–9.5). The cumulative risk among the 185 patients of being MACE-free decreased from 99.4% after 1 year up to 94.1% after 11 years of follow-up. Comparison of baseline variables between patients with and without incidental MACE is summarized in Table 4, and shows that more patients from the former group were aged ≥ 45 years, had systolic blood pressure ≥ 140 mmHg, and had BMI > 30 kg/m^2.

Cox regression analysis was performed in the entire cohort (185 patients who had 6 incidental MACE) and in the restricted subpopulation of patients with ACC/AHA age criteria (84 patients who had 5 incidental MACE). In both analyses, high-CV risk score at baseline, which

Table 3 Description of the patients with incidental MACE

Age at and year of RA diagnosis	Disease behavior[a,b,c]	RA-related treatment at MACE	Charlson score at MACE	MACE description
39 years 2005	[c]= 4.8	PDN, 10 mg/day MTX, 20 mg/week TD, 100 mg/day	1	Sudden death (2017)
52 years 2005	[a, b](2008) [c]= 2.49	PDN, 2.5 mg/day MTX, 15 mg/week ET, 50 mg/week	3	Left humeral artery occlusion (2015)[d]
46 years 2006	[b](2013) [c]= 3.4	PDN, 10 mg/day MTX, 17.5 mg/week	1	Pulmonary thromboembolism (2011)[d]
46 years 2006	[a,b](2018) [c]= 4.46	PDN, 2.5 mg/day MTX, 25 mg/week	1	Acute myocardial infarction (2011)[d]
57 years 2007	[a], [b](2014) [c] = 1.93	PDN, 10 mg/day MTX, 30 mg/week CQ, 150 mg/day	3	Sudden death (2016)
50 years 2012	[a] [c] = 2.82	PDN, 2.5 mg/day MTX, 25 mg/week	1	Acute coronary disease (2013)

[a]Patients who achieved at least one sustained remission status

[b]Patients with incidental erosions (year of detection)

[c]Cumulative DAS28 during the year previous to incidental MACE

[d]Confirmed MACE

PDN prednisone, *MTX* methotrexate, *TD* thalidomide, *ET* etanercept, *CQ* chloroquine

Table 4 Comparison of baseline CV-RF between patients with and without incidental MACE

CV-RF[a]	Patients with incidental MACE, $N=6$	Patients MACE-free, $N=179$	p
Age > 45 years old	5 (83.3)	58 (32.4)	0.018
Smoking status	0	32 (17.9)	0.592
Systolic blood pressure ≥ 140 mmHg	3 (50)	17 (9.5)	0.018
Diastolic blood pressure ≥ 90 mmHg	1 (16.7)	17 (9.5)	0.464
Increased serum CHO	2 (33.3)	143 (24)	0.634
Low serum HDL	6 (100)	130 (72.6)	0.344
Use of anti-hypertensive drugs	2 (33.3)	13 (7.3)	0.076
Diabetes mellitus diagnosis	0	11 (6.1)	1
BMI > 30 kg/m^2	4 (66.7)	30 (16.8)	0.011
First-degree relatives with premature heart disease	0	0	N.A
Advanced chronic kidney failure	1 (16.7)	1 (0.6)	0.064
CRP > 1 mg/L	4 (66.7)	75 (41.9)	0.404
Castelli ratio > 3	6 (100)	149 (83.2)	0.592
DAS28 > 2.6	6 (100)	177 (98.9)	1
Corticosteroid use	3 (50)	82 (45.8)	1

CV-RF cardiovascular risk factor, *CHO* serum total cholesterol, *HDL* high-density lipoprotein, *BMI* body mass index, *CRP* C-reactive protein, *DAS28* disease activity score (28 joints evaluated)

[a]No (%) of patients

was forced as the independent variable, failed to predict incidental MACE.

Discussion

The present study was developed in a well-characterized inception cohort of recent-onset Hispanic RA patients, in whom comprehensive rheumatologic evaluations were performed from 2004 onwards. In addition, cohort methodological recommendations were followed to ensure the quality of the data [20]. The analyzed patient data were from a real clinical setting, where patients had substantial comorbidities and were treated with traditional DMARDs [8, 11]. Accordingly, we consider our results to be of practical relevance, because they reflect the daily condition of the patients.

We first found that individual CV risk factors exhibited opposite behaviors during the first year of follow-up. The most prevalent baseline CV risk factors were high CRP (as expected in recent-onset RA patients) along with a high Castelli ratio and low HDL serum levels, which were present in the vast majority of our patients. Although a relationship between inflammation and lipid regulation and function has been described, the percentages of lipid-related abnormalities were similar to those detected in our national survey performed in adult Mexicans [11] and in a Dutch cohort of RA patients with controlled disease, in which 84% of the patients had high serum low-density lipoprotein (LDL) levels [25]. Conversely, hypertension, which is considered the most common comorbidity in Hispanic RA patients, demonstrated a lower prevalence than that reported in other countries [14] and was detected in a minority of our patients, and the finding may be related to our population age at disease presentation.

During follow-up, the prevalence of the most potentially reversible CV risk factors significantly decreased, although the high CRP and Castelli ratio > 3 were maintained in the vast majority of the patients after 1 year, when disease activity was under control and the lipid paradox might not be applicable. Concomitantly, the prevalence of obesity and corticosteroid use increased. Finally, the most frequent incident CV risk factors were related to dyslipidemia and obesity. In the literature, there are reports highlighting the under-identification and under-treatment of traditional (reversible) CV risk factors [25–29] which has been recognized by rheumatologists [30] and by primary care providers [31]. Moreover, in addition to being under-treated, treatment-related goals targeting CV risk factors appear unrealistic. Alemao et al. [32] found that a limited number of RA patients achieved hypertension target levels (25.8%), dyslipidemia target levels (16.4%), and diabetes target levels (48.7%) at 1 year after the index date. Interestingly, among patients with the same CV risk factor, RA patients less frequently achieved lipid and diabetes goals than non-RA patients. Van Breukelen-van der Stoep et al. [25] reported that only a minority of Dutch RA patients who had an indication were treated with antihypertensive drugs and statins, but among them, 50% and 86%, respectively, did not achieve the treatment target. Our data revealed that a higher percentage of patients achieved

the hypertension goals (50–75%), while few attained the lipid goals (16.7–28.6%) during the first year of follow-up, which was selected as it has been suggested that medical interventions are more intensive after patients enter a particular health care system [22]. The discrepancy between the treatment indication and the goals attained within CV risk factors may be related to a selective impact of inflammation on serum lipid levels [33]; a preferential awareness from (the) rheumatologist(s) regarding hypertension identification and its treatment; available low-cost therapies directed toward CV comorbidities; disparities in the indication and adherence of/to CV risk factor-directed-lifestyle interventions [34]; a lack of clear recommendations and conflicting advice, particularly regarding lipid management in RA patients [18, 31]; and evidence suggesting that strategies to prevent CV morbidity and mortality focused solely on controlling traditional CV risk factors may be less beneficial in RA compared with non-RA patients [35]. In addition, clinical inertia, which has been defined as a failure in starting or intensifying therapy when indicated by clinical guidelines [36], is common in the treatment of chronic diseases [37–40].

Finally, while both smoking cessation and weight loss guidance are considered of limited efficacy, a smoking habit and obesity did have opposite behaviors in our population; importantly, the percentage of RA patients with a smoking habit significantly decreased after 1 year (a similar tendency was seeing in trend analysis), as observed in Swedish and Danish patients [4, 19], highlighting the relevance of conceiving it as an achievable target. Conversely, high BMI progressively increased in our population, which differed from the BMI results obtained after 5 years of follow-up in early RA Swedish patients [4]. This finding may be unique to our population, as 30% of Mexican adults are obese, and it is projected that by 2050, the proportion of obese adult men and women will rise to 54% and 37%, respectively [41].

The second relevant result from our study was that only a minority of our patients met the age requirement to apply specific CV risk scores and a high-CV risk score at baseline was exceptional, particularly when the RRS was applied. A younger age at presentation in Latin American RA patients compared to Caucasians has been previously described and recognized [7, 8, 42], which may impact the epidemiology of CV comorbidity in Hispanic RA patients. Galarza-Delgado et al. [15] predicted the CV risk using six different risk calculators in 116 Mexican mestizo RA patients; similar to our findings, the ACC/AHA 2013 criteria classified the larger number of patients into the high-risk category; women also accounted for the majority of their patients, although the patient mean age was higher and disease duration longer compared to our patients, which may explain their higher percentage of patients in the high-risk category (23.2% vs. 17.9%).

Finally, we also found that few patients developed incidental MACE, and that age ≥ 45 years, high BMI, and high systolic blood pressure at baseline were more frequently identified in the patients with incidental MACE. In Mexico, five studies have reported an overall prevalence of 21% for CV disease in RA patients [14]. The lowest prevalence in our study (3.3%, none of the patients in the cohort had prevalent MACE at cohort entry) might be related to the identification and treatment of patients with recent-onset disease, the patient's age at presentation and a treat-to-target approach. In addition, important variations in CV event rates have been described across countries [43]. Regarding obesity, a "paradoxical" protective effect against CV disease has been described in RA patients [33, 44] or no effect at all [45]; importantly, the protective effect of obesity has been described in several chronic diseases and health statuses, but mostly in the elderly [46]. In addition, Stavropoulos-Kalinoglou et al. [47] observed an almost a linear relationship between BMI and CV disease risk in 378 RA patients, which were highly represented by women with a median age of 63 years and long-standing disease.

Some limitations of our study must be addressed. First, the study was conducted in a single tertiary care level center and in an observational cohort and, therefore, has the limitations of such cohorts [21], particularly follow-up losses that may be due to CV deaths; loss-to-follow-up bias occurs in prospective cohort studies and is considered a type of selection bias, which comes from any error in selecting the cohort participants (for instance, those with a more aggressive spectrum disease) and/or from factors affecting follow-up in the cohort [48]; in addition to the selection bias, internal validity of our study may had been affected by a type of information bias, namely misclassification bias [48]; we minimized misclassification bias applying standard definitions for MACE which were confirmed by an independent observer. Second, the number of MACE was limited; accordingly, regression analysis could not be performed. Third, we did not split clinical inertia into two separate concepts, namely appropriate and inappropriate inaction, to better account for the inner complexity of the doctor–patient relationship and shared decision-making; in such a context, clinical inertia may be a reasonable and adequate choice [39]. Fourth, BMI has been associated with the presence of additional CV risk factors [46], and our results may have been affected by such associations. Finally, the cohort was initiated in 2004 and we are presenting data from patients with follow-up up to June 2018; CV risk calculators measure a 10-year risk and only 42% of our patients had at least 10 years of follow-up, which limits the interpretation and generalization of the results related to the ability of CV risk calculators to predict MACE.

Conclusions

In conclusion, Hispanic RA patients represent a unique population in terms of disease presentation and outcomes; differences may be extended to CV-related risk factors and events. The literature evaluating this topic is scarce, and it remains unclear how the characteristics of the Latin American population, such as a younger age at presentation, high prevalence of lipid-related abnormalities and obesity, and disease control complexity, integrate and modulate CV events. An attempt to extrapolate international recommendations derived from patients from different ethnic groups, social determinants, and health care delivery systems to our population could be a mistake. In Mexico, obesity is at epidemic proportions, and our study demonstrated its association with CV events in RA patients. Realistic interventions are a priority and should include the patient's (and health professional) education and focus on strategies that translate patient education theory into practice [49]. In such a complex conceptual map, patient-centered care [50] emerges as a universal, practical, and ethical answer, which is increasingly recognized as necessary to complement the evidence-based health care imposed in the last decades.

Author contributions ICY: she participated in the conception and design of the study; she performed the statistical analysis; she is in charge of databases integrity of the early arthritis clinic; GGB: he participated in the conception and design of the study, he performed patient´s charts evaluations, and he reviewed the manuscript; VPR: she participated in the conception and design of the study, performed patient´s clinical evaluations; performed the statistical analysis, and drafted the manuscript; in charge of the early arthritis clinic.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval All procedures performed this study were in accordance with the ethical standards of the Institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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