Incidence and predictors of cardiovascular events in a cohort of patients with rheumatoid arthritis

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ABSTRACT

Introduction: An excess in cardiovascular (CV) morbidity and mortality has been recognized in Rheumatoid Arthritis (RA) patients when compared to the general population. Given the paucity of prospective data, our aim was to estimate the incidence of CV events and the contribution of traditional CVD risk factors and RA-related parameters to future events.

Methods: Incident fatal and non-fatal CV events (hospitalizations due to unstable angina, myocardial infarction, coronary artery revascularization procedures, stroke, or CV death) were assessed in a prospective cohort of RA women followed since 2007 and without CV events at cohort entry. The presence of traditional CV risk factors, disease characteristics, medication, carotid ultrasound, and biomarkers of inflammation and endothelial activation were evaluated at baseline. Univariate Cox proportional hazard models were used to identify risk factors for CV events.

Results: Among 106 women followed over 565 patient-years we identified 4 CV events (1 fatal stroke, 2 myocardial infarction and 1 unstable angina), which contributed to an incidence rate of 7 per 1000 person-years (95%CI 2.0- 13.9). Patients who developed CV events were older, but the distribution of other traditional CV risk factors was otherwise similar in both groups. Also, corticosteroid dosage and proportion of patients with carotid atherosclerotic plaques was higher in those with CV events. Erythrocyte sedimentation rate (ESR) (HR 1.036; 95%CI 1.005-1.067) and soluble intercellular adhesion molecule-1 (sICAM-1) serum levels (HR 1.002; 95%CI 1.000-1.003) significantly contributed to CV events. These results remained significant after adjusting for patients' age.

Conclusion: We found an incidence of cardiovascular events in women with RA of 7 per 1000 patent-years. This value is similar to that found in other Portuguese cohort of RA patients[1] and much higher than the incidence reported for the general Portuguese population. Markers of inflammation and endothelial activation contributed significantly to CV events, but the limited number of events prevents further analysis.

Keywords: Cardiovascular risk; Rheumatoid arthritis; Carotid intima-media thickness

INTRODUCTION

Cardiovascular disease (CVD) is a major public health problem and the leading cause of death in industrialized nations. In Portugal more than 37 000 deaths per year are attributed to CVD[1], representing almost 40% of all deaths.

Patients with inflammatory rheumatic diseases die prematurely, largely due to CVD. Atherosclerosis is now accepted to be a multifactorial process where inflammation plays a crucial role at each stage of the pathology. Atherosclerosis, the main determinant of cardiovascular (CV) morbidity and mortality, occurs prematurely in patients with inflammatory rheumatic diseases, such as Rheumatoid Arthritis (RA)[1]. These patients have almost a two-fold increased risk of CV events in comparison to the general population[2-3]. Traditional risk factors such as hypercholesterolemia, hypertension, diabetes, smoking and family history have long been identified as major contributors to the patho-

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genesis of atherosclerotic lesions. However, these risk factors are present in only about 50% of RA patients with CV events[7] and do not fully explain this increased risk. Moreover, Framingham 10-year risk equation underestimates the true CV risk in these patients[6]. Increased CV risk is likely to be an effect of the disease *per se*, reinforced by the presence of traditional CV risk factors[3-5]. Therefore, the search for additional mechanisms linking RA to CV disease is relevant.

Data deriving from cross-sectional studies have shown that RA patients have evidence of advanced preclinical carotid atherosclerosis compared to healthy controls [8] to a magnitude similar to that observed in patients with diabetes mellitus (DM)[9]. High-resolution B-mode ultrasonography of the carotid artery provides a non-invasive, valid and reproducible method for identifying atherosclerotic plaques, which reflect prevalent, clinical or preclinical CV disease and may predict future CV events[10]. Notably, in RA patients without traditional CV risk factors or events, an increased intima-media thickness (IMT) of the common carotid artery and evidence of focal plaques were predictive of incident CV events[11,12]

Given the paucity of prospective data, the extent to which traditional CV risk factors and RA-related parameters (inflammatory burden, activity and/or remission and treatment modalities) interact and/or contribute to atherosclerosis acceleration remains inconclusive[13]. According to a recent study, both traditional CV risk factors and markers of RA severity at baseline contribute to models predicting CV events in the subsequent 22 months[14].

In the present work, we re-evaluated at 5 years a prospective cohort of 106 women with RA, that were recruited between 2007 and 2008 for a cross sectional study of subclinical atherosclerosis[3]. At cohort entry none had clinically apparent CV disease or previous CV events. Baseline assessment included demographic and clinical characteristics, evaluation of traditional CV risk factors, biomarkers of inflammation and endothelial activation and carotid artery ultrasound.

AIMS

1. To estimate the incidence rate of CV events in women with RA
2. To identify baseline predictors of future CV events in RA.

MATERIAL AND METHODS

STUDY POPULATION AND DESIGN

To address the objectives mentioned above, we used a unique prospective cohort comprising 106 women who met the American College of Rheumatology (ACR) classification criteria for RA, without previous CV events at the time of inclusion in the study. At baseline a clinical and laboratorial evaluation of patients was performed. A carotid ultrasound to measure the intima media thickness (IMT) was performed in 61 patients. Patients were prospectively followed up for approximately 5 years and incident CV events identified. Additionally, we performed a reassessment of patient charts to identify the possible occurrence of CV events over that period. We defined as CV events acute myocardial infarction, unstable angina and coronary revascularization through percutaneous coronary intervention or coronary artery bypass grafting, stroke, transient ischemic attack, peripheral artery disease and death due to any of these events.

The subjects provided their informed consent. The study was conducted according to the Declaration of Helsinki and was approved by the Ethics Committee of Hospital Garcia de Orta.

EVALUATION AND MANAGEMENT OF RA PATIENTS

The following variables were assessed at baseline:

RA MANIFESTATIONS

A physician assessed patients for tenderness, swelling or deformity in 28 joints and for subcutaneous nodules, erosions, pulmonary fibrosis, *sicca* syndrome, serositis, amyloidosis, vasculitis and episcleritis. We used the 28-joint count and the erythrocyte sedimentation rate (ESR) to calculate the disease activity score (DAS 28) and Health Assessment Questionnaire (HAQ) to assess functional status.

CV RISK FACTORS ASSESSMENT

Hypertension was defined by the use of antihypertensive medications, diastolic blood pressure >= 90 mmHg or systolic blood pressure >= 140 mmHg; Diabetes Mellitus by the use of antidiabetic medications or fasting blood sugar >=126 mg/dL; hypercholesterolemia by the use of lipid lowering medications or fasting plasma cholesterol >=190 mg/dl or low-density lipoprotein (LDL) cholesterol 130 mg/dl. Patients were considered current smokers if they smoked at

baseline and former smokers if they had quit. We defined obesity as a body mass index > 30 Kg/m^2.

Anti-rheumatic medication

The use of methotrexate, biologic agents and corticosteroids was registered. In the case of corticosteroids starting date, baseline and cumulative dose were also recorded.

Laboratory studies

Laboratory tests [erythrocyte sedimentation rate (ESR), rheumatoid factor (RF), anti-cyclic citrullinated peptides (ACPA), cholesterol, low density proteins (LDL) and C-reactive protein (CPR)] were performed at baseline. Cytokines, biomarkers of endothelial cell activation and adipokines, such as OPG (osteoprotegerin), sRANKL (receptor activator of nuclear factor (NF)-kB ligand), TNF (tumor necrosis factor), tissue factor, thrombomodulin, sVCAM (soluble vascular cell adhesion protein 1), sICAM (soluble intracellular adhesion molecule 1), leptin, adiponectin, MIF (macrophage migration inhibitory factor), MCP-1 (monocyte chemoattractant protein 1), IL-10, IL-18 and insulin were also assayed.

Carotid ultrasound

Carotid intima-media thickness (cIMT) and the identification of carotid atherosclerotic plaques were assessed by B-mode ultrasonography in 61 patients at baseline.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 20 software and significance was defined as $p<0.05$ throughout.

Patients with incident CV events over the follow-up period were compared with those who did not by using an independent sample t-test and the Mann-Whitney test (comparison of continuous variables as appropriate), as well as the χ^2 for comparison of categorical variables.

Univariate Cox regression proportional hazard models were used to identify traditional and non-traditional risk factors for a CV event.

Follow-up was calculated as the period between first and last observation or the date of occurrence of a first CV event.

RESULTS

INCIDENCE OF CV EVENTS OVER A PERIOD OF FIVE YEARS

Among 106 women followed up over 565 patient-years

TABLE I. BASELINE CHARACTERISTICS OF RA WOMEN. RESULTS ARE EXPRESSED AS MEANS ± STANDARD DEVIATION, EXCEPT OTHERWISE STATED

Demographics	
Age, years	49.87±13.96
Caucasian race, n (%)	94 (88,7%)
Cardiovascular rick factors	
Current tobacco use	18 (17%)
Hypertension, n (%)	35 (33%)
Dislipidemia	21 (19.8%)
Diabetes, n (%)	5 (4,7%)
Obesity (BMI>30)	33 (31.1%)
Atherosclerotic carotid plaques (n=61)	9 (14.8%)
Disease characteristics at baseline	
Disease duration at baseline, years	9.68±7.34
DAS 28	4,17±1.31
HAQ	1.11±0.71
RF positive, n (%)	79 (74.5%)
ACPA positive, n (%)	68 (64.2%)
Erosions, n (%)	60 (56.6%)
Rheumatoid nodules, n (%)	15 (14.2%)
Vasculitis, n (%)	2 (1.9%)
Amiloidosis	0
Episcleritis	0
Sicca syndrome, n (%)	16 (15.1%)
Serositis, n (%)	1 (0.9%)
Pulmonary fibrosis, n (%)	2 (1.9%)
Medication	
Corticosteroids use, n (%)	58 (54.7%)
Corticosteroids dose at baseline, mg	3,05±3,29
Cumulative dose of corticosteroids at baseline, mg	11139.45±11660.9
Methotrexate, n (%)	89 (84.0%)
Biologic therapy, n (%)	67 (63.2%)

RF: Rheumatoid Factor; ACPA: anti-cyclic citrullinated peptides; DAS: Disease Activity Score; HAQ: Health Assessment Questionnaire; BMI: Body Mass Index; CRP: C-Reactive Protein; ESR: Erythrocyte Sedimentation Rate; n: number

we identified 4 CV events, which contributed to an incidence rate of 7 per 1000 person-years (95%CI 2.0--13.9), a higher incidence when compared to the general Portuguese population.

a) Characteristics of the patients

All the 106 RA women included in the original study were re-accessed in December 2014. One death was registered and no patients were lost to the follow-up. At inception, the average age was 49.87 ± 13.96 years and most patients were Caucasian (88,7%). 74.5% (79) were RF-positive and 62,3% (66) had ACPA antibodies at baseline. 56.6% (60) had erosions on the X-rays, 14.2% (15) had rheumatoid nodules, 1.9% (2) had vasculitis, 15.1% (16) had sicca syndrome, 0.9% (1) had serositis and 1.9% (2) had pulmonary fibrosis.

Patients had an average disease duration > 9 years (9.68 ± 7.34 y) and active disease, with a mean DAS28 of 4.2 (4.17 ± 1.31). Furthermore, most patients were on a disease-modifying anti-rheumatic drug (DMARD) at baseline (89% methotrexate, 63.2% biological agents and 54.7% prednisolone). The average dose of prednisolone at baseline was 3.05 ± 3.29 mg.

Hypertension, dyslipidemia, current tobacco use, diabetes mellitus and obesity were present in 33% (71), 19.8% (21), 17% (18), 4.7% (5) and 31.1% (33) of patients, respectively. Carotid ultrasound was performed in 61 patients, of which 14.8% had at least one carotid plaque (CP) at baseline. According to ultrasound characteristics, three types of CP were identified in the cohort studied (types 1, 2 and 4). Type 4 CP (homogeneous and hyperechoic) were the most frequently founded.

b) Occurrence of CV events

During 565 patient-years we identified 4 CV events (1 fatal stroke, 2 myocardial infarction and 1 unstable angina).

Patients who developed CV events were older, but the distribution of other traditional CV risk factors was otherwise similar in both groups. Also, corticosteroid dose and the proportion of patients with carotid

TABLE II. BASELINE CHARACTERISTICS OF RA WOMEN WITH AND WITHOUT CV EVENTS

	With CV event (n=4)	Without CV event (n=102)	p value
Age, years	63.5 ± 4.2	49.3 ± 13.9	0.039
Caucasians, n (%)	3 (75)	91 (89.2)	0.673
RA duration, years	6.57 ± 7.13	9.80 ± 7.35	0.304
RF positive, n (%)	4 (100)	75 (73.5)	0.570
ACPA positive, n (%)	4 (100)	64 (62.7)	0.384
Mean DAS 28	4.34 ± 1.30	4.17 ± 1.31	0.676
Mean HAQ	1.5 ± 0.89	1.10 ± 0.70	0.356
Corticosteroids dose at baseline, mg	6.25 ± 4.79	2.93 ± 3.2	0.104
Smokers, n (%)	1 (25)	17 (16.7)	0.740
Hypertension, n (%)	2 (50)	69 (67.6)	0.597
Dyslipidemia, n (%)	1 (25)	20 (19.6)	0.796
Diabetes, n (%)	0	5 (4.9)	1.000
Obesity (BMI>30), n (%)	2 (50)	31 (30.4)	0.438
Atherosclerotic carotid plaques (n=61), n (%)	2 (50)	7 (12.3)	0.100
Type of atherosclerotic plaques	4	4, 2, 1	–
CRP, mg/dL	0.78 ± 0.91	1.0 ± 2.52	0.987
ESR, mm/h	66.25 ± 30.84	36.43 ± 23.01	0.049
sVCAM1, ng/ml	1034.92 ± 458.49	1147.20 ± 450.33	0.629
sICAM1, ng/ml	1226.69 ± 568.25	637.88 ± 418.07	0.006

Results are expressed as means ± standard deviation, except otherwise stated. RA: Rheumatoid Arthritis; RF: Rheumatoid Factor; ACPA: anti-cyclic citrullinated peptides; DAS: Disease Activity Score; HAQ: Health Assessment Questionnaire; BMI: Body Mass Index; CRP: C-Reactive Protein; ESR: Erythrocyte Sedimentation Rate; sVCAM1: Soluble Vascular Cell Adhesion Protein 1; sICAM1: Soluble intracellular adhesion molecule 1; n: number

atherosclerotic plaques was higher in those with CV events (Table I). Erythrocyte sedimentation rate (ESR) (HR 1.036; 95%CI 1.005-1.067) and soluble intercellular adhesion molecule-1 (sICAM-1) serum levels (HR 1.002; 95%CI 1.000-1.003) significantly contributed to CV events. These results remained significant after adjusting for patients' age.

Disease duration, DAS28 and treatment modalities used were not significantly different between groups. All other RA-related parameters, such as the presence of extra-articular manifestations, the presence of RF or ACPA antibodies were not significantly different between groups.

c) Factors associated with occurrence of CV events

We searched for parameters predictive of the occurrence of CV events over the time in our cohort. Comparison between groups showed that, independently of other covariates, patients with CV events were significantly older. ESR and levels of sICAM at the baseline seem to be independent predictors of the occurrence of CV events.

DISCUSSION

In this prospective study we examined factors contributing to the occurrence of CV events in RA patients. Patients with RA die prematurely of CVD and although the inflammatory component of RA is better controlled with the current standard of care, CV risk remains the double of that observed in individuals without RA[21]. As reported before, carotid atherosclerosis predicts future coronary events in RA, whereas those patients with carotid plaques (CP), multiple CV risk factors, active disease and high corticosteroids dose are at an even higher risk[16]. Additionally, not only the presence of CP but also certain characteristics of these plaques seem to be of great importance. A thin cap and less fibrous tissue inside atherosclerotic plaques make them more vulnerable to rupture leading to CV events. It has been proposed that the proinflammatory status in patients with RA causes more and/or more vulnerable plaques, explaining part of the elevated risk of CV events in RA[17].

We focused on the identification of predictive factors for the occurrence of CV events over 5 years in our cohort of RA women with moderate disease activity and we studied the differences between groups with CV events and those without. The main finding of our study was that ESR and the levels of sICAM seem to be independent predictors for the occurrence of CV events. It has been suggested that the proinflammatory status of RA patients is associated with a higher CV risk. Indeed, Semb *et al.* showed that lowering disease activity could lower CV risk in RA patients[22]. These results led to the assumption that active disease with higher cytokine levels is associated with higher CV risk. ICAM-1 has been implicated in the development of a large number of diseases. Many studies have hypothesized that increased production of cell adhesion molecules (CAMs) on the vascular endothelium plays a role in the development of arterial plaque, with the suggestion from both in vitro and in vivo studies that the CAM production is increased by dyslipidemia.

In addition there was a trend suggesting that higher doses of corticosteroids at baseline (6.25 ± 4.79 *vs.* 2.93 ± 3.2; p=0.103) and higher prevalence of carotid atherosclerotic plaques (50% *vs.* 12.2%; p=0.100) were associated with CV events. As reported by Evans *et al*, a higher cumulative corticosteroid dose confers a higher risk of acute coronary syndromes in RA patients[12]. More recently Giles *et al.*[15] reported prospective data suggesting that subclinical carotid atherosclerosis progression in RA patients is potentially modified detrimentally by cumulative prednisone exposure. Zampeli *et al*. demonstrated that formation of new atherosclerotic plaques depended on traditional CVD risk and corticosteroid use[16].

The presence of CP can be helpful in identifying RA patients at risk for future CV events, as some characteristics of these plaques seem to be of great importance. Different types of CP have been identified together with their specific CV risk. Reilly *et al*[25] reported that plaques could be characterized as homogeneous (types 3 and 4) or heterogeneous (types 1 and 2), with the latter being described as a combination of hyperechoic, isoechoic, and hypoechoic plaques. They also concluded that homogeneous plaques were correlated with a fibrous lesion on pathological examination and the heterogeneous plaques were correlated with the presence of intraplaque hemorrhage and ulceration. Previous studies[24,26] reported that heterogeneous plaques were more likely to result in plaque hemorrhage and adverse neurological events. Cerebrovascular events were mainly present in type 1 and type 2 lesions, whereas, type 3 and type 4 lesions were mainly asymptomatic. They also reported that type 1 and type 2 lesions were associated more frequently with intraplaque hemorrhage or ulceration.

Echodopler can detect carotid atherosclerosis before the occurrence of events, thus identifying patients at higher risk. However, it is not yet clear in which patients performing this exam in cost-effective.

In this cohort of patients with moderate disease activity, those with CV events had mainly type 4 CP at baseline, unlike to what would be expected since they developed CV events. However, we only have data from baseline and it would be interesting to re-evaluate these patients by carotid ultrasound to find what happened to CP characteristics. Together with traditional CV risk factors, the higher levels of sICAM and high dose of corticosteroids used may have influenced the increased vulnerability of the CP leading to the occurrence of CV events.

Our cohort was followed up over 565 patient-years and four CV events were identified, which contributed to an incidence rate of 7 per 1000 person-years (95%CI 2.0-13.9). Curiously, despite our sample size this value was similar to that previously found in another Portuguese RA patients cohort[18] and much higher than the estimated incidence for the general Portuguese population without RA (estimated annual incidence of stoke – 2.99 and ischemic heart disease – 0.9 per 1000 women)[19, 20].

The main limitation of this study arises from being based on a small sample size. Consequently, a low number of events were found, probably resulting in insufficient statistical power to detect small differences between the patients with and without CV events and thereby limiting the conclusions that we can address.

Another limitation of our study is we only included women in order to eliminate the variability associated with gender and select a more robust and consistent sample. Cardiovascular disease is one area in which there are significant gender differences. Estrogens are responsible for the most important differences between men and women with regard to the prevalence of cardiovascular disease. Loss of estrogen-related protection is possibly the main reason for the increased incidence of cardiovascular disease after menopause. Although gender is increasingly perceived as a key determinant in health and illness, gender studies are still lacking and we consider that our study could represent an added value in this regard.

The fact that a significant percentage of patients are under biological therapy may have impacted the incidence of CV events by reducing the inflammatory burden. Yet, and despite biological therapy, incident CV events in Portuguese RA women is still higher than the estimated incidence for the general Portuguese women. In order to clarify the role of biologics we need to analyze a larger sample.

Taken together, these data imply that tight control of RA disease activity combined with strict CV risk factor management deserves further study as a strategy to reduce atherosclerosis and the occurrence of CV events in these patients. Therefore, optimal RA management should aim to achieve not only sustained disease remission but also successful traditional CV risk reduction and this may have implications in terms of treatment regimen selection.

CONCLUSION

We found an incidence of cardiovascular events in women with RA of 7 per 1000 patent-years. This value is similar to that found by another Portuguese RA patients cohort[18] and higher than the incidence estimated for the general Portuguese women. Markers of inflammation and endothelial activation contributed significantly to CV events, though the limited number of events prevents further analysis.

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