Cardiovascular Disease Is Related to Hypertension in Patients with Rheumatoid Arthritis: A Greek Cohort Study

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ABSTRACT. ***Objective.*** To evaluate the incidence of cardiovascular disease (CVD) among Greek patients with rheumatoid arthritis (RA) under medical followup, and to assess the contribution of traditional CVD and RA-specific factors associated with CVD development.

Methods. This is a historic cohort study; information was collected from medical records of patients who had > 2 years' followup. Sociodemographic, clinical, laboratory, and therapeutic variables were evaluated for association with development of CVD.

Results. A total of 325 RA patients were studied: 250 women, mean age at RA onset 44 ± 15 years, and 75 men, mean age at RA onset 51 ± 15 years; median followup was 10 years. Fourteen women (5.6%) and 12 men (16%) developed CVD (p = 0.004). Multi-adjusted analysis revealed that hypertension (hazard ratio 3.76, 95% CI 0.99–15.06) was associated with incidence of CVD; late age at disease onset (HR 1.07, 95% CI 1.04–1.11), elevated C-reactive protein (CRP) level 1 year after start of followup (HR 1.03, 95% CI 1.00–1.05), and leflunomide treatment (HR per 1 year of treatment = 1.02, 95% CI 1.00–1.05) were also positively associated with CVD development.

Conclusion. Hypertension was an important risk factor for CVD development in patients with RA. Late RA onset and inadequate early control of disease activity (as attested by CRP) remain additional risk factors. Leflunomide treatment may have a contributing effect. Early and effective treatment of RA and strict control of hypertension may modify the burden of CVD in RA patients. (J Rheumatol First Release Nov 15 2010; doi:10.3899/jrheum.100564)

Key Indexing Terms:
RHEUMATOID ARTHRITIS CARDIOVASCULAR DISEASES HYPERTENSION
LEFLUNOMIDE REMISSION INDUCTION

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disorder associated with excess cardiovascular morbidity and mortality in comparison with the general population. This is due to a combination of traditional and disease-specific risk factors, the relative contribution of which is open to debate, depending on the population studied and study design[1,2,3]. RA in Greece is milder due to a combination of genetic and environmental factors[4]. Results from a study in which 3 Greek rheumatologic centers participated showed that disease in the majority of RA patients in Greece was controlled[5].

There is a lack of studies evaluating the development of cardiovascular disease (CVD) and its contributing factors among the Greek RA population; our aim was to assess the epidemiology of CVD and to evaluate the effect of sociodemographic, lifestyle, clinical, and therapeutic factors on CVD development.

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MATERIALS AND METHODS

Data source. This was a historic cohort study: information was retrospectively collected for all RA patients from their medical records located at the Athens Euroclinic and the private practice of one author (FNS). RA was defined according to the 1987 revised American Rheumatism Association classification criteria[6].

Study sample. Three hundred thirty-nine patients with RA that visited our institutions from 1994 to 2007 and had followup of at least 2 years were included in the study. All patients had their last followup visit during 2007. Seven patients were excluded from this analysis because of history of CVD; 7 others were excluded because they had a diagnosis of RA before the age of 15 years. Thus, a total of 325 RA patients were studied: 250 women, mean age at RA onset 44 ± 15 years; and 75 men, mean age at RA onset 51 ± 15 years. Age at RA onset, duration of RA until the end of followup, and age at diagnosis of CVD were recorded for all patients. During followup all patients had regular visits, at least once a year, where complete physical examination was carried out and laboratory measures and therapeutic interventions were recorded.

Outcomes and definitions of variables. The main outcome of interest was CVD development. CVD events were defined according to the World Health Organization (WHO) International Classification of Diseases-10 as follows: (1) any coronary heart disease deaths or nonfatal events including myocardial infarction, angina pectoris, and other identified forms of

ischemia or heart failure as well as a number of chronic arrhythmias; (2) stroke; (3) hypertensive heart disease; and (4) peripheral artery disease. The definition used for CVD events was similar for the whole study period. Age at CVD event was also recorded.

Disease activity at enrolment in the study and at every followup visit was calculated using the Disease Activity Score 28-joint count (DAS28)[7]. Rheumatoid factor (RF) defined as a categorical variable was considered to be present if found to be positive during the disease course. The biochemical evaluation was carried out following the criteria of the WHO Lipid Reference Laboratories. C-reactive protein (CRP) data, when available, were recorded in the first year of followup, and then at least once every 6 months; CRP was measured using a latex enhanced immunoturbidimetric assay (Roche Integra, Athens, Greece). Hyperlipidemia was defined as total serum cholesterol level > 200 mg/dl, or low-density lipoprotein-cholesterol > 150 mg/dl, or the use of lipid-lowering agents. Blood lipids were measured using a chromatographic enzyme method. Diabetes mellitus was defined by history, fasting glucose > 125 mg/dl, or the use of hypoglycemic medications or insulin. Blood pressure was measured by the physician, with auscultation by mercury sphygmomanometer, following standard procedures. Systolic and/or diastolic blood pressure levels > 140/90 mm Hg at at least 2 different followup visits or use of antihypertensive medication characterized the participants as having hypertension. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2), and waist circumference was measured at the last visit. Obesity was defined as BMI > 30 kg/m^2. Menopause, years of menstruation, and use of hormone replacement therapy were recorded in all female patients.

Lifestyle characteristics at enrolment included evaluation of smoking habit (classified as never, current, or former smoker), as well as pack-years of smoking, physical activity status, and dietary habits. Classification of physical activity was based on the patients' responses to questions at the last visit, with the aim of identifying physical activity during the whole study course at the patient's occupation and during usual activities, including part-time jobs and notable non-occupational exercise (classified as sedentary or < 2400 kcal/day; moderately active during a substantial part of the day or 2400–3700 kcal/day; and hard physical work much of the time or > 3700 kcal/day). For dietary evaluation the MedDietScore at the most recent visit was used to assess the level of adherence to the Mediterranean diet, as validated[8]. The theoretical range of the score is 0–55; higher values indicate greater adherence to the Mediterranean diet.

The internal review board of our institution approved the study protocol. All patients were informed about the procedures and aims of the study, and gave consent to participate.

Statistical analysis. Continuous variables are presented as mean ± standard deviation, while categorical variables are presented as absolute and relative frequencies. CRP concentrations were expressed as median values because of the skewed distribution. CVD incidence was calculated as the ratio of events divided by total person-years of RA patients. Student's t test, Mann-Whitney U test, and chi-square criterion were used to evaluate crude associations between investigated variables and the development of CVD. Multi-adjusted analysis was performed using the Cox proportional hazards model with CVD event as endpoint. The proportion of event-free persons was recorded every year. Variables included in the model were age at start of followup, sex, history of hypertension, hyperlipidemia and diabetes, smoking habit, obesity, physical activity status, and adherence to Mediterranean diet through the MedDietScore at the start of followup. Colinear variables were not entered simultaneously in the model. From the factors relating to RA disease duration, DAS28, RF positivity, and CRP at start of followup and various visits were tested, as well as the use of antirheumatic drugs before CVD event. The assumption of proportionality was graphically assessed. SPSS 14 software (SPSS BI, Athens, Greece) was used for all calculations.

RESULTS

The median patient followup period was 10 years (first and third quartiles 6 and 17 yrs, respectively). The median time from disease onset to the visit to the clinic was 2 years (first and third quartiles 1 and 8.5 yrs). During the followup period, 14 out of 250 women and 12 of 75 men (5.6% and 16.0%, respectively; p = 0.004) developed a CVD event; thus, the incidence of CVD was 4 events per 3088 person-years among female RA patients and 14 events per 801 person-years among male RA patients (p = 0.001). In men, one of these events was fatal, 9 were acute coronary syndromes, and 2 were strokes; while in women the findings were 8 acute coronary syndromes, and the remainder were strokes or other CVD. All female CVD patients with the exception of one were postmenopausal. Among the demographic variables, RA onset was approximately 7 years earlier in women compared with men (p < 0.001; Table 1). Further, the mean duration from RA onset to CVD event was 11 ± 7 years in men (median 8, quartiles 5.25–15 yrs) and 12 ± 8 years in women (median 11, quartiles 6–18 yrs) (p = 0.09). Additionally, male patients were less physically active compared with females (p = 0.09). Patients of both sexes had similar dietary habits, and a moderate adherence to the Mediterranean diet was observed: the overall score achieved in both sexes was far from the theoretical highest value (i.e., 55) of the MedDietScore (for men 32 ± 6 and for women 31 ± 6).

Regarding the traditional CVD risk factors, unadjusted analyses revealed that prevalence of hypertension was at least 2 times more frequent in RA CVD patients compared with non-CVD patients (Table 2). Among the anthropometric indices, only waist circumference was greater in female CVD patients compared with non-CVD patients. Number of pack-years of smoking was borderline higher in CVD compared with non-CVD patients (p values < 0.10). History of diabetes, hyperlipidemia, obesity, BMI, menopausal status, family history of CVD, and level of adherence to the Mediterranean diet were found not to be associated with incidence of CVD (Table 2).

Regarding RA related risk factors for CVD, it was observed that age at onset of RA was positively associated with development of CVD (Table 3). In particular, a 1-year later age of RA onset was associated with 9% higher risk of CVD among women (hazard ratio per 1 year = 1.09, 95% CI 1.04–1.14), while in men the risk increased by 4% (hazard ratio per 1 year = 1.04, 95% CI 0.99–1.09). RF was associated with CVD development: RF-positive participants had a 2.39-times (95% CI 0.89–6.45) higher risk for developing a CVD event compared with those who were RF-negative. CRP levels at 12 months of followup were 2.5-times higher in CVD patients compared with non-CVD patients. None of the other RA related variables was associated with incidence of CVD. Regarding treatment, the use of leflunomide was more frequent in RA patients who developed CVD compared with the non-CVD group (Table 3). No association was observed between hypertension and use of leflunomide (p = 0.50). Results regarding combination drug treatment

Table 1. Sociodemographic and lifestyle characteristics and prevalence of CVD in male and female patients with RA. Data are mean ± standard deviation or median for the skewed variables, and relative frequencies.

Characteristic	Male, n = 75	Female, n = 250	p
Mean age at RA onset, yrs	51 ± 14	44 ± 15	0.001
Mean age at followup onset, yrs	56 ± 15	50 ± 15	0.005
Mean age at CVD event, yrs	62 ± 10	61 ± 13	0.86
Antirheumatic drugs, %			
Low-dose glucocorticoids	100	93	0.02
COX-2	2.7	6	0.11
Methotrexate	95	93	0.72
Cyclosporine	35	40	0.44
Gold	19	28	0.07
TNF-α inhibitors	69	68	0.77
Leflunomide	24	26	0.69
Prevalence of CVD, age, yrs (%)			Male-to-Female Ratio
< 30	0/6 (0)	1/59 (1.7)	0:1.7
30–39	1/7 (14.3)	0/40 (0)	> 1:0
40–49	3/21 (14.3)	4/52 (7.7)	1.85:1
50–59	5/20 (25)	5/55 (9.1)	2.75:1
60+	3/21 (14.2)	4/34 (11.8)	1.20:1
Total	12/75 (16.0)	14/250 (5.6)	2.85:1
Types of CVD events, n			
Fatal event	1	0	
Myocardial infarction	6	4	
Unstable angina	3	4	
Other CVD	0	3	
Stroke	2	3	

COX: cyclooxygenase; TNF: tumor necrosis factor; CVD: cardiovascular disease.

Table 2. Baseline sociodemographic, lifestyle, and clinical characteristics of RA patients according to development of cardiovascular disease (CVD). Data are mean ± standard deviation or median (for the skewed variables) and relative frequencies.

Characteristic	CVD Event, n = 26	CVD Event-Free, n = 299	p
Age at RA onset, yrs			
Men	53 ± 9	50 ± 15	0.43
Women	53 ± 15	44 ± 15	0.04
Physically active, %	5	25	0.01
MedDietScore (range 0–55)	32 ± 7	32 ± 6	0.98
Smoking, %	41	31	0.32
Pack-years	17 ± 23	7 ± 16	0.09
Hypertension, %	85	38	< 0.001
Hypercholesterolemia, %	73	63	0.34
Diabetes, %	23	13	0.24
Family history of CVD, %	47	27	0.17
Body mass index, kg/m^2	26.5 ± 6	25.6 ± 4	0.64
Obesity, %	24	15	0.44
Waist circumference, cm			
Men	92 ± 23	78 ± 23	0.26
Women	97 ± 3	82 ± 20	0.001
Menopause (% females)	93	75	0.001

are given in Table 3. As shown, the combination used most frequently was methotrexate and tumor necrosis factor-α (TNF-α) inhibitors, followed by methotrexate and cyclosporine, whereas leflunomide combinations were also associated with more frequent CVD events (Table 3).

The results of multi-adjusted analysis are presented in Table 4. Due to missing information, mainly on physical inactivity and MedDietScore, 174 patients were included in the model. Increased age at onset of followup was positively associated with the risk of CVD development. As for the traditional risk factors, only a history of hypertension considerably increased the risk of CVD after adjustment for age, sex, and other factors (Table 4), with a high hazard ratio of 3.76 (95% CI 0.99–15; which corresponds to a marginally nonsignificant value of p = 0.056). BMI was not associated with development of CVD; however, waist circumference in women was positively associated with CVD development: a 1-cm increase was independently associated with a 7% higher risk of CVD (95% CI 1–14). Nevertheless, the latter variable was not entered into the model because of colinearity with physical activity. The lifestyle factors (i.e., physical inactivity, dietary and smoking habits) did not seem to play a significant role in the development of CVD in patients with RA. Regarding use of antirheumatic drugs, leflunomide use was positively associated with the development of CVD, even after various adjustments were made (Table 4).

DISCUSSION

This was a historic cohort study of Greek patients with RA;

Table 3. Clinical, laboratory, and treatment characteristics related to RA according to the development of CVD. Data are mean ± standard deviation and median (for the skewed variables) as well as relative frequencies.

Characteristic	CVD Event, 26	CVD Event-Free, 299	p
Age at RA onset, yrs			
Men	53 ± 9	50 ± 15	0.43
Women	53 ± 15	44 ± 15	0.04
RA variables			
DAS28 at start of followup, % of > 3.6	81	83	0.48
Rheumatoid nodules, %	7.7	10.0	0.70
Bone erosions, %	60	55	0.82
RF-positive, %	78	55	0.02
CRP at start of followup, mg/l	23.4 ± 23.1; 18.0	17.8 ± 19.5; 10.0	0.35
CRP at 12 months of followup, mg/l	25.8 ± 26.9; 18.0	11.0 ± 12.7; 6.0	0.001
ESR at start of followup	47 ± 35	36 ± 26	0.36
Antirheumatic drugs (ever used), %			
Low-dose glucocorticoids	100	96	0.20
COX-2	4	9	0.38
Hydroxychloroquine	34	35	0.97
MTX	96	94	0.61
Cyclosporine	46	38	0.40
Gold	35	26	0.32
TNF-α inhibitors	77	67	0.31
Leflunomide	50	24	0.004
Antirheumatic drug combinations, %			
MTX and cyclosporine	24	20	0.63
MTX and leflunomide	27	6	< 0.001
Cyclosporine and leflunomide	12	3	0.02
Hydroxychloroquine and leflunomide	8	1	0.005
MTX and TNF-α inhibitors	77	63	0.15
Leflunomide and TNF-α inhibitors	0	8	0.13
Cyclosporine and TNF-α inhibitors	4	1	0.18
MTX, hydroxychloroquine, and gold	0	2	0.46

DAS: Disease Activity Score 28-joints; RF: rheumatoid factor; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; TNF: tumor necrosis factor; MTX: methotrexate.

the development of CVD events was evaluated and the contribution of traditional as well as RA related risk factors was assessed. The overall prevalence of CVD during the whole study period was 8%: 16% in men and 5% in women. The prevalence of CVD in RA patients, among different ethnic populations, has been reported to vary widely. Naranjo, *et al*, for the Quest-RA group in their multicenter study showed that the prevalence of CVD ranged from 3.7% in Argentina to 11.6% in the USA and 17.8% in Germany[9]. Variables such as genetics, lifestyle, diet, environment, or therapeutic interventions in different ethnic populations may contribute to these differences[10]. The incidence of CVD events in the general population in the USA is 21.4 and 8.9 events per 1000 person-years for men and women, respectively, by age 55–64 years[11]. In a recent study in Greece, the prevalence of CVD in the general population aged > 18 years was estimated to be 4.7% for men and 2.9% for women. However, the mean age of that cohort was 45 years at the beginning of followup. The same population was examined 5 years later and the CVD incidence was 15.2% for men and 9.2% for women[12]. Our cohort of RA patients had a mean age of 52 years at the beginning of followup and a median followup of 10 years. Thus, taking the observations above into consideration it can be estimated that the prevalence of CVD in RA patients in Greece is not greater than that observed in the Greek general population; however, the absolute risk for CVD in RA may be greater in younger patients. Patients, especially men, in the age group 30–39 years had 14.3% prevalence of CVD events (Table 1), similar to that observed in the 40–49 age group, as well as those over age 60 years. Although the number of patients is small, these observations are in accord with findings of Kremers, *et al*, that the absolute CVD risk in RA patients is similar to that in non-RA subjects who are 5–10 years older[13].

We think the major contributor to the relatively low incidence of CVD events in our RA population is the adequate disease control. Fifty-two percent of the patients had DAS28 > 5.5 at start of followup. Sixty-six percent had DAS28 < 3.6 at the first year and 72% after the second year of followup (data not shown). In our practice we advocate early use of disease-modifying antirheumatic drugs, in combina-

Table 4. Results from Cox proportional hazards model that evaluated sociodemographic, lifestyle, and clinical characteristics of RA patients (n = 174) in relation to development of cardiovascular disease (CVD) events (n = 13).

Factors	Hazard Ratio (95% CI)
Sociodemographic factors	
Age at start of followup (per 1 year)	1.07 (1.01–1.12)
Sex, female vs male	0.28 (0.07–1.05)
Traditional risk factors	
Hypertension (yes/no)	3.76 (0.99–15.06)
Hyperlipidemia (yes/no)	1.03 (0.22–4.75)
Diabetes (yes/no)	1.09 (0.20–5.92)
Family history of CVD (yes/no)	1.89 (0.58–6.09)
Obesity (yes/no)	0.71 (0.13–3.85)
Smoking (yes/no)	2.02 (0.53–7.69)
Physical inactivity (yes/no)	2.53 (0.31–20.56)
MedDietScore (0–55)	0.93 (0.82–1.04)
RA variables	
Duration of RA (per 1 year)	1.00 (0.92–1.09)
DAS28 at start of followup (> 3.6 vs < 3.6 yrs)	0.80 (0.41–1.54)
RF-positive (yes/no)	1.52 (0.35–6.62)
CRP at 12 mo of followup (per 1 mg/l)	1.03 (1.00–1.05)
Antirheumatic drugs	
Leflunomide use (per year of treatment)	1.02 (1.00–1.05)

RF: rheumatoid factor; CRP: C-reactive protein.

tion with small doses of steroids[14,15]. We do not use nonsteroidal antiinflammatory drugs (NSAID), since they are not disease-modifying agents and their prolonged use substantially increases cardiovascular risk[16]. To our knowledge our patient population was one of the best controlled in collaborative studies[5,17].

Aggressive control of RA disease in our cohort may have minimized the influence of RA related factors in CVD development. RF showed a positive correlation with CVD events, but this effect lost its significance, when age at start of followup, sex, and CRP levels at 12 months of followup were included in the multi-adjusted model. Conversely, inadequate control of disease 1 year after onset, expressed by high CRP levels, was associated with CVD development. Thus, the inflammatory burden of the RA disease may contribute significantly to development of CVD[18].

Among various bio-clinical and demographic variables, hypertension was the strongest factor associated with CVD development. Hypertension in RA is very important, highly prevalent, and may have strong relation to medications, and merits aggressive treatment[19]. Our cohort of patients, although they were not treated with NSAID and had close global monitoring (the department has a special clinical interest in prevention of CVD), revealed hypertension as the strongest variable related to development of CVD. The borderline lack of statistical significance can be attributed more to statistical limitations of the model. The absence of association with the other classical risk factors is in accord with recent studies showing that the presence of RA interacts with classical risk factors, ameliorating their significance[20].

In our study the patients with earlier disease onset were less likely to experience a CVD event compared with patients who had disease onset after 50 years of age. A 1-year difference in the age of RA onset was associated with 9% higher risk in women and 4% higher risk in men. Thus, late-onset RA should alert the doctor for tight control of coexisting traditional risk factors, since the possibility of CVD development is higher in those with recent-onset RA[21].

As for the contribution of medications to the development or prevention of CVD, treatment with TNF-α inhibitors did not show any association with CVD events. However, leflunomide use was associated with the development of CVD, although a direct relation with hypertension was not evident[22]. Solomon, *et al* described similar observations and pointed out that this finding may be related to inadequate control of systemic inflammation[23]. It is possible that leflunomide may interact with another medication; however, the numbers of events in our study were small and it did not have the power to detect the effect of leflunomide combinations.

Limitations of our study were the retrospective design, although we used data derived from accurate medical records over the years, and the small number of patients with CVD events. The study was not designed specifically to determine the relation between hypertension in RA patients and CVD development. A prospective study with long followup, preferably including a cohort of patients with early RA treated aggressively from the beginning, is needed.

We have shown that the prevalence of CVD events in a Greek RA population under successful treatment is not greater than that in the general population. Hypertension is an important risk factor for CVD events in patients with RA. Older age at RA onset is also associated with CVD events. Finally, when dealing with RA patients, aggressive treatment should be pursued from the onset of disease, aiming for remission; however, leflunomide use should be considered carefully in patients with RA when other classical or RA related risk factors for CVD are present.

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