Increase in Cardiovascular and Cerebrovascular Disease Prevalence in Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To determine whether the risk for cardiovascular and/or cerebrovascular disease (CCVD) is increased in rheumatoid arthritis (RA) compared to osteoarthritis (OA), a disease not known to be associated with increased CCVD.

Methods. In July 1999, a survey was administered to a sample of 11,572 patients (9,093 with RA, 2479 with OA) from the practices of 709 US community-based rheumatologists. Patients reported past and current myocardial infarction (MI), stroke (cerebrovascular accident, CVA), and lifetime congestive heart failure (CHF), and also provided demographic and clinical information. To estimate the impact of recall bias, medical records were obtained and reviewed for a 50% random sample of the patients reporting CCVD events, with 95% of CCVD reported events confirmed by record review.

Results. Patients with RA and OA differed across all demographic variables. In addition, each variable was significantly associated with MI, CHF, and CVA outcomes. Logistic regression was performed to measure the associations of these outcomes with RA as compared to OA, adjusting for age, sex, education level, smoking, income, hypertension, and body mass index. Compared with OA, patients with RA had the following increased risks: for current MI [odds ratio (OR), 95% confidence interval (95% CI)] 2.14, (1.48, 3.09), lifetime MI 1.28 (1.24, 1.33), CHF 1.43 (1.28, 1.59), current CVA 1.70 (1.29, 2.24), and lifetime CVA 1.005 (0.931, 1.196). The adjusted current and lifetime prevalences of MI were 0.76 and 4.14% for RA versus 0.35 and 3.23% respectively for OA; 0.86 and 3.02% (RA) versus 0.50 and 3.03% (OA) for CVA; and for lifetime CHF, 2.34% (RA) versus 1.64% (OA), respectively.

Conclusions. RA is associated with an increased risk for CCVD morbidity due to MI, CHF, and probably for CVA, and may be an independent risk factor for these events. (J Rheumatol 2003;30:36–40)

Key Indexing Terms:
RHEUMATOID ARTHRITIS OSTEOARTHRITIS
CARDIOVASCULAR DISEASE CEREBROVASCULAR DISEASE RISK

Once considered a disease of inflamed joints, rheumatoid arthritis (RA) is now recognized as a chronic progressive disease involving multiple organ systems. Among the cardiac manifestations, pericardial involvement received the most attention of clinicians[1,2]. Within the past 25 years, there has been mounting evidence for an increased burden of cardiovascular (CV) disease in patients with RA[3].

As early as 1976, studies suggested that patients with RA might suffer an increased risk of CV disease[4]. Since then, several studies have demonstrated an association between RA and CV disease mortality[4-14]. Reilly suggested that about half of all RA deaths can be attributed to CV disease[15].

To our knowledge, no studies to date have evaluated overall CV as well as cerebrovascular disease (CCVD) morbidity or the prevalence of CCVD events in patients with RA. Prevalence offers another insight into CCVD, as it serves as a measure of morbidity regardless of the association of CCVD and mortality. To further illustrate the role of RA in CCVD events, we used the National Data Bank for Rheumatic Diseases (NDB) to compare the prevalence of CCVD events in patients with either RA or osteoarthritis (OA).

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MATERIALS AND METHODS

Study sample. In July 1999, 11,572 patients registered in the NDB received a survey questionnaire in the mail. The NDB is a chronic rheumatic disease data bank in which enrolled patients complete detailed surveys at 6 month intervals[16]. Patients are added to the NDB on an ongoing basis. In July 1999 detailed questions regarding CV problems were added to the questionnaire.

Patients in the NDB were recruited by several methods. Seven hundred and eighty-three patients with OA (31.6% of all OA patients) and 464 patients with RA (5.1% of all RA patients) were seen for patient care at the Wichita Arthritis Center and followed in the Wichita data bank. Patients in this group have been described previously[17,18]. Five hundred and seventy-three RA patients were participants in a national inception cohort of RA (6.3% of all RA patients). Two thousand four hundred forty-six patients with RA (26.9 % of all RA patients) were recruited from community rheumatologists at the time leflunomide therapy was initiated as part of their routine medical care; 1,696 patients with OA (68.4% of all OA patients) and 5,610 patients with RA (61.7% of all RA patients) were contributed from the practices of US community rheumatologists.

Demographic and clinical data. At each questionnaire assessment, demo-

graphic variables were recorded, including sex, age, ethnic origin, education level, current marital status, smoking status, and total income. Study variables included the Stanford Health Assessment Questionnaire functional disability index (HAQ disability)[19,20], a visual analog (VAS) pain scale, a VAS global disease severity, and the Medical Outcome Study Short Form-36 (SF-36) mental and physical component scales[21]. To measure health related quality of life we used the VAS scale from the EuroQol[22,23]. Comorbidity was summarized in a major comorbidity score that included self-reported CV disease, cancer, stroke (cerebrovascular accident, CVA), diabetes and other endocrinopathies, renal disease, fractures, pulmonary disorders, neurological illnesses, and psychiatric illness[24]. These self-reported illnesses have been validated by comparison with data obtained by interviews, but specific validation studies have not been published. The comorbidity index was scored as the sum of the diseases reported by each patient.

Study questions. CCVD events were evaluated in 2 ways. First, a series of specific questions inquired about past (or lifetime) events such that patients reported any experience of heart attack/myocardial infarction (MI), coronary artery bypass surgery (CABG), balloon angioplasty, heart catheterization, heart valve problem, congestive heart failure (CHF), CHF treatment, high blood pressure, or CVA. Event responders were asked to indicate the date of the illness or procedure. Patients were provided with a check box next to the procedure and a place to write in the date. These past events represented the patients' CCVD experience up to the date of the questionnaire.

To validate patients' self-reporting accuracy, with patients' written consent and IRB approval, we reviewed medical records from a random sample of 50% (n = 395) of the patients reporting a CV event or procedure within the last 2 years. Ninety-five percent of patient reports were confirmed.

A second set of questions was a series of general comorbidity questions. For each health problem, e.g., heart attack, CVA, other heart condition (each one of these was a separate question) patients were asked to endorse up to 3 responses: I have this problem now, I had this problem in the past, and This problem limits my activities. There was no question regarding CHF in this section. Within the context of the recurring 6 month questionnaire, having a problem now refers to the last 6 months. We used these questions as a source of current or recent MI and CVA data.

Statistical methods. Logistic regression analysis was used to estimate the risk of CCVD among RA patients compared with OA patients. Covariates were selected on the basis of known demographic risk factors for CCVD. For covariates such as body mass index (BMI) and total income, data were missing in 10.4 and 8.1% of patients, respectively. To make use of these variables in multivariable regressions, missing values for the dependent variables in Tables 2-4 were imputed using the hot-deck method[25] and Solas software[26]. In these analyses we clustered on the 4 separate patient groups listed in the study sample description above. Clustering specifies that the observations are independent across groups (clusters) but not necessarily within groups[27]. In addition, specifying the cluster option in the Stata software used in these analyses also implies robust analyses, or the use of the Huber/White/sandwich estimator of variance in place of the traditional calculation. Statistical significance was set at p = 0.05, and all tests were 2-tailed.

RESULTS

Demographic and clinical status. Of a total sample of 11,572 patients, 78.6% had RA, and 21.4% had OA (Table 1). Most differences in demographic and clinical variables were statistically significant between the RA and OA groups, although such differences are not necessarily clinically significant. The OA patients tended to be older than the RA patients; the mean age was 66.0 in OA, and 59.8 in RA. OA patients were also more overweight; the mean BMI was 29.9 (SD 7.0) in OA patients, and 27.0 (SD 6.1) in RA patients.

The prevalence of hypertension was higher among OA patients (37.4%) than in RA patients (28.1%). Forty-four percent and 13.1% of RA patients were either former or current smokers, respectively, compared to only 36.5 and 6.1% of OA patients. The OA group also had a higher prevalence of comorbidity than the RA group, as measured by the Major Comorbidity Score. OA patients scored 0.9 points out of a possible 11, while the RA patients scored 0.8.

Table 1. Demographic and clinical characteristics of study patients.

	RA (n = 9093)		OA (n = 2479)		
	% Reporting	Mean (SD) or %	% Reporting	Mean (SD) or %	p*
Age, yrs	99.0	59.8 (13.0)	99.9	66.0 (11.2)	0.000
Sex, % male	99.9	23.1	99.9	18.3	0.000
High school graduate	99.0	88.2	98.9	91.5	0.000
Total income	91.9	43,296 (28002)	91.3	42,296 (26978)	0.121
Caucasian	99.9	91.3	100	94.7	0.000
Current smoker	95.4	13.1	96.0	6.1	0.000
Past smoker	95.4	44.0	96.0	36.5	0.000
Hypertension	99.9	28.1	99.9	37.4	0.000
BMI	89.6	27.0 (6.1)	89.2	29.9 (7.0)	0.000
Major comorbidity score	99.9	0.8 (1.0)	99.9	0.9 (1.1)	0.000

* p value is for t test for continuous variables and chi-square test for categorical variables.

Disease severity. Scores on the Stanford Health Assessment Questionnaire (HAQ) index of functional disability were slightly higher in RA patients (Table 2); 1.1 versus 0.9 in OA patients out of a possible 0–3 score range. RA patients scored better on the 36 Item SF-36 mental and physical component scales, scoring 30.7 out of a possible 50, while the OA patients scored 29.7. Scores on the European Quality of Life Visual Analogue Scale (EuroQol VAS) and the Visual Analogue Global Disease Severity scale were equivalent between the 2 groups.

Associations with CCVD. To illuminate the risk of CCVD associated with RA versus OA, we used age, sex, ethnicity, education, BMI, smoking status, and hypertension as covariates (Tables 3–5). Comorbidity was not included as a covariate due to possible confounding effects. However, analyses including comorbidity variables did not show altered regression results (data not shown).

Table 2. Measures of disease severity.

	RA (n = 9093)		OA (n = 2479)		
	% Reporting	Mean (SD)	% Reporting	Mean (SD) or %	p*
HAQ	99.2	1.1 (0.7)	98.7	0.9 (0.6)	0.000
SF-36 PCS	90.5	30.7 (8.8)	89.8	29.7 (8.5)	0.000
Global Severity, VAS	98.6	3.4 (2.5)	97.7	3.4 (2.5)	0.057
EuroQol QOL	95.2	65.3 (20.8)	94.9	65.0 (20.9)	0.437
Pain, VAS	98.5	3.4 (2.8)	98.1	4.1 (2.7)	0.000

Table 3. The association of myocardial infarction with RA.

	OR	z	p	95% CI
Current (n = 11,572)				
Full model				
RA, y/n	2.137	4.040	0.000	1.479–3.088
High school graduate, y/n	0.472	–9.270	0.000	0.402–0.553
Smoking, current/never	2.055	3.960	0.000	1.439–2.935
Smoking, past/never	1.179	4.120	0.000	1.090–1.276
White, y/n	3.288	1.920	0.055	0.973–11.104
Current hypertension, y/n	2.211	6.510	0.000	1.741–2.808
Age, yrs	1.050	9.000	0.000	1.039–1.062
Sex, male/female	2.116	4.780	0.000	1.556–2.876
Body mass index, units	1.031	2.590	0.010	1.007–1.055
Lifetime (n = 11,572)				
Full model				
RA, y/n	1.284	15.427	0.000	1.244–1.325
High school graduate, y/n	0.798	–3.233	0.001	0.696–0.915
Smoking, current/never	1.750	3.713	0.000	1.303–2.352
Smoking, past/never	1.589	23.974	0.000	1.530–1.650
White, y/n	1.437	2.269	0.023	1.051–1.966
Current hypertension, y/n	1.491	3.666	0.000	1.204–1.845
Age, yrs	1.053	11.938	0.000	1.044–1.062
Sex, male/female	2.470	15.229	0.000	2.199–2.775
Body mass index, units	1.019	17.450	0.000	1.017–1.021

Table 5. The association of stroke with RA.

	OR	z	p	95% CI
Stroke current (n = 11,572)				
Full model				
RA, y/n	1.703	3.837	0.000	1.298–2.236
High school graduate, y/n	0.706	–2.662	0.008	0.546–0.912
Smoking, current/never	1.002	0.007	0.995	0.569–1.763
Smoking, past/never	1.166	0.447	0.655	0.595–2.281
White, y/n	1.374	0.713	0.476	0.574–3.287
Current hypertension, y/n	2.045	4.396	0.000	1.487–2.814
Age, yrs	1.031	4.574	0.000	1.017–1.044
Sex, male/female	0.824	–1.220	0.222	0.604–1.124
Body mass index, units	0.989	–0.733	0.463	0.960–1.018
Stroke ever (n = 11,572)				
Full model				
RA, y/n	1.055	0.830	0.404	0.931–1.198
High school graduate, y/n	0.949	–0.520	0.606	0.777–1.159
Smoking, current/never	1.281	6.330	0.000	1.187–1.384
Smoking, past/never	1.133	1.070	0.285	0.902–1.423
White, y/n	1.039	0.250	0.803	0.768–1.406
Current hypertension, y/n	1.963	13.320	0.000	1.778–2.168
Age, yrs	1.040	6.530	0.000	1.028–1.053
Sex, male/female	1.197	2.510	0.012	1.040–1.376
Body mass index, units	1.002	0.180	0.855	0.981–1.024

After adjusting for the covariates, RA was associated with an increased risk for current MI of [odds ratio, OR (95% confidence interval, CI)] 2.14 (1.48, 3.09) and lifetime MI of 1.28 (1.24, 1.33). For current CHF, the results were 1.43 (1.28, 1.59). For current CVA the results were 1.70 (1.29, 2.24), and for lifetime CVA the results were 1.005 (0.931, 1.196).

The current and lifetime adjusted rates for MI and CVA, and the current CHF rates among RA and OA patients are shown in Table 6.

To be certain that these results were not unduly influenced by the group of patients with more severe disease enrolled just as they were initiating leflunomide therapy, analyses were conducted after excluding these RA patients. The OR and 95% CI for these analyses were very close to the results using the full data set. Specifically, for current and lifetime MI the results were 2.05 (1.47, 2.86) and 1.27 (1.25, 1.30); for CHF 1.36 (1.18, 1.57); and for CVA 1.90 (1.74, 2.07).

Finally, to examine the association of CCVD with RA and OA with risk factors removed, we re-ran the analyses in Tables 3–5 after removing the adjustments for hypertension, smoking, and BMI. The odds ratios were as follows: current MI, 1.94 (1.15, 3.27), lifetime MI 1.26 (1.20, 1.33), CHF 1.29 (0.98, 1.70), current CVA 1.71 (1.01, 2.90), and CVA ever 1.02 (0.93, 1.12). These data are very similar to the results in Tables 2–5, the small differences reflecting differences in the groups for the adjustment variables.

Table 4. The association of lifetime congestive heart failure with RA (n = 11,572).

	OR	z	p	95% CI
Full model				
RA, y/n	1.426	6.446	0.000	1.280–1.588
High school graduate, y/n	0.792	–2.072	0.038	0.636–0.987
Smoking, current/never	1.319	1.209	0.227	0.842–2.067
Smoking, past/never	1.390	6.194	0.000	1.252–1.542
White, y/n	1.389	2.026	0.043	1.011–1.900
Current hypertension, y/n	1.479	3.076	0.002	1.153–1.897
Age, yrs	1.057	19.242	0.000	1.051–1.062
Sex, male/female	1.227	6.462	0.000	1.153–1.305
Body mass index, units	1.037	5.013	0.000	1.023–1.052

Table 6A. Adjusted* prevalence (per 100 patients) of current cardiovascular and cerebrovascular events among patients with RA and OA.

	MI	Stroke
RA, % (95% CI)	0.76 (0.68, 0.84)	0.86 (0.71, 1.03)
OA, % (95% CI)	0.35 (0.26, 0.28)	0.50 (0.42, 0.60)

* Adjusted for variables in Tables 2–5.

Table 6B. Adjusted* prevalence (per 100 patients) of lifetime cardiovascular and cerebrovascular events among patients with RA and OA.

	MI	CHF	Stroke
RA, % (95% CI)	4.14 (4.11, 4.19)	2.34 (1.95, 2.81)	3.02 (3.03, 3.38)
OA, % (95% CI)	3.23 (3.15, 3.31)	1.64 (1.51, 1.78)	3.03 (2.68, 3.41)

* Adjusted for variables in Tables 2–5.

DISCUSSION

For many years, it has been recognized that mortality from CCVD is increased in RA patients compared to the general population[4-10]. However, there have been limited data on the effect of RA on CV and cerebrovascular-related morbidity. Recently a study of 76 RA patients compared with 641 community controls in Glasgow suggested a borderline increase in CVA in RA patients but not an increase in MI[28], although the sample may have been too small to adequately assess the endpoints. Our results suggest that patients with RA are at increased risk of MI, CHF, and probably CVA when compared to the general age and sex matched population.

Until recently, there has been limited information on the potential pathologic relationship between RA and CCVD. Several studies have now demonstrated an association between markers of inflammatory activity and manifestations of CV disease. Liuzzo, *et al* found that higher levels of C-reactive protein (CRP) was associated with poorer outcome for patients with unstable angina[29]. This finding is supported by van der Wal, *et al*, who found infiltration of T cells and macrophages to be present in the initiation and progression of atherosclerotic lesions[30]. Moreover these inflammatory infiltrates were present in the majority of thrombotic lesions associated with fatal MI and with lesions of patients with unstable angina. In a nested case control study, Ridker and colleagues found high sensitivity CRP to be the strongest predictor of CV disease in women, greater in fact than lipid or homocysteine levels[31]; and McEntegart, *et al* found an increase in thrombotic markers in RA patients compared to community controls[28]. Additionally, we have recently shown in abstract form that erythrocyte sedimentation rates predict mortality in patients with RA, OA and fibromyalgia[32].

Although we found an increase in current CVA in RA compared to OA patients, we did not find such an increase when lifetime history of CVA was considered. The reason for this is not clear, but might be related to the general seriousness of CVA and the decreased overall survival associated with that condition, thereby limiting our ability to identify a true difference between the groups.

Like other cross sectional surveys this study is subject to bias in patient recall. We were reassured, however, to find that among the sample of patients for whom we validated their reported CCVD events > 95% had those events confirmed by medical chart review. Our study can also be criticized in the selection of control patients. We utilized responses from OA patients recruited from the same practices as the RA patients. We assumed that OA is not associated with CCVD, and that the risk of CCVD among patients with OA is similar to that of the general population. However, to fully understand the association of CCVD and RA, population based controls are necessary, as controls with OA derived from specialty practices may have characteristics that differ significantly from the general population.

Among the biases of our study that relate to left censoring by death, it is known that CV mortality is increased in RA. It is therefore likely that some individuals who might have become cases died before they had a chance to enter the cohort. In this instance, our data will reflect possible additional cases of CV morbidity. An additional possible bias is that patients may have died of CV disease and are not identified by the study. Once again, this would mitigate against finding an increase in CCVD events. Therefore, the likely possibility of such biases, if they are operative, would be to reduce the apparent risk of CCVD in this cohort of RA patients.

An additional limitation of our study is that we did not investigate corticosteroid usage. The effect of steroid usage is known to be cumulative. Because steroids are used periodically and in varying doses, and may have been used for very many years, we did not believe that data collected using a patient-based survey would be sufficiently accurate to measure lifetime steroid exposure. Studies are currently under way using reliable contemporary measurement of steroid use, and these data will be the subject of future reports.

To our knowledge, this is the first study examining CCVD morbidity among RA patients. Our data confirm the association of RA with CCVD as compared to patients with OA, after adjusting for demographic and clinical factors. As such, the effects of RA on morbidity as well as mortality should be accounted for in estimates of the RA burden of illness and should be considered in future studies examining therapies for RA.

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