ARTHRITIS & RHEUMATISM
Vol. 52, No. 3, March 2005, pp 722–732
DOI 10.1002/art.20878

Cardiovascular Death in Rheumatoid Arthritis

A Population-Based Study

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Objective. **To determine whether systemic inflammation confers any additional risk for cardiovascular death among patients with rheumatoid arthritis (RA), after adjusting for traditional cardiovascular risk factors and comorbidities.**

Methods. **Using the population-based data resources of the Rochester Epidemiology Project, we assembled an incidence cohort of all Rochester, Minnesota residents ages ≥18 years who first fulfilled the American College of Rheumatology 1987 criteria for RA between January 1, 1955 and January 1, 1995. All subjects were followed up longitudinally through their complete (inpatient, outpatient) medical records, beginning at age 18 years and continuing until death, migration, or January 1, 2001. Detailed information on the occurrence of various cardiovascular risk factors (personal history of coronary heart disease [CHD], congestive heart failure, smoking, hypertension, dyslipidemia, body mass index [BMI], diabetes mellitus, menopausal status) as well as indicators of systemic inflammation and RA disease severity (rheumatoid factor [RF] seropositivity, erythrocyte sedimentation rate [ESR], joint swelling, radiographic changes, RA nodules, RA complications, RA treatments, disease duration) and comorbidities were collected on all subjects. Causes of death were ascertained from death certificates and medical records. Cox regression models were used to estimate the independent predictors of cardiovascular death.**

Results. **This inception cohort comprised a total of 603 RA patients whose mean age was 58 years, of whom 73% were women. During a mean followup of 15 years, 354 patients died and cardiovascular disease was the primary cause of death in 176 patients. Personal history of CHD, smoking, hypertension, low BMI, and diabetes mellitus, as well as comorbidities, including peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, dementia, ulcers, malignancies, renal disease, liver disease, and history of alcoholism, were all significant risk factors for cardiovascular death ($P < 0.01$ for each). Multivariable Cox regression analyses, controlled for cardiovascular risk factors and comorbidities, revealed that the risk of cardiovascular death was significantly higher among RA patients with at least 3 ESR values of ≥60 mm/hour (hazard ratio [HR] 2.03, 95% confidence interval [95% CI] 1.45–2.83), RA vasculitis (HR 2.41, 95% CI 1.00–5.81), and RA lung disease (HR 2.32, 95% CI 1.11–4.84).**

Conclusion. **These results indicate that markers of systemic inflammation confer a statistically significant additional risk for cardiovascular death among patients with RA, even after controlling for traditional cardiovascular risk factors and comorbidities.**

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease of unknown etiology, affecting ~1% of the adult general population (1,2). Patients with RA not only have a higher chronic disease burden (3,4) but also may have increased morbidity and mortality from cardiovascular disease compared with persons without RA (2,5–21).

Although the ultimate cause of atherosclerosis is unknown, evidence from both laboratory and epidemiologic research suggests that systemic inflammation

Supported in part by the NIH (grant R01-R4-6849 from the National Institute of Arthritis and Musculoskeletal and Skin Diseases and grant AR-30582 from the USPHS). Dr. Nicola's work was supported by a fellowship from the Luso-American Foundation.

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Submitted for publication August 29, 2003; accepted in revised form December 2, 2004.

plays a critical role (22–25). If this is so, it could explain the higher than expected rates of cardiovascular disease observed in patients with chronic systemic inflammatory diseases such as RA (26). However, observational studies published to date provide little insight as to the etiologic mechanisms behind these findings. The aim of the present study was to determine whether markers of systemic inflammation and indicators of RA disease severity confer any additional risk for cardiovascular death after adjusting for traditional cardiovascular risk factors and comorbidities in a population-based incidence cohort of patients with RA.

PATIENTS AND METHODS

Data collection. The population of Rochester, Minnesota is optimally suited for investigation of the long-term outcomes of patients with RA. A medical records linkage system allows ready access to the complete (inpatient and outpatient) records from all health care providers for the local population, including the Mayo Clinic and its affiliated hospitals, the Olmsted Medical Center and its affiliated community hospital, local nursing homes, and the few private practitioners. The potential of this data system for population-based research has been previously described (27,28). This system ensures virtually complete clinical and vital status information on all clinically recognized cases of RA among Rochester residents.

Using this data resource, we retrospectively assembled a population-based incidence cohort of all patients with RA first diagnosed between January 1, 1955 and January 1, 1995 among Rochester, Minnesota residents ≥18 years of age, as previously described (29–31). All patients fulfilled the American College of Rheumatology (ACR; formerly, the American Rheumatism Association) 1987 criteria for RA (32). The RA incidence date was defined as the first date of fulfillment of 4 of the 7 diagnostic criteria. All subjects were followed up longitudinally through their complete medical records beginning at age 18 years (or date of migration to Olmsted County for those who first became residents after age 18 years) and continuing until death, migration from Olmsted County, or January 1, 2001.

Three trained nurse abstractors collected the data according to a prespecified and pretested protocol. Iterative comparative studies were performed in which samples of medical records were reviewed by all nurse abstractors. Guided by the results of these studies, the protocol and data entry instruments were revised to reduce ambiguity and ensure agreement. Regular weekly meetings were held throughout the data abstraction period to identify and correct problems in data collection, interpretation of definitions, and application of study criteria. Before commencing data analysis, an extensive series of checks for data consistency, proper sequences of dates, and an evaluation of missing or incomplete data were performed. When necessary, medical records were reviewed again, and questions were resolved by consensus of the investigative team.

Ascertainment of outcomes. All causes of death (including both underlying and contributory causes) as reported in the medical records and/or death certificates were collected for all deceased patients. All patients (irrespective of residency status) were tracked nationally to ascertain vital status, and death certificates were obtained from the respective states for subjects who were deceased out of state. For this study, cardiovascular death included the following causes of death: coronary heart disease (CHD) deaths (i.e., old or previous or acute myocardial infarction, stable or unstable angina pectoris, CHD, other forms of chronic ischemic heart disease), arrythmias, dysrhythmias, hypertension, congestive heart failure (CHF), pulmonary edema, rheumatoid heart disease, valvular stenosis or insufficiency, and ruptured aortic aneurysm. As reported previously (33), the death certificate diagnoses of out-of-hospital CHD deaths and sudden cardiac deaths in Rochester, Minnesota have high sensitivity and positive predictive values of 91% and 96%, respectively.

Cardiovascular risk factors. Detailed information was collected regarding each clinically documented occurrence of the following cardiovascular risk factors during the entire followup period. Dyslipidemia was defined according to the cutoff values proposed by the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) guidelines (34,35). Elevated levels of low-density lipoprotein cholesterol were defined as values ≥160 mg/dl, elevated total cholesterol as ≥240 mg/dl, below-normal high-density lipoprotein cholesterol as <40 mg/dl, and elevated triglycerides as ≥150 mg/dl. Diabetes mellitus was defined according to the diagnostic criteria adopted by the World Health Organization consultation group in 1998, with a determination of fasting plasma glucose ≥126 mg/dl or a 2-hour plasma glucose ≥200 mg/dl following a glucose load, a clearly documented history of diabetes, and/or current treatment for hypoglycemia (including insulin) (36). The date at which subjects first fulfilled these diagnostic criteria was considered the diabetes mellitus incidence date. Hypertension was defined according to the criteria of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure (37,38). Subjects with 2 or more ambulatory blood pressure readings ≥140 mm Hg systolic and/or 90 mm Hg diastolic were considered to have hypertension, and the first date of fulfillment of these criteria was considered the hypertension incidence date. Subjects who did not fulfill these criteria but who had a physician's diagnosis of hypertension in their medical records and/or were receiving antihypertensive agents were also considered to have hypertension, and the earliest recorded date of hypertension diagnosis was considered the hypertension incidence date.

Cigarette smoking status was determined at the RA incidence date and categorized as current, former, or never. Use of other tobacco products (e.g., pipe, cigar) was not considered. We recorded the first documentation of the adult (≥18 years) patient's height and weight as well as all weight changes of ±15 pounds (6.8 kg) and all height changes of ±2 inches (6 cm) over the entire followup period. Body mass index (BMI) (defined as weight in kilograms divided by the square of the height in meters) was calculated at each encounter. High BMI (obesity) was defined as ≥30 kg/m^2 and low BMI as <20 kg/m^2. Obesity was defined in accordance with the guidelines

on the Identification, Evaluation and Treatment of Overweight and Obesity in Adults (39). Other variables included as potential predictors of cardiovascular death were personal history of CHD, family history of CHD in first-line descendents, and menopausal status at RA incidence (pre- versus postmenopausal). Personal history of CHD included angina pectoris, coronary artery disease, coronary insufficiency, ischemic heart disease, myocardial infarction (including silent events), CHF, pulmonary edema, and coronary revascularization procedures (i.e., coronary artery bypass graft, percutaneous angioplasty, insertion of stents, and atherectomy). CHF was defined according to the Framingham Heart Study criteria (40). Selected comorbid conditions were ascertained through review of the medical records and classified using the Charlson comorbidity index (41), and included peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, dementia, ulcers, malignancies, renal disease, liver disease, and history of alcoholism.

RA disease characteristics. RA-related risk factors included RF seropositivity (≥40 IU/ml), erythrocyte sedimentation rate (ESR), tender and/or swollen joint counts, erosions, periarticular osteoporosis, and/or destructive changes on radiographs, rheumatoid nodules (absent/present), RA complications, disease duration, and the use of disease-modifying antirheumatic drugs (DMARDs) and/or corticosteroids. The ESR at the RA incidence date was defined as the highest recorded ESR during the first year after the RA incidence date. Sustained elevation of the ESR was defined as ≥3 recorded ESR values of ≥60 mm/hour, with a minimum interval of 30 days between 2 measurements. Joint tenderness and/or swelling was categorized as small-joint involvement (including wrists, ankles, metacarpophalangeal, metatarsophalangeal, distal interphalangeal, and/or proximal interphalangeal joints of the hand and foot) and large-joint involvement (including the elbow, shoulder, hip, and knee joints). RA complications included rheumatoid lung disease (i.e., pulmonary vasculitis, intrapulmonary rheumatoid nodules, Caplan's syndrome, chronic pleuritis, interstitial pneumonitis and fibrosis, bronchiolitis), vasculitis (i.e., various forms of vasculitis, arteritis, vasculopathy, mononeuritis multiplex), Felty's syndrome, Sjögren's syndrome, rheumatoid myocarditis, and others (e.g., scleritis, episcleritis, uveitis, bronchiolitis obliterans). Use of corticosteroids and DMARDs was classified as use within the first year after the RA incidence date, and separately as ever/never, and included intramuscular or oral gold, sulfasalazine, hydroxychloroquine, azathioprine, D-penicillamine, methotrexate, leflunomide, etanercept, infliximab, immunosuppressants, and alkylating agents.

Statistical analysis. Potential predictors of cardiovascular death included cardiovascular risk factors, comorbidities, and RA disease characteristics (see Table 1 for complete list). All potential predictors were assessed at the RA incidence date and throughout followup, except family history of CHD, smoking status, and menopausal status, which were assessed only at baseline. Laboratory values and radiographic assessments closest to the RA incidence date (within 30 days) were considered to be baseline values. DMARD exposures of <30 days' duration were not included in the analyses.

Cox regression models were used to estimate the influence of all potential predictors on cardiovascular death. The primary analyses included cardiovascular deaths listed as the underlying cause of death. All analyses were also repeated by including patients whose cardiovascular disease was listed as a contributory cause of death. Age was used as the time scale for these models, and the analyses were stratified by sex. The age at which patients entered the study was their age at the RA incidence date, with the end point being death or last followup. Hazard ratios (HRs) were computed univariately for each potential predictor. Factors assessed throughout followup were modeled as dichotomous time-dependent covariates. These time-dependent covariates allow patients to be changed from the unexposed category to the exposed category at the time of diagnosis of a particular risk factor during followup. In the analysis of disease duration, the exposure status of patients changed in yearly intervals throughout the followup period. A series of dichotomous time-dependent variables (duration <X [with X being the number of years] versus duration >X) were examined.

A multivariable model was developed using a hierarchical process. First, the cardiovascular risk factors were entered into the model. Time-dependent covariates were used for hypertension, diabetes, and BMI. Smoking status at baseline was modeled using 2 indicator variables comparing former and current smokers with subjects who never smoked. Personal history of CHD at baseline, rather than time-dependent CHD events, was included in the model. Propensity scoring was used in order to correct for potential biases associated with missing lipid values (see Table 1). Because cholesterol screening was not performed routinely during the early years of our study period, lipid values may not be missing at random. Logistic regression models were used to determine predictors of the absence of lipid values. Separate models were developed for the periods before and after 1980, when cholesterol screening became more prevalent. The reciprocals of the predicted probabilities from these models were then used as case weights in Cox models that assessed the importance of dyslipidemia as a predictor of cardiovascular death (42).

Next, a stepwise process was used to assess the impact of adding comorbidities to the multivariable model containing the cardiovascular risk factors. All comorbidities were modeled as time-dependent covariates, and only significant predictors were included in the multivariable model. Following the addition of comorbidities, the RA disease characteristics were considered. In adjusted univariate models, we included each RA disease characteristic one at a time in a multivariable model that already included the cardiovascular risk factors and comorbidities. All RA factors were modeled as time-dependent covariates, and a stepwise process was used to determine which factors contributed independently to the model already developed. All 2-way interactions between significant RA disease characteristics and cardiovascular risk factors were assessed. Cox model diagnostics were examined (42,43). Multidimensional scaling analysis was used to examine the stability of the multivariable model (44).

RESULTS

The study population comprised 603 patients with RA. These patients had a mean age of 58 years, and 73.1% were female (Table 1). By January 1, 2001, 354 subjects were deceased, 201 were still under observation,

Table 1. Characteristics of 603 Rochester, Minnesota residents (≥18 years of age) who first fulfilled the 1987 criteria for RA between January 1, 1955 and January 1, 1995 and who were followed up until January 1, 2001*

Characteristic	At RA incidence date		Ever	
	Observed no. of patients	Value	Observed no. of patients	Value
Demographics				
Age, mean ± SD years	603	58.0 ± 15.2	–	–
Female	603	441 (73.1)	–	–
Length of followup, mean ± SD years	–	–	603	15.0 ± 9.9
Cardiovascular risk factors				
Family history of CHD	451	287 (63.6)	–	–
Personal history of CHD	603	93 (15.4)	603	328 (54.4)
Congestive heart failure	603	33 (5.5)	603	210 (34.8)
Cigarette smoking status†	573			
Never smoked	–	255 (44.5)	–	–
Former smoker	–	148 (25.8)	–	–
Current smoker	–	170 (29.7)	–	–
Hypertension	603	312 (51.7)	603	494 (81.9)
Treated‡	–	91 (29.2)	–	237 (48.0)
Dyslipidemia	330	163 (49.4)	504	326 (64.7)
Treated‡	–	11 (6.7)	–	49 (15.0)
BMI				
≥30.0 kg/m^2	516	69 (13.4)	574	137 (23.9)
<20 kg/m^2	516	63 (12.2)	574	205 (35.7)
Diabetes mellitus	603	44 (7.3)	603	113 (18.7)
Treated‡	–	12 (27.3)	–	37 (32.7)
Postmenopausal§	441	299 (67.8)	441	398 (90.2)
Hormone replacement therapy	441	66 (15.0)	441	126 (28.6)
Comorbidities				
Peripheral vascular disease	603	23 (3.8)	603	106 (17.6)
Cerebrovascular disease	603	20 (3.3)	603	126 (20.9)
Chronic pulmonary disease	603	75 (12.4)	603	203 (33.7)
Dementia	603	6 (1.0)	603	104 (17.2)
Ulcers	603	76 (12.6)	603	235 (39.0)
Malignancies	603	33 (5.5)	603	145 (24.0)
Renal disease	603	7 (1.2)	603	56 (9.3)
Liver disease	603	5 (0.8)	603	17 (2.8)
History of alcoholism	603	13 (2.2)	603	42 (7.0)
RA disease characteristics				
Rheumatoid factor titer ≥1:40	514	302 (58.8)	574	393 (68.5)
ESR¶	576	46.7 ± 30.1	573	179 (31.2)
Joint swelling				
Small joints	571	542 (94.9)	603	591 (98.0)
Large joints	558	233 (41.8)	603	506 (83.9)
Radiographic changes				
Destructive changes	453	93 (20.5)	535	243 (45.4)
Erosions	453	34 (7.5)	535	94 (17.6)
Periarticular osteoporosis	453	24 (5.3)	535	57 (10.6)
Rheumatoid nodules	603	35 (5.8)	603	197 (32.7)
RA complications#	603	0 (0.0)	603	151 (25.0)
RA vasculitis	603	0 (0.0)	603	21 (3.5)
RA lung disease	603	0 (0.0)	603	24 (4.0)
Medication use ≥30 days				
DMARDs	603	216 (35.8)	603	345 (57.2)
Corticosteroids	603	148 (24.5)	603	332 (55.1)

* Except where indicated otherwise, values are the number (%) of patients. RA = rheumatoid arthritis; CHD = coronary heart disease; BMI = body mass index; ESR = erythrocyte sedimentation rate; DMARDs = disease-modifying antirheumatic drugs.
† The few patients who were known to have smoked but for whom it was unclear whether they were current or former smokers were categorized as former smokers.
‡ Percentages are the percentage of pharmacologically treated patients among patients with RA.
§ Among female patients.
¶ The value for the RA incidence date is the mean ± SD of the highest recorded ESR values in the first year after the RA incidence date. The ever value is the number (%) of patients with ≥3 recorded ESR values of ≥60 mm/hour.
# Includes complications such as rheumatoid lung disease, vasculitis, Felty's syndrome, Sjögren's syndrome, and rheumatoid myocarditis.

Table 2. Demographic and traditional predictors of cardiovascular death among the 603 patients with incident RA*

Predictor	At RA incidence date		Time-dependent	
	HR	95% CI	HR	95% CI
Cardiovascular risk factors				
Family history of CHD	1.04	0.71–1.52	–	–
Personal history of CHD	1.91	1.38–2.66	6.52	4.24–10.03
Cigarette smoking status			–	–
Never smoked	1.00	–	–	–
Former smoker	1.48	0.99–2.22	–	–
Current smoker	1.82	1.21–2.73	–	–
Hypertension	1.44	1.01–2.04	2.58	1.33–5.03
Treated†	2.61	1.71–3.99	3.42	1.72–6.81
Not treated	1.14	0.78–1.65	2.12	1.07–4.21
Dyslipidemia	1.00	0.64–1.55	1.14	0.80–1.61
Treated†	0.80	0.19–3.39	0.85	0.36–2.00
Not treated	1.01	0.65–1.58	1.16	0.82–1.66
BMI				
≥30 kg/m^2	0.67	0.39–1.17	1.11	0.78–1.60
<20 kg/m^2	2.39	1.50–3.80	2.16	1.57–2.96
Diabetes mellitus	2.17	1.38–3.44	1.55	1.09–2.19
Treated†	1.27	0.51–3.13	1.84	0.97–3.48
Not treated	2.74	1.64–4.57	2.62	1.41–4.87
Postmenopausal	1.73	0.90–3.30		–
Hormone replacement therapy	1.28	0.80–2.04	0.98	0.62–1.54
Comorbidities				
Peripheral vascular disease	1.10	0.59–2.06	1.86	1.30–2.65
Cerebrovascular disease	1.22	0.63–2.39	2.11	1.49–2.97
Chronic pulmonary disease	1.38	0.92–2.08	1.93	1.42–2.64
Dementia	NA	–	2.46	1.65–3.66
Ulcers	1.29	0.88–1.89	1.59	1.17–2.17
Malignancies	1.33	0.80–2.21	1.46	1.03–2.01
Renal disease	NA	–	4.19	2.82–6.22
Liver disease	NA	–	2.77	1.00–7.64
History of alcoholism	3.76	1.70–8.30	2.51	1.48–4.27
RA disease characteristics				
Rheumatoid factor titer ≥1:40	1.22	0.87–1.71	1.62	1.15–2.27
ESR	1.10‡	1.04–1.15	2.12§	1.55–2.89
Joint swelling				
Small joints	0.98	0.52–1.87	1.72	0.70–4.20
Large joints	1.48	1.09–2.01	1.80	1.19–2.73
Radiographic changes				
Destructive changes	1.46	0.98–2.18	1.43	1.03–1.98
Erosions	1.60	0.83–3.10	1.41	0.86–2.31
Periarticular osteoporosis	0.38	0.09–1.55	0.78	0.40–1.55
Rheumatoid nodules	1.54	0.85–2.79	1.55	1.10–2.16
RA complications	NA	–	1.43	1.01–2.04
RA vasculitis	NA	–	2.29	1.03–5.10
RA lung disease	NA	–	2.68	1.43–5.01
Medication use				
DMARDs	1.24¶	0.88–1.76	1.28	0.93–1.76
Corticosteroids	1.14¶	0.79–1.64	1.70	1.26–2.29
Duration of RA				
<1 year	–	–	1.00	–
1 to <4 years	–	–	0.65	0.28–1.52
4 to <8 years	–	–	0.89	0.41–1.94
≥8 years	–	–	0.87	0.42–1.79

* Values are the hazard ratio (HR) (95% confidence interval [95% CI]) calculated from the estimated coefficients (and standard errors) in univariate Cox regression models. NA = number of cases too small to warrant analysis (see Table 1 for other definitions).
† Treated versus nontreated groups were compared using a Cox model (with 2 degrees of freedom) examining the effect of treatment after adjusting for the diagnosis of hypertension, dyslipidemia, or diabetes mellitus.
‡ Highest recorded ESR within the first year after the RA incidence date (HR per 10 mm/hour).
§ For patients with ≥3 recorded ESR values of ≥60 mm/hour.
¶ Medication use within the first year.

and 48 were lost to followup. Of the 354 deaths in our cohort, the underlying cause of death was classified as cardiovascular in 176 patients (49.7%). In 38 additional patients, cardiovascular disease was listed as a contributory cause of death. Table 1 shows the characteristics of the study population at the RA incidence date and over the mean followup of 15 years (9,045 person-years).

At the RA incidence date, 93 patients (15.4%) had a history of CHD and 33 patients (5.5%) had a previous diagnosis of CHF. More than half of the patients were either former smokers (25.8%) or current smokers (29.7%). In addition, the frequencies, at the RA incidence date, of hypertension, dyslipidemia, obesity, and diabetes mellitus were 51.7%, 49.4%, 13.4%, and 7.3%, respectively. By the end of the followup period, 81.9% of the subjects fulfilled the criteria for hypertension, 64.7% for dyslipidemia, 23.9% for obesity, and 18.7% for diabetes mellitus. Table 1 also shows the prevalence of selected comorbid conditions and RA disease characteristics as well as use of DMARDs and corticosteroids both at the RA incidence date and by the end of the entire followup period. The proportion of patients with missing data were as follows: 25% for family history of CHD, 16% for dyslipidemia, 9% for BMI, 5% each for RF and ESR, and 11% for radiographic changes (Table 1).

Cox regression models were used to examine the association between cardiovascular death and traditional cardiovascular risk factors, comorbidities, and RA disease characteristics (Table 2). Predictor variables were tested one at a time, first at the RA incidence date, and then considering the covariates as time-dependent (Table 2). All models were stratified by sex. In Cox models considering the status of risk factors at the RA incidence date, personal history of CHD (HR 1.91, 95% confidence interval [95% CI] 1.38–2.66), current smoking status (versus never smoked, HR 1.82, 95% CI 1.21–2.73), hypertension (HR 1.44, 95% CI 1.01–2.04), low BMI (HR 2.39, 95% CI 1.50–3.80), and diabetes mellitus (HR 2.17, 95% CI 1.38–3.44) were statistically significantly associated with cardiovascular death (Table 2). The findings were similar in time-dependent analyses, which evaluated the changes in risk factors over the followup period (Table 2). The diagnoses of dyslipidemia and obesity, either at baseline or over the followup period, did not show a statistically significant association with cardiovascular death. After incorporating weights from the propensity scoring analysis, dyslipidemia remained a nonsignificant predictor of cardiovascular death.

Among the various comorbidities examined at the RA incidence date, only history of alcoholism was a significant predictor of cardiovascular death. In time-dependent analyses, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, dementia, ulcers, malignancies, renal disease, and liver disease were all significant predictors of cardiovascular death, with HR values ranging from 1.46 (for malignancies) to 4.19 (for renal disease) (Table 2).

In a similar manner, Cox models were used to assess RA disease characteristics as predictors of cardiovascular death, both at the RA incidence date and during followup (Table 2). At the RA incidence date, higher ESR values (HR 1.10 per 10 mm/hour, 95% CI 1.04–1.15) and swelling of large joints (HR 1.48, 95% CI 1.09–2.01) were both significant predictors of cardiovascular death. The association between each of these variables and the risk of cardiovascular death remained statistically significant in time-dependent analyses (Table 2). Over the followup period after the RA incidence date, RF seropositivity (HR 1.62, 95% CI 1.15–2.27), destructive changes on radiographs (HR 1.43, 95% CI 1.03–1.98), rheumatoid nodules (HR 1.55, 95% CI 1.10–2.16), complications of RA (HR 1.43, 95% CI 1.01–2.04), and treatment with corticosteroids (HR 1.70, 95% CI 1.26–2.29) significantly increased the likelihood of dying of cardiovascular causes.

We further evaluated the independent contribution of RA disease characteristics to the risk of cardiovascular death by including them, first, in adjusted univariate models, and then, in multivariable Cox regression models (Table 3). In these models, all covariates were considered as time-dependent, except for personal history of CHD and smoking status. In the adjusted univariate Cox models, ESR, small- and large-joint swelling, destructive changes, rheumatoid nodules, vasculitis, rheumatoid lung disease, and corticosteroid use were significantly associated with increased risk of cardiovascular death, after adjusting for cardiovascular risk factors and comorbidities. We observed no association with RA disease duration. Put another way, these data indicate that the risk of cardiovascular death for a 50-year-old woman who had RA for >8 years was similar to that for another 50-year-old woman who had RA for <1 year.

The significant associations between some of these disease characteristics and cardiovascular death persisted in multivariable analysis (Table 3). Patients with ≥ 3 recorded ESR values of ≥ 60 mm/hour (HR 2.03, 95% CI 1.45–2.83), RA vasculitis (HR 2.41, 95% CI 1.00–5.81), and rheumatoid lung disease (HR 2.32, 95% CI 1.11–4.84) had a significantly higher risk of

Table 3. Univariate adjusted and multivariable Cox regression models for the risk of cardiovascular death according to various RA clinical characteristics among the 603 patients*

Characteristic	Adjusted univariate†		Multivariable‡	
	HR	95% CI	HR	95% CI
Cardiovascular risk factors				
Personal history of CHD	–	–	§	
Smoking (ever versus never)	–	–	1.34	0.90–2.01
Hypertension	–	–	1.98	0.93–4.24
Diabetes mellitus	–	–	1.15	0.77–1.72
BMI ≥30 kg/m^2	–	–	0.93	0.60–1.45
BMI <20 kg/m^2	–	–	1.80	1.27–2.54
Comorbidities				
Peripheral vascular disease	–	–	1.75	1.18–2.58
Chronic pulmonary disease	–	–	1.27	0.88–1.85
Ulcers	–	–	1.44	1.03–2.02
Malignancies	–	–	1.44	1.00–2.08
Dementia	–	–	2.58	1.71–3.87
Renal disease	–	–	3.64	2.34–5.66
History of alcoholism	–	–	1.84	1.04–3.25
RA disease characteristics				
Rheumatoid factor seropositivity	1.40	0.98–2.02		
ESR¶	2.10	1.51–2.94	2.03	1.45–2.83
Joint swelling				
Small joints	2.86	1.13–7.22	–	–
Large joints	1.86	1.20–2.89	–	–
Radiographic changes				
Destructive changes	1.55	1.09–2.19	–	–
Erosions	1.32	0.79–2.19	–	–
Periarticular osteoporosis	0.90	0.45–1.79	–	–
Rheumatoid nodules	1.73	1.20–2.50	–	–
RA complications	1.39	0.96–2.00	–	–
RA vasculitis	3.30	1.38–7.87	2.41	1.00–5.81
RA lung disease	3.10	1.52–6.30	2.32	1.11–4.84
Medication use				
DMARDs	1.15	0.82–1.62	–	–
Corticosteroids	1.54	1.12–2.11	§	–
Duration of RA				
<1 years	1.00			
1 to <4 years	0.80	0.32–2.02	–	–
4 to <8 years	1.00	0.42–2.37	–	–
≥8 years	0.84	0.37–1.90	–	–

* See Tables 1 and 2 for definitions.
† From a Cox regression model adjusting for personal history of CHD, smoking, hypertension, diabetes mellitus, BMI, peripheral vascular disease, chronic pulmonary disease, ulcers, malignancies, dementia, renal disease, and history of alcoholism.
‡ From a multivariable Cox regression model (n = 548). Patients with missing smoking data were combined with never smokers. Likewise, those missing BMI data were included in the reference group for the BMI covariates.
§ See Table 4 for details.
¶ For patients with ≥3 recorded ESR values of ≥60 mm/hour.

cardiovascular death, even after adjusting for cardiovascular risk factors and comorbidities.

We observed a significant interaction between personal history of CHD and use of corticosteroid therapy ($P = 0.003$) in multivariable analysis (Table 4). Among patients with no history of CHD, corticosteroid use during the disease course was associated with a 78% increased risk of cardiovascular death (HR 1.78, 95% CI 1.19–2.67) as compared with those who did not receive corticosteroids (reference group). However, among patients with a history of CHD, the risk of cardiovascular death among those who received corticosteroids (HR 2.42, 95% CI 1.37–4.26) was less than the risk among those who did not receive corticosteroids (HR 3.07, 95% CI 1.91–4.95). These findings indicate that the impact on cardiovascular mortality by CHD and corticosteroid use together was less than would be expected based on the separate effects of each alone.

Table 4. Risk of cardiovascular death according to history of coronary heart disease (CHD) at the rheumatoid arthritis incidence date and corticosteroid use

	No corticosteroids, HR (95% CI)*	Any corticosteroids, HR (95% CI)*
No personal history of CHD	1	1.78 (1.19–2.67)
Personal history of CHD	3.07 (1.91–4.95)	2.42 (1.37–4.26)

* From a multivariable Cox regression model, adjusting for smoking, hypertension, diabetes mellitus, body mass index, peripheral vascular disease, chronic pulmonary disease, ulcers, malignancies, dementia, renal disease, history of alcoholism, erythrocyte sedimentation rate, vasculitis, and lung disease. See Table 2 for other definitions.

DISCUSSION

We have herein reported the predictors of cardiovascular death in a community-based inception cohort of 603 RA patients followed up over a mean of 15 years. Our results indicate that various traditional cardiovascular risk factors and comorbidities increased the risk of cardiovascular death in RA patients. Furthermore, higher ESR values, the occurrence of RA vasculitis, and the occurrence of RA lung disease emerged as strong disease-specific predictors of cardiovascular mortality, even after accounting for demographics, traditional cardiovascular risk factors, and comorbidities. Lack of any association with disease duration suggests that the increased risk of cardiovascular death precedes the RA incidence date. To our knowledge, this is the largest study that has been undertaken to date for the identification of RA disease characteristics that jointly, as well as independently, contribute to cardiovascular mortality in RA patients, after accounting for traditional cardiovascular risk factors. These disease-specific markers indicate systemic inflammatory activity and RA disease severity. Although these markers are routinely used in monitoring RA disease activity, our results demonstrate that they also identify RA patients who have a higher risk of cardiovascular mortality.

Various possible mechanisms have been proposed to explain the excess rate of cardiovascular mortality in patients with RA (5,45,46). First, undertreatment of cardiovascular comorbidity in RA may contribute to increased cardiovascular mortality. Second, RA and cardiovascular disease share some of the same risk factors, such as smoking and obesity (47). Third, patients with established RA may have a higher prevalence of traditional risk factors compared with persons without RA (48–50). Fourth, systemic inflammation in RA may act independently of traditional risk factors to increase the risk through biologic mechanisms (21,51,52). Fifth, both the RA-related inflammatory mechanisms and the traditional risk factors may operate in a synergistic manner. Our results are consistent with the latter 2 possible mechanisms.

The associations observed with diabetes and hypertension are consistent with findings from the general population (53,54). The roles of diabetes and hypertension in the risk of cardiovascular morbidity and mortality in RA have been examined in a limited number of studies (11,20,21,52). In a study by Wallberg-Jonsson et al (11), hypertension was significantly associated with CHD events but not mortality. Del Rincon et al (21) examined cardiovascular events and reported significant associations with both diabetes and hypertension. Smoking is an established risk factor for atherosclerosis and is also associated with the development and severity of RA (47,55–57). In our study, we demonstrated, by univariate analysis, that a history of smoking prior to the RA incidence date increased the risk of cardiovascular death in a dose-dependent manner, but the association was no longer significant when other cardiovascular variables were considered. We also did not observe any interaction between smoking and RA disease characteristics in association with the risk of cardiovascular death.

The association observed with dyslipidemia was somewhat weaker than that demonstrated in the general population (34,58–60). Although hyperlipidemia is associated with higher levels of inflammatory markers in healthy persons (61), there is limited evidence on whether it is associated with an increased risk of RA (62). Findings in the current literature suggest that lipid levels are altered considerably depending on the status of RA disease activity and the extent of antirheumatic drug treatment (63), and RA patients typically visit their physicians (and obtain lipid measurements) when their disease is active. Thus, lipid measurements obtained during times of active disease may not reflect the true burden of hyperlipidemia in this population.

The interaction observed between personal history of CHD and corticosteroid use is noteworthy. Corticosteroids are typically prescribed for patients with more severe disease. Corticosteroids can also promote hypertension, dyslipidemia, and diabetes. Therefore, it has been suggested that these agents may be risk factors for cardiovascular mortality in RA (64,65). In our study, corticosteroid use was associated with an increased risk of cardiovascular death, even after adjusting for cardiovascular risk factors associated with corticosteroid use. However, corticosteroid use among patients with a his-

tory of CHD attenuated the risk of cardiovascular death associated with CHD. These findings are consistent with a previous study conducted in Sweden (51) in which corticosteroid treatment early in the RA disease course increased the risk of cardiovascular events, but among the subset of patients with CHD, corticosteroids delayed the event. These findings suggest that the antiinflammatory effects of corticosteroids may, in fact, be beneficial in RA patients with a history of CHD.

Our findings are consistent with prior observations that various markers of RA disease activity and severity are associated with either all-cause or cardiovascular mortality. Joint swelling, even in the absence of a diagnosis of RA, has been shown to be a predictor of death (9,52,66). Similarly, rheumatoid nodules (9,17,18,20), erosions (17,20), RA vasculitis (67,68), and higher ESR levels (9,51) were all reported to be significantly associated with mortality.

The strengths of our investigation include the population-based design, which comprised a large community-based RA cohort with extensive followup, the completeness of ascertainment for both outcomes and predictors, the use of standardized measurements and consistent diagnostic criteria for both cardiovascular outcomes and RA-specific events, and the availability of data on risk factors over a long time period, both prior to RA diagnosis and during the entire course of the disease. Most previous studies of mortality in RA relied on either patient recall or measurements of the risk factors at a single point in time. Such approaches may underestimate risk relationships due to regression dilution bias (69).

It is nevertheless important to acknowledge some of the potential limitations of our study. The study findings may not be generalizable to nonwhite individuals, because the Rochester population during the calendar years under investigation was >95% white. With the exception of a higher proportion of the working population employed in the health-care industry (24% versus 8% nationally) and correspondingly higher education levels, the sociodemographic characteristics of Olmsted County residents resemble those of the US white population (28). Moreover, the incidence of RA in local residents resembles that in other white populations (2). Nevertheless, the generalizability of our study findings to populations with sociodemographic characteristics different from those in Olmsted County is unknown.

The RA incidence date was assigned according to fulfillment of the ACR 1987 criteria. These criteria are useful in comparisons across epidemiologic studies, but they may have lower sensitivity in identification of subjects with early disease (70). Missing data are likely to occur in any observational study, despite the extent of followup. When the entire followup period is considered, ≤5% of the data are missing for various cardiovascular and RA disease characteristics, except lipid values and radiographic evaluations. Almost 8% of the patients were lost to followup at the end of the study. However, these patients remained under observation for a mean of 11.5 years (median 9.5 years, interquartile range 4.5–17.3 years). Since we relied on medical records, we were not able to capture the data on individuals who were asymptomatic or did not seek medical attention.

Although we were unable to ascertain use of nonsteroidal antiinflammatory drugs (NSAIDs) in our cohort, we expect that all of the patients had substantial exposure to NSAIDs, and it is likely that some of the comorbidities (i.e., ulcers and renal disease) that were significant predictors of cardiovascular death were related to the extent of NSAID use in these patients. We were not able to examine the effect of methotrexate therapy, because only 57% of the patients in our study ever received a DMARD and only 23% ever received methotrexate. However, this allowed us to assess the risk of cardiovascular death in RA patients during the early years, when cardiovascular risk would be minimally confounded by aggressive RA therapy.

In addition, we did not have data on some inflammatory markers, such as fibrinogen or cytokines. It is possible that monitoring the levels of these markers throughout the disease course could substantially add to the prognostic information provided by the traditional risk factors and RA disease–specific indicators. We also did not have data on socioeconomic status and physical activity. Our study was not designed to address the issue of whether patients with RA have a higher prevalence of cardiovascular risk factors compared with general population control subjects. This is the subject of our ongoing analyses.

In summary, our findings demonstrate that higher ESR values, swelling of large joints, RA vasculitis, and RA lung disease are independent risk factors for cardiovascular death in RA patients, even after accounting for the influence of traditional cardiovascular risk factors and multiple comorbidities. These findings demonstrate that markers of systemic inflammation in RA act independently to increase the risk of cardiovascular mortality. Future studies should address whether aggressive interventions to tightly control systemic inflammation in RA would reduce the risk of cardiovascular mortality in a manner similar to that shown for tight

control of glycemia among patients with diabetes mellitus (71).

ACKNOWLEDGMENTS

We are grateful to Vicky Roeder, Deanne Stiebner, Denise Herman, and Glenda Kendall for data collection and editing from the medical records.

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