

All-Cause Mortality and Vascular Events Among Patients with Rheumatoid Arthritis, Osteoarthritis, or No Arthritis in the UK General Practice Research Database

DOUGLAS J. WATSON, THOMAS RHODES, and HARRY A. GUESS

ABSTRACT. Objective. To compare all-cause mortality rates and the incidence of major vascular events among patients with rheumatoid arthritis (RA), osteoarthritis (OA) without RA, or no arthritis using the UK General Practice Research Database (GPRD) while adjusting for age and sex. Clinic-based studies have found that patients with RA have higher all-cause and cardiovascular (CV) mortality than those without RA, after adjusting for age and sex. Much smaller elevations in risk have been found in the few community-based studies that have addressed this question.

Methods. After excluding patients with a history of myocardial infarction or cerebrovascular events, we followed a retrospective cohort of patients 40 years and older from GPRD practices until the earliest of death, disenrollment, or the occurrence of an incident vascular event. Using Poisson regression we compared age and gender adjusted incidence rates for RA, OA, or no arthritis.

Results. Five hundred and ninety-four practices contributed 2.37 million patients (1.11 million men and 1.26 million women) to the analysis. Over a mean duration of followup of almost 5 years, age and gender adjusted all-cause mortality rates were 60 to 70% higher in patients with RA compared to patients with OA and those with no arthritis. For the various vascular endpoints, the age and gender adjusted incidence rates were 30 to 60% higher in patients with RA compared to both patients with OA and those with no arthritis during the study period. The rates in patients with OA and those with no arthritis were essentially the same.

Conclusion. Compared to patients with OA and those with no arthritis, patients with RA had a higher age and gender adjusted incidence of all-cause mortality and of major vascular events during almost 5 years of followup. (J Rheumatol 2003;30:1196–202)

Key Indexing Terms:

RHEUMATOID ARTHRITIS
MORTALITY

OSTEOARTHRITIS
EPIDEMIOLOGY

CARDIOVASCULAR
INCIDENCE

Previous studies have shown that patients with rheumatoid arthritis (RA) have higher all-cause mortality compared with patients of the same age and gender without RA. Clinic-based studies have found age and gender standardized mortality ratios (SMR) for all-cause mortality of 1.1 to 3.0 or more for RA patients relative to the general population, while the few community based studies conducted have found SMR of 1.2 to 1.3¹⁻⁶. In most but not all studies (the majority of which are clinic or hospital based), vascular mortality was increased in RA patients relative to the general population^{4,7}.

The reasons for increased cardiovascular (CV) mortality in patients with RA are not completely understood. Potential explanations include traditional CV risk factors, the medications used to treat RA, enhanced atherosclerotic plaque instability, and the effects of chronic systemic inflammation⁸. There is evidence that inflammation also plays a role in osteoarthritis (OA), although this appears to be mostly confined to the affected joints⁹. Nevertheless, patients with OA and RA may share traditional and lifestyle risk factors for CV disease, such as a sedentary lifestyle and obesity.

We examined the incidence of all-cause mortality, myocardial infarction (MI), sudden/unknown cause of death, cerebrovascular events, vascular death, and all vascular events among patients 40 years or older with RA in the UK General Practice Research Database (GPRD). For comparison, we chose 2 control groups, patients with OA but without RA (hereafter referred to as OA), and patients with neither RA nor OA (no arthritis) in the population-based GPRD. The scientific and ethical review group that oversees analyses using the GPRD approved the protocol.

From the Department of Epidemiology, Biostatistics and Research Decision Sciences, Merck Research Laboratories West Point, Pennsylvania, USA.

Sponsored by Merck & Co., Inc.

D.J. Watson, PhD, Director; T. Rhodes, MSPH, Senior Epidemiologist; H.A. Guess, MD, PhD, Vice President.

Address reprint requests to Dr. D.J. Watson, Department of Epidemiology, Merck Research Laboratories, 10 Sentry Parkway (BL1-7), Blue Bell, PA, 19422. E-mail: Watsond@merck.com

Submitted November 7, 2001; revision accepted November 9, 2002.

MATERIALS AND METHODS

Database. The GPRD was initiated in 1987. Practices were recruited from all 4 countries of the UK with the aim of creating a national research database. The GPRD now contains over 35 million patient-years of data from UK general practice, and represents a sample covering 6% of the population of England and Wales. Confidentiality of information in the GPRD is ensured by deleting or encoding personal and clinic identifiers. Data are collected according to agreed standards, and include all prescriptions, significant medical events, hospital referrals, and demographic details. Data from a given practice are incorporated in the GPRD only after that practice has met predetermined quality standards and is deemed up to standard. Comparisons of the GPRD population by age and gender with data from the 1991 UK Census show that these distributions are broadly similar to that of the general population for the UK. A number of independent studies confirm the validity of the diagnostic and prescribing data contained in the GPRD¹⁰⁻¹², and more than 100 epidemiological studies using GPRD data have been published¹³.

Study design and patient selection. This study was a retrospective, observational cohort study of patients 40 years or older with a valid registration date. We excluded patients with a MI or cerebrovascular event documented in the GPRD prior to their start of followup. To avoid practices where data might be incompletely recorded, we excluded practices in which 20% or more of patients had no recorded health care visits. We performed sensitivity analyses including these practices.

For each eligible patient, we categorized gender and age specific person-time in 5-year age intervals between 40 and 84 years of age and in a single category for patients ages 85 years or older. We examined each patient's record for a diagnosis of RA and OA and counted the first occurrence in the age and gender specific stratum in which it occurred. We apportioned each patient's person time to the 3 categories of RA, OA, and no arthritis according to the rules below. The same patient may have contributed to more than one category at different points in time¹⁴.

We counted person-time in the RA group starting from the latest of (1) the patient's 40th birthday, (2) the up-to-standard date for the practice plus 6 months, (3) the date of registration of the patient plus 6 months, or (4) the date of first diagnosis of RA. In the OA group we defined the start of person-time analogously, using the first OA diagnosis instead of the first RA diagnosis. For RA, person-time ended with the earliest of (1) last date of data from the practice, (2) the last encounter date for the patient, (3) date of death, or (4) date of an endpoint. For the OA group, date of first RA diagnosis was an additional end date for person-time accounting. Person-time in the no arthritis group was counted in a similar manner except that it ended with the date of first RA or OA diagnosis. Patients whose first RA diagnosis preceded or coincided with their first OA diagnosis contributed person-time to the RA group but did not contribute person time to the OA group. A patient diagnosed with OA and later diagnosed with RA contributed time to the OA group after the OA diagnosis until the time of the RA diagnosis, after which he or she only contributed person-time to the RA group.

The codes for RA and OA were intentionally broad so as to maximize sensitivity. The diagnoses were not verified by inspection of clinical records. We also performed a sensitivity analysis using a more restrictive set of diagnosis codes to define the presence of RA or OA, while retaining the same codes as the original list to define the absence of RA or OA.

We examined each patient's computer-based record for death from any cause and the vascular diagnoses of interest. Death was assessed by a code of deceased in the patient status field of the patient record. The date of death was taken as that associated with the status field. Recording guidelines for the GPRD specify that a code for death, and the date and cause of death be entered in the patient record. Deaths of unknown cause are to be recorded as such. These data elements are subject to quality assurance checks for sites to be certified up to standard. Because all patient identifiers are removed from the GPRD database, and because after 3 years records for patients who have died are purged, it is difficult to verify death by review of death certificates and doing so was beyond the scope of this study.

Cerebrovascular events included stroke, subarachnoid hemorrhage, and subdural hematoma but excluded transient ischemic attack. Since hemorrhagic and ischemic cerebrovascular events cannot always be distinguished by the diagnoses in the database, we included both; however, a sensitivity analysis was performed restricting cerebrovascular events to diagnoses most likely to represent ischemic strokes. Events were designated fatal if the patient died within 30 days of the diagnosis. The endpoint of vascular death was a composite of fatal MI, sudden/unexplained death, and fatal cerebrovascular event. The endpoint of all vascular events included fatal and nonfatal MI or cerebrovascular event, or sudden/unexplained death. For each patient, the analysis counted only the first occurrence of any of the endpoints. All endpoints were attributed to the gender, age, and arthritis stratum category in which they occurred. The endpoint diagnoses were not verified by inspection of clinical records.

Analysis. For each separate endpoint, we calculated the patient-years contributed by each patient to the RA, OA, and no arthritis groups. We then calculated, for each separate endpoint, the incidence per 1000 patient-years within each age and gender stratum, as well as the age adjusted total for each gender, and the overall gender and age adjusted rates for the RA, OA, and no arthritis groups. For each endpoint, we compared age and gender adjusted rates for RA, OA, and no arthritis using Poisson regression. We also separately computed the incidence of RA per 1000 patient-years for each age stratum and the overall age-adjusted rate for each gender separately.

RESULTS

The primary analysis included 594 (86.6%) of 686 practices. The remaining practices did not meet the inclusion criteria for the primary analysis because they had no health visit data for 20% or more of patients. A total of 1,109,574 men and 1,263,977 women met eligibility criteria for the study (Table 1). The mean duration of followup was 4.7 years for men and 4.8 years for women; the minimum and maximum years of followup were 0 and 12 years for both genders. The mean age at study start was 54.5 for men and 57.2 for women (Table 1). A higher proportion of men died, had an MI, and had any vascular event compared to women.

A total of 3510 men and 8123 women were diagnosed with RA during the study period. The overall incidence of RA was 0.7/1000 and 1.3/1000 patient years, in men and women, respectively (Table 2). In both genders, the inci-

Table 1. Characteristics of the study population.

Variable	Men n = 1,109,574	Women n = 1,263,977
Person-years of followup		
Mean (SD)	4.7 (2.6)	4.8 (2.6)
Median	4.7	4.9
Minimum, maximum	0, 12	0, 12
Age at study start		
Mean (SD)	54.5 (13.7)	57.2 (15.1)
Median	52.3	55.5
Number (%) with endpoint		
Any death	98,756 (8.9)	104,401 (8.3)
Myocardial infarction	32,009 (2.9)	21,785 (1.7)
Sudden death	3435 (0.3)	2484 (0.2)
Cerebrovascular event	24,703 (2.2)	30,898 (2.4)
Vascular death	16,680 (1.5)	18,729 (1.5)
Any vascular event	53,968 (4.9)	50,691 (4.0)

Table 2. RA incidence rate (per 1000 patient-years), by gender and age.

Age	Patients n	Patient-Years	Incidence Rate
Men			
40-44	277	854,247	0.3
45-49	371	841,611	0.4
50-54	435	699,802	0.6
55-59	479	618,817	0.8
60-64	540	573,140	0.9
65-69	440	523,306	0.8
70-74	442	443,602	1.0
75-79	300	309,827	1.0
80-84	157	195,870	0.8
85+	69	109,717	0.6
All ages	3510	5,169,937	0.7
Women			
40-44	678	883,954	0.8
45-49	859	881,848	1.0
50-54	961	740,051	1.3
55-59	1038	649,538	1.6
60-64	946	613,455	1.5
65-69	1027	595,177	1.7
70-74	994	575,692	1.7
75-79	792	478,126	1.7
80-84	510	380,903	1.3
85+	318	306,678	1.0
All ages	8123	6,105,422	1.3

dence of RA increased with age and peaked in the 7th and 8th decades of life. Rates for women were approximately twice those for men in most age strata, and for all ages combined. A total of 61,517 men and 101,757 women were diagnosed with OA during the study period. The overall incidence of OA was 12.9/1000 and 18.6/1000 patient years, in men and women, respectively.

In both genders, crude rates of all-cause mortality and all of the vascular endpoints increased with age in all 3 diagnosis groups (data not shown). As expected, men had higher crude rates compared with women at most ages for all endpoints. In general, both men and women with RA had higher age-specific and overall crude incidence rates of all endpoints except sudden death compared to those with OA. For sudden death, the rates were highly variable due to the small numbers of events. Similar results were seen when patients with RA were compared to patients with no arthritis.

Standardized overall incidence rates of death and all vascular endpoints are shown in Table 3. Patients with RA had higher rates of all endpoints compared to both OA and no arthritis. Age adjusted (within gender) and age and gender adjusted incidence rate ratios for RA compared to the other 2 groups are shown in Table 4. In men and women separately, the rate ratios of all endpoints were significantly greater than 1.0, except for sudden death. For both genders combined, the rate ratios were significantly higher for all endpoints in the RA group compared to each of the other 2 groups.

Table 3. Standardized incidence rates (per 1000 patient-years) of all-cause mortality and vascular events by arthritis diagnosis. Rates in the RA and OA populations are age and gender standardized to the person-time in the no arthritis population by the direct method.

	RA	OA	No Arthritis
Men			
All-cause mortality	32.1	19.5	20.6
Myocardial infarction	10.1	8.3	7.1
Sudden/unknown cause of death	0.9	0.8	0.7
Cerebrovascular event	7.6	5.9	5.2
Vascular death	5.3	3.6	3.6
All vascular events	17.6	13.9	12.1
Women			
All-cause mortality	27.7	15.9	17.3
Myocardial infarction	5.8	4.4	3.5
Sudden/unknown cause of death	0.6	0.5	0.4
Cerebrovascular event	6.8	5.6	5.1
Vascular death	4.6	3.2	3.1
All vascular events	12.6	9.8	8.4

The results of analyses using all GPRD practices, and those using a more restrictive set of RA and OA diagnoses, were almost identical to the primary analyses (data not shown).

DISCUSSION

Our study examined the incidence of all-cause mortality and vascular events in patients age 40 years or older with RA relative to those with OA and those with no arthritis in the GPRD. During the study period, patients with RA were 60–70% more likely to die and 30–60% more likely to suffer a vascular event compared to patients in either of the other groups. To our knowledge this is the first study to compare RA with OA with respect to these endpoints in a population based study.

Almost all previous studies of vascular disease among patients with RA compared to non-RA populations have used all-cause or vascular disease mortality as the endpoint of interest. Despite differences in methodology and endpoints, our results are generally consistent with previous population-based studies. In one such study done in the US, 25-year rates of all-cause mortality, ischemic heart disease, and cerebrovascular events in patients with RA were 16%, 1%, and 36% higher, respectively, compared to the general population¹⁵. In a Swedish population-based study RA patients were found to have all-cause SMR of 1.2 in women and 1.9 in men compared to the general population¹⁶. In a population-based study of Pima Indians with followup for up to 25 years, those with definite or likely RA had SMR of 1.3 for all-cause mortality and 1.8 for coronary heart disease relative to those without RA². For the most part, as might be expected, studies done with RA patients attending specialty clinics or hospitals have noted that patients with RA have

Table 4. Age-adjusted and gender and age adjusted incidence rate ratios of all-cause mortality and vascular events for RA compared with OA and with no arthritis*.

	RA vs OA		RA vs No Arthritis	
	Rate Ratio	(95% CI)	Rate Ratio	(95% CI)
Men				
All-cause mortality	1.7	1.6, 1.8	1.6	1.5, 1.6
Myocardial infarction	1.3	1.1, 1.4	1.4	1.3, 1.6
Sudden/unknown cause of death	1.3	1.0, 1.8	1.3	0.9, 1.7
Cerebrovascular event	1.2	1.1, 1.4	1.4	1.2, 1.6
Vascular death	1.4	1.2, 1.6	1.4	1.2, 1.6
All Vascular events	1.3	1.2, 1.4	1.4	1.3, 1.5
Women				
All-cause mortality	1.8	1.7, 1.8	1.6	1.6, 1.7
Myocardial infarction	1.4	1.3, 1.5	1.6	1.5, 1.8
Sudden/unknown cause of death	1.4	1.1, 1.8	1.3	1.0, 1.7
Cerebrovascular event	1.3	1.2, 1.4	1.4	1.3, 1.5
Vascular death	1.5	1.4, 1.6	1.5	1.4, 1.6
All Vascular events	1.3	1.3, 1.4	1.5	1.4, 1.6
Both Genders				
All-cause mortality	1.7	1.7, 1.8	1.6	1.6, 1.6
Myocardial infarction	1.3	1.2, 1.4	1.6	1.5, 1.7
Sudden/unknown cause of death	1.3	1.1, 1.6	1.3	1.1, 1.6
Cerebrovascular event	1.3	1.2, 1.3	1.4	1.3, 1.5
Vascular death	1.5	1.4, 1.6	1.5	1.4, 1.6
All Vascular events	1.3	1.3, 1.4	1.5	1.4, 1.5

* Results for each gender are age-adjusted, and results for both genders combined are age- and gender-adjusted using Poisson regression analysis.

elevated mortality and higher rates of vascular disease compared to controls or with the general population^{3,5,17-41}.

The specific risk factors for the increased risk of death and vascular disease in RA patients have not been fully explained. Previous studies have implicated age, male gender, prior CV disease, cancer, hypertension, use of gold, penicillamine or steroids, worse physical functioning or disability, elevated erythrocyte sedimentation rate, and positive rheumatoid factor^{1,42-52}. Traditional CV risk factors do not completely explain the increased risk of CV among patients with RA. A recent study examined risk factors for CV-related hospitalizations or death in 236 patients with RA followed for one year, compared to a prospective cohort of patients without RA followed for the occurrence of CV events over 8 years. In a multivariable model adjusting for multiple risk factors, the RA cohort was about 3 times more likely to experience a CV event than the non-RA cohort⁵³. Other factors significantly related to CV outcome included increased age, male gender, the presence of diabetes, higher systolic blood pressure, cigarette smoking, and hypercholesterolemia. In another recent study of the effect of nonsteroidal antiinflammatory drugs (NSAID) on major thromboembolic events in an RA population, risk factors related to the outcome included current use of naproxen, calendar year the patient entered the study, use of corticosteroids or disease modifying antirheumatic drugs, comorbidity, and diabetes, as well as the traditional CV risk

factors⁵⁴. In addition, chronic inflammation has been implicated in atherogenesis⁵⁵, and both anticardiolipin antibodies and other predictors of thrombosis have been noted to be significantly elevated in patients with RA compared to controls⁵⁶⁻⁵⁹ and thus may predispose to vascular events. Our study did not examine CV risk factors other than RA, age, and gender.

Recently published studies in Western Caucasian populations estimate the overall incidence of RA to be from 12–50 and 5–98 per 100,000 person-years in men and women, respectively⁶⁰⁻⁶⁸. In contrast to our study, these estimates are derived from RA cases verified by review of medical records by rheumatologists or other specially trained personnel. The incidence of RA in our study was about 50% higher than these previous estimates, perhaps reflecting the different methods and resulting over-ascertainment of RA by general practitioners compared to rheumatologists.

Our study has several strengths. It was conducted using a very large, well characterized general practice clinical database that is judged to be representative of all general practices in England and Wales. The data were collected over a period of up to 10 years. We applied methods that estimated the incidence rates of events in terms of person-time within the 3 diagnosis categories of RA, OA, and no arthritis, which allowed for very precise estimation of rates and rate ratios. In addition, by comparing the experience of patients with RA to both those with no arthritis and those with OA,

it provided more than one point of comparison for the RA group.

This study also has limitations. First, the RA incidence rates estimated in this study reflect diagnoses recorded by general practitioners, either as a result of their own clinical evaluations of the patients or those of consultants, and strict clinical criteria for the diagnosis of RA were not applied in this study. As such, they represent the incidence of disease from the perspective of the general practice setting. Similarly, the diagnosis codes for OA did not conform to a standardized definition; as a result, in this study the diagnosis of OA represents a mix of patients with symptomatic and radiological disease of varying severity and clinical significance. Second, RA and OA are chronic diseases whose onset will most likely predate the date of initial diagnosis. Hence, the above definition will likely result in the no arthritis group including some person-time of patients with arthritis. However, this misclassification of exposure would likely bias toward unity any incidence rate ratios computed using the no arthritis category as the reference. We did not use the alternate approach of including only those persons who were never diagnosed with either RA or OA in the no arthritis category because this approach is known to have the potential for a high degree of selection bias⁶⁹. Third, the primary analysis excluded practices in which fewer than 20% of patients had no visits. This was done to eliminate practices in which it was possible that the practitioner was not consistently entering clinical data for his patients. However, a secondary analysis was conducted to include such practices and the results were not different. Fourth, the diagnostic codes for RA and OA were heterogeneous and their sensitivity and specificity were unknown. Because there are so many different codes, it was not feasible to verify their overall sensitivity and specificity by medical record review. As an alternative approach additional rate ratio calculations were performed in which RA and OA are defined using a subset of the original list of diagnostic codes chosen for high presumed specificity, while the absence of RA and OA was defined in terms of the absence of any diagnostic codes on the original full list. This approach improves specificity at the expense of sensitivity. Since the incidence rate ratios in this alternative analysis were nearly identical to those computed using the original definitions it can be concluded that the original results were relatively robust to the diagnosis codes used. Last, we did not validate the outcomes of mortality and major vascular diagnoses in this study. However, previous studies have confirmed the completeness of recording death⁷⁰, and the validity of the diagnosis data in the GPRD¹⁰⁻¹².

In summary, we examined the incidence of all-cause mortality and vascular events in patients with a diagnosis of RA, relative to that in patients with no arthritis and with OA. The results are consistent with previous studies showing increased all-cause mortality among people with RA relative

to the general population. In addition, this study extended our knowledge by demonstrating increases in combined fatal and non-fatal vascular disease, specifically MI and cerebrovascular events, among patients with RA relative to those without arthritis. Moreover, our results show that RA patients are at increased risk of death and vascular events relative to patients with a diagnosis of OA to approximately the same extent as to those with no arthritis diagnosis. The results of this and other studies suggest that physicians should consider the potential risk of vascular events in patients with RA and counsel and treat such patients accordingly.

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