ARTHRITIS & RHEUMATISM
Vol. 54, No. 10, October 2006, pp 3104–3112
DOI 10.1002/art.22117

Clinical Assessment of the Long-Term Risk of Fracture in Patients With Rheumatoid Arthritis

T. P. van Staa,[1] P. Geusens,[2] J. W. J. Bijlsma,[3] H. G. M. Leufkens,[4] and C. Cooper[5]

Objective. **To determine whether patients with rheumatoid arthritis (RA) have an increased risk of fracture, and to estimate their long-term absolute fracture risk.**

Methods. **We studied patients with RA ages ≥40 years in the British General Practice Research Database, each matched by age, sex, calendar time, and practice to 3 control patients. Incident fractures, as recorded in the computerized medical records, were ascertained over a median followup of 7.6 years. The fracture rate in RA patients compared with controls was adjusted for smoking, body mass index (BMI), and several clinical risk factors, and Cox proportional hazards models were used to calculate the relative risk (RR) of fracture in RA. A risk score was then developed to provide an estimate of the 5- and 10-year fracture risk among RA patients.**

Results. **There were 30,262 patients with RA, of whom 2,460 experienced a fracture during followup. Compared with controls, patients with RA had an increased risk of fracture, which was most marked at the hip (RR 2.0, 95% confidence interval [95% CI] 1.8–2.3) and spine (RR 2.4, 95% CI 2.0–2.8). Indicators of a substantially elevated risk of fracture (at the hip) included >10 years' duration of RA (RR 3.4, 95% CI 3.0–3.9), low BMI (RR 3.9, 95% CI 3.1–4.9), and use of oral glucocorticoids (RR 3.4, 95% CI 3.0–4.0). Modeling of the long-term risk profiles revealed that, for example, in a woman age 65 years with longstanding RA whose risk factors also included low BMI, a history of fracture, and frequent use of oral glucocorticoids, the 5-year risk of hip fracture was 5.7% (95% CI 5.3–6.1%).**

Conclusion. **Patients with RA are at increased risk of osteoporotic fractures. This increased risk is attributable to a combination of disease activity and use of oral glucocorticoids.**

Osteoporosis is a well-known complication of rheumatoid arthritis (RA), and results of population-based studies suggest that patients with RA have an increased risk of hip fracture (1–10). There are fewer data on the relationship between RA and the risk of fracture at other sites. Furthermore, the relative contributions of oral glucocorticoids and the underlying inflammatory disease process to any increased risk of fracture remain unclear. Oral glucocorticoids are known to have deleterious effects on bone (11–13) and are frequently used in RA to suppress inflammation. In a large case–control study from the UK, the risk of hip fracture was increased, although not statistically significantly, in RA patients who had not been treated with oral glucocorticoids (1). Some, but not all, clinical studies have shown that bone mineral density (BMD) is decreased among patients with RA who have not taken oral glucocorticoids (14,15). Nevertheless, previous studies have not provided estimates of the absolute fracture risk in patients with RA, nor have they assessed the

Supported by the Medical Research Council, Arthritis Research Campaign, and Procter & Gamble Pharmaceuticals, UK.

[1]T. P. van Staa, PhD: MRC Epidemiology Resource Centre, University of Southampton, Southampton, UK, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands, and General Practice Research Database, London, UK; [2]P. Geusens, MD: University Hospital, Maastricht, The Netherlands, and Limburg University Center, Diepenbeek, Belgium; [3]J. W. J. Bijlsma, MD: University Medical Center, Utrecht, The Netherlands; [4]H. G. M. Leufkens, PhD: Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands; [5]C. Cooper, MA, DM, FRCP: MRC Epidemiology Resource Center, University of Southampton, Southampton, UK.

Dr. van Staa was previously employed by Procter & Gamble. Dr. Cooper has received honoraria (less than $10,000) from Procter & Gamble, Lilly, and Servier.

Address correspondence and reprint requests to Cyrus Cooper, MA, DM, FRCP, Professor of Rheumatology, Director, MRC Epidemiology Resource Centre, Southampton General Hospital, Tremona Road, Southampton SO16 6YD, UK. E-mail: cc@mrc.soton.ac.uk.

Submitted for publication December 2, 2005; accepted in revised form June 16, 2006.

utility of clinical risk factors in predicting this absolute risk.

We therefore performed a large, population-based cohort study that aimed to assess the risk of fracture in patients with RA, to identify the characteristics of RA and the possible effects of treatment that could modify this risk, and to develop a clinical algorithm for estimating the 5- and 10-year risk of fracture in patients with RA (16–18).

PATIENTS AND METHODS

Data source. Information for this study was obtained from the General Practice Research Database (GPRD), comprising the computerized medical records of all patients under the care of general practitioners in the UK. General practitioners play a key role in the UK health care system, since they are responsible for providing primary health care and specialist referrals. Medical information (including general practitioner records and data on specialist referrals and hospitalizations) on patients who are registered for medical care with a practice is supplied to the GPRD. These data include the patient's demographic information, prescription details, clinical events, preventive care provided, specialist referrals, hospital admissions, and major outcomes (19). The information is recorded at the time of a patient's contact with the general practitioner, when information is received from specialists or hospitals, or when drugs are prescribed by the physician. Hospitals are required to inform general practitioners of the diagnoses made at the hospital or emergency room.

This database has been the source for numerous epidemiologic studies in recent years, and the accuracy and completeness of these data have been well documented and validated (20,21). A study evaluating cardiovascular risks in RA patients indicated that ~80% of the RA diagnoses were confirmed in a questionnaire sent to the general practitioner for a sample of patients (22). Previous studies of GPRD data have shown a high level of data validity with respect to the reporting of fractures (>90% of fractures were confirmed) (20,21).

Study population. The study population consisted of all patients ages ≥40 years with at least one recorded diagnosis of RA during the period of GPRD data collection (for this study, data collection started in 1987 and ended in 2002). Only permanently registered patients were included (i.e., patients who were resident in the proximity of the practice). Each RA patient was matched by age, sex, calendar time, and practice to 3 patients without a history of RA. For the age matching, RA patients and controls were matched by year of birth. If no control was found, this age-matching criterion was expanded stepwise, in age increments of 1 year, to a maximum of 5 years. In the event that no eligible control patient could be matched to a patient within 5 years of age, a control patient was selected from another practice. The index date of RA diagnosis was the date of the first record of RA after GPRD data collection started. The control patients also had to be enrolled in the GPRD at the time of the index date of their matched RA patient. The study patients were followed up from this index date to either the end of GPRD data collection, the date of transfer of the patient out of the practice area, or the patient's death, whichever came first. As as result, 99.6% of the RA patients were matched to controls by year of birth, sex, clinical practice, and calendar time.

Patients were followed up for the occurrence of fracture. The fracture types were classified according to the International Classification of Diseases, Ninth Revision (ICD-9) categories. These included skull (ICD-9 categories 800–804), vertebral (805 or 806), rib (807), pelvis (808), clavicle (810), scapula (811), humerus (812), radius/ulna (813), carpal (814–817), femur/hip (820/821), patella (822), tibia/fibula/ankle (823 or 824), foot (825 or 826), or unspecified fractures (809, 818, 819, or 827–829). A clinical osteoporotic fracture was defined as a fracture of the radius/ulna, humerus, rib, femur/hip, pelvis, or vertebrae. In this population, the vertebral fractures were mostly clinically symptomatic vertebral fractures, which were confirmed radiographically (15).

The total followup period was divided into 6-month intervals. The presence of risk factors and indicators of RA severity were assessed by reviewing the computerized medical records for any record of risk factors prior to the start of an interval. The risk factors and indicators of RA severity selected for the study were chosen on the basis of whether there was a record in the GPRD. Indicators of RA severity included a general practitioner visit for stiff or painful joints in the previous 6 months, history of knee or hip arthroplasty, hospitalization for musculoskeletal disorder in the previous year, or history of carpal tunnel syndrome, Raynaud's phenomenon, amyloidosis, uveitis/scleritis/iritis, pericarditis/myocarditis/endocarditis, neuropathy, hearing loss, pulmonary fibrosis, or skin ulcer. Medication indicated for the treatment of RA in the previous 6 months was noted, and this included use of aspirin or nonsteroidal antiinflammatory drugs (NSAIDs), oral glucocorticoids, and disease-modifying antirheumatic agents (sulfasalazine, aurothiomalate, auranofin, penicillamine, [hydroxy] chloroquine, azathioprine, leflunomide, methotrexate, cyclosporine, etanercept, anakinra, or cyclophosphamide).

General risk factors considered in this study included a record of falls in the previous 12 months, history of fracture, history of a chronic disease (cerebrovascular disease, heart failure, inflammatory bowel disease, and asthma/chronic obstructive pulmonary disease), body mass index (BMI), smoking history, and a prescription for hypnotic/anxiolytic, antipsychotic, antidepressant, or antiepileptic agents, as well as drugs for the treatment of Parkinson's disease, in the previous 6 months. In addition, RA disease duration was noted, as measured from the index date (first record of RA). The general practitioners are expected to record the approximate date of onset of any chronic condition that is present at the start of GPRD data collection.

Statistical analysis. Two main analyses were conducted using Cox proportional hazards models. The first analysis compared the fracture rate in RA patients with that in control patients, to yield an estimate of the relative risk (RR) of fracture in RA. In this analysis, the calculations were adjusted for BMI, smoking, fracture history, fall history, general risk factors, and use in the prior 6 months of bisphosphonates, hormone replacement therapy, and thiazides. The second analysis calculated the long-term risk of fracture. The Cox model also allows calculation of an individual's probability

of fracture (i.e., survivor function) for each set of patient characteristics.

For the analysis of long-term risk, we first fitted the regression model with duration of RA, medication, and disease indicators of RA severity, as well as BMI, smoking, fracture history, fall history, and general risk factors. These characteristics were treated as time-dependent variables in the analysis. All characteristics, except age, were included as categorical variables in the regression models. Backward regression was conducted, and statistical significance was defined as a P value less than or equal to 0.05. For the variables of age, sex, and each of the risk factors, we also investigated possible statistical interactions with RA, although none were subsequently added to the model.

The beta coefficients in the final Cox model (the exponential of these predictors is the RR) were converted into integer risk scores. The value of each integer was calculated as the rounded sum of the Cox model predictor scores, multiplied by 10; since exposure variables were time dependent, the risk score for a patient was averaged over the total followup period. The 5- and 10-year risks of fracture were then estimated using these scores, conditional on patient survival. Various methods were used to test the fitting of the Cox models (23), including a test of the proportional hazards assumption. We also compared the observed 5-year probability of fracture (based on the Kaplan-Meier estimate) with the probability predicted by the Cox model. This was done by dividing the study population into 10 groups based on the predicted probability of fracture; the observed and predicted probabilities of fracture were then compared. Receiver operating characteristic (ROC) curves and the areas under the ROC curve were estimated.

Information on BMI and smoking history was not routinely recorded for all patients in the GPRD. We therefore included indicators in the regression analyses for the missing values on BMI and smoking history. Possible collinearity between risk factors was assessed using correlation coefficients.

RESULTS

Baseline characteristics. A total of 30,262 patients in the study population had a recorded diagnosis of RA, of whom 71.1% were female and 32% were older than age 70 years. As shown in Table 1, the mean duration of followup after the index date (first record of RA) was 4.3 years (median 3.8 years) for the RA patients, and 4.4 years (median 3.9 years) for the control patients. The 5-year mortality was higher among patients with RA (17.5%) compared with controls (11.8%).

Risk of fractures in RA patients compared with controls. Patients with RA had an increased risk of fracture (adjusted RR for clinical osteoporotic fractures 1.5, 95% confidence interval [95% CI] 1.4–1.6). The increased risk of fracture was most marked at the hip and spine (Figure 1). The risk of radius/ulna fracture was reduced in patients with RA. Men and women with RA had comparable increases in fracture risk, with an adjusted RR for clinical osteoporotic fracture of 1.4 (95% CI 1.2–1.7) in men and 1.5 (95% CI 1.4–1.6) in women. The RR for clinical osteoporotic fracture was 1.2 (95% CI 1.0–1.4) in RA patients ages 40–54 years, 1.5 (95% CI 1.4–1.7) in those ages 55–69 years, and 1.5 (95% CI 1.4–1.6) in those ages older than 80 years.

Patients with longstanding RA (>10 years' duration) had a substantially increased risk of fracture (Table 2); the risk of hip fracture in these patients was increased 3-fold. Patients with RA who had a low BMI also had a higher risk of hip fracture. Approximately 24% of the

Table 1. Characteristics of the patients with rheumatoid arthritis (RA) and control patients

Characteristic	RA patients (n = 30,262)	Controls (n = 90,783)
Age, no. (%)		
40–54 years	8,700 (28.7)	26,109 (28.8)
55–69 years	12,018 (39.7)	36,051 (39.7)
≥70 years	9,544 (31.5)	28,623 (31.5)
Sex, no. (%)		
Female	21,507 (71.1)	64,519 (71.1)
Male	8,755 (28.9)	26,264 (28.9)
Fracture history, no. (%)	3,337 (11.0)	9,152 (10.1)
Total followup, years		
Mean	7.1	7.6
Median	7.5	8.1
Followup after index date, years		
Mean	4.3	4.4
Median	3.8	3.9
Mortality, %		
1 year	3.8	2.3
5 years	17.5	11.8

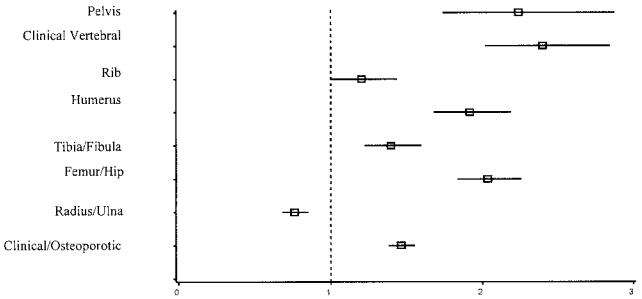

Figure 1. Relative risk of fracture in patients with rheumatoid arthritis (RA) as compared with control patients (the dotted line indicates the cutoff point for fracture risk relative to controls). Values are the relative risk (bars) and 95% confidence interval (boxes) in RA patients, adjusted for body mass index, smoking history, fall and fracture history, history of cerebrovascular disease, heart failure, inflammatory bowel disease, and asthma/chronic obstructive pulmonary disease, and use of hypnotic/anxiolytic, antipsychotic, antidepressant, and antiepileptic agents, as well as drugs for the treatment of Parkinson's disease, bisphosphonates, hormone replacement therapy, and thiazides.

Table 2. Risk of fracture in RA patients compared with control patients, according to disease severity or medication use*

	Prevalence of fracture in RA cohort, %	Clinical osteoporotic fracture		Femur/hip fracture		Clinical vertebral fracture	
		Age- and sex-adjusted RR (95% CI)	Fully adjusted RR (95% CI)	Age- and sex-adjusted RR (95% CI)	Fully adjusted RR (95% CI)	Age- and sex-adjusted RR (95% CI)	Fully adjusted RR (95% CI)
RA duration							
<2 years	29.8	1.3 (1.2–1.4)	1.2 (1.1–1.4)	1.6 (1.3–1.9)	1.5 (1.3–1.9)	2.1 (1.6–2.8)	1.9 (1.4–2.5)
2–10 years	45.1	1.5 (1.3–1.6)	1.4 (1.3–1.5)	2.0 (1.7–2.3)	1.8 (1.6–2.1)	2.5 (1.9–3.2)	2.2 (1.7–2.8)
>10 years	25.1	2.1 (1.9–2.3)	1.9 (1.7–2.0)	3.4 (3.0–3.9)	2.9 (2.5–3.3)	4.2 (3.3–5.3)	3.4 (2.7–4.4)
Body mass index†							
<20 kg/m^2	5.7	2.0 (1.7–2.4)	1.9 (1.6–2.2)	3.9 (3.1–4.9)	3.6 (2.9–4.6)	3.1 (2.0–5.1)	2.4 (1.5–3.9)
20–26 kg/m^2	36.6	1.6 (1.5–1.7)	1.5 (1.4–1.7)	2.1 (1.8–2.4)	2.0 (1.7–2.4)	2.7 (2.1–3.4)	2.2 (1.7–2.9)
≥26 kg/m^2	30.8	1.2 (1.0–1.3)	1.1 (1.0–1.2)	1.4 (1.1–1.7)	1.4 (1.1–1.7)	2.0 (1.5–2.8)	1.7 (1.2–2.3)
Use of NSAIDs/aspirin in prior 6 months							
No	38.9	1.5 (1.4–1.7)	1.4 (1.3–1.5)	2.0 (1.8–2.3)	1.8 (1.6–2.1)	2.5 (2.0–3.2)	2.2 (1.7–2.8)
1–2	19.1	1.4 (1.3–1.6)	1.4 (1.2–1.5)	1.9 (1.5–2.3)	1.7 (1.4–2.1)	3.2 (2.4–4.3)	2.8 (2.1–3.8)
>2	42.1	1.7 (1.5–1.8)	1.5 (1.4–1.7)	2.7 (2.3–3.0)	2.3 (2.1–2.7)	2.8 (2.3–3.6)	2.5 (2.0–3.1)
Use of oral glucocorticoids in prior 6 months							
No	76.6	1.3 (1.2–1.4)	1.2 (1.1–1.3)	1.8 (1.6–2.1)	1.7 (1.5–2.0)	1.6 (1.2–1.9)	1.5 (1.2–1.9)
1–2	6.6	1.9 (1.6–2.2)	1.7 (1.4–2.0)	2.6 (2.0–3.4)	2.3 (1.7–3.0)	3.8 (2.5–5.8)	2.9 (1.9–4.4)
>2	16.8	2.6 (2.4–2.9)	2.3 (2.1–2.5)	3.4 (3.0–4.0)	2.8 (2.4–3.3)	7.1 (5.7–8.8)	5.5 (4.4–6.8)
Use of disease-modifying antirheumatic agents in prior 6 months							
No	62.2	1.6 (1.5–1.7)	1.5 (1.4–1.6)	2.1 (1.9–2.4)	1.9 (1.7–2.1)	2.6 (2.1–3.1)	2.3 (1.9–2.8)
1–2	10.9	1.5 (1.3–1.8)	1.4 (1.2–1.6)	2.5 (1.9–3.3)	2.2 (1.7–2.9)	3.8 (2.7–5.5)	3.3 (2.3–4.7)
>2	26.8	1.6 (1.4–1.8)	1.5 (1.4–1.7)	2.6 (2.2–3.1)	2.3 (2.0–2.8)	3.0 (2.3–3.9)	2.5 (1.9–3.3)
Hospitalization for musculoskeletal disorder in previous year							
No	96.9	1.5 (1.4–1.6)	1.4 (1.4–1.5)	2.2 (1.9–2.4)	2.0 (1.8–2.2)	2.6 (2.2–3.1)	2.3 (1.9–2.8)
Yes	3.1	2.5 (2.1–3.1)	2.1 (1.7–2.6)	4.4 (3.3–6.1)	3.4 (2.5–4.6)	7.6 (4.9–11.6)	5.5 (3.6–8.5)
Prior arthroplasty							
No	88.5	1.5 (1.4–1.6)	1.4 (1.3–1.5)	2.0 (1.8–2.3)	1.9 (1.7–2.1)	2.6 (2.2–3.1)	2.3 (1.9–2.8)
Knee	6.9	2.1 (1.8–2.4)	1.9 (1.7–2.2)	3.5 (2.8–4.4)	3.1 (2.5–4.0)	2.6 (1.7–4.1)	2.3 (1.5–3.6)
Hip	6.0	1.5 (1.2–1.7)	1.3 (1.1–1.6)	1.5 (1.1–2.0)	1.3 (1.0–1.7)	2.1 (1.3–3.4)	1.7 (1.1–2.8)
History of pulmonary fibrosis							
No	99.6	1.6 (1.5–1.6)	1.5 (1.4–1.5)	2.2 (2.0–2.5)	2.0 (1.8–2.2)	2.7 (2.3–3.2)	2.4 (2.0–2.8)
Yes	0.4	4.3 (2.7–6.7)	3.5 (2.2–5.6)	6.2 (2.9–13.0)	4.9 (2.3–10.2)	18.5 (8.7–39.2)	11.9 (5.6–25.4)
History of skin ulcer							
No	92.8	1.5 (1.4–1.6)	1.4 (1.3–1.5)	2.1 (1.8–2.3)	1.9 (1.7–2.1)	2.7 (2.3–3.2)	2.3 (2.0–2.9)
Yes	7.2	2.2 (2.0–2.5)	1.9 (1.7–2.2)	3.5 (2.9–4.2)	2.8 (2.3–3.4)	3.5 (2.5–5.1)	2.7 (1.9–3.9)

* Except where indicated otherwise, values are the relative risk (RR) (95% confidence interval [95% CI]) of fracture in the presence of each risk factor. There was no statistically significant difference in the risk of osteoporotic fracture between rheumatoid arthritis (RA) patients with and those without any of the following indicators of disease severity: a general practitioner visit for stiff or painful joints, history of carpal tunnel syndrome, Raynaud's phenomenon, amyloidosis, uveitis/scleritis/iritis, pericarditis/myocarditis/endocarditis, neuropathy, and hearing loss. NSAIDs = nonsteroidal antiinflammatory drugs.
† Information missing for 27.8% of the patients.

Table 3. Risk score of fracture in relation to age, sex, duration of rheumatoid arthritis (RA), indicators of RA severity, and general clinical risk factors

Risk factor	Type of fracture		
	Clinical osteoporotic	Femur/hip	Clinical vertebral
Age (for each 10 years)	5	9	5
Sex, male	−7	−6	−4
Body mass index <20 kg/m^2	3	7	1
Body mass index ≥26 kg/m^2	−2	−3	−3
RA duration			
<2 years	1	3	2
2–10 years	1	4	3
>10 years	3	7	6
1–2 oral glucocorticoids in prior 6 months	3	2	7
>2 oral glucocorticoids in prior 6 months	6	4	13
Recent hospitalization for musculoskeletal disorder	2	4	7
History of knee arthroplasty	2	4	–
History of pulmonary fibrosis	6	–	13
History of skin ulcer	2	3	–
History of fall	5	4	–
History of fracture	6	6	8
Smoker	1	2	2
Use of CNS medications (for each different drug)*	2	3	2
Other chronic disease (for each disease)	2	2	5

* CNS = central nervous system.

RA patients reported current use of oral glucocorticoids, and this was associated with a substantially increased risk of fracture. The fracture risk in patients with RA remained elevated after excluding patients who had taken oral glucocorticoids at any time during the period of followup (adjusted RR for clinical osteoporotic fracture 1.3 [95% CI 1.2–1.4], adjusted RR for hip fracture 1.7 [95% CI 1.5–2.0]).

Long-term risk of fracture in RA patients. Table 3 presents the risk score according to various patient profiles. This risk score represents a cumulative score of the various risk factors associated with the occurrence of fracture over the followup. For example, in a woman age 65 years with longstanding RA, a low BMI, a history of fracture, and frequent oral glucocorticoid use (>2 prescriptions in the prior 6 months), the hip fracture risk score was 85. This score was calculated as follows: +9 points for each 10 years of age and, because of an age midpoint of 67.5 years, 9 × 6.75, to yield a score of 61 for age, +7 points for RA duration, +7 points for low BMI, +6 points for fracture history, and +4 points for use of oral glucocorticoids. The corresponding 5-year risk of hip fracture in a patient with this risk profile was 5.7% (95% CI 5.3–6.1%). The 5-year risks of hip fracture in patients with risk scores of 60, 80, and 100 were 0.6% (95% CI 0.5–0.6%), 3.6% (95% CI 3.4–3.9%), and 20.8% (95% CI 18.8–22.8%), respectively (Figure 2).

Table 4 shows the distribution of the 5-year fracture risks among patients with RA. For example, among women with RA ages 70–79 years, the median 5-year incidence of hip fracture was 3.0%; however, there was considerable variation in the risk of hip fracture in this age range, since the risk was 1.2% for the women in the 5th percentile of risk score and 10.6% for the women in the 95th percentile of risk score. The area under the ROC curve was 0.72 for clinical osteoporotic fractures, 0.84 for hip fractures, and 0.77 for clinical vertebral fractures.

Sensitivity analyses. Several sensitivity analyses were conducted, specifically because of concerns about the accuracy of RA diagnosis (in terms of inaccurate recording or assessment of RA) in the GPRD, as well as to explore factors that might modify the effects of RA on fracture risk. When the analysis was restricted to RA patients who had received NSAIDs, oral glucocorticoids, or disease-modifying antirheumatic agents, the adjusted RR for clinical osteoporotic fracture was 1.3 (95% CI 1.3–1.4) and the adjusted RR for hip fracture was 2.0 (95% CI 1.8–2.3). Similar results were obtained when including only patients with records indicating the 3 most frequently used codes for RA (RR for clinical osteoporotic fracture 1.5 [95% CI 1.4–1.6], RR for hip fracture 2.1 [95% CI 1.9–2.4]) or when excluding patients with other inflammatory conditions (RR for clin-

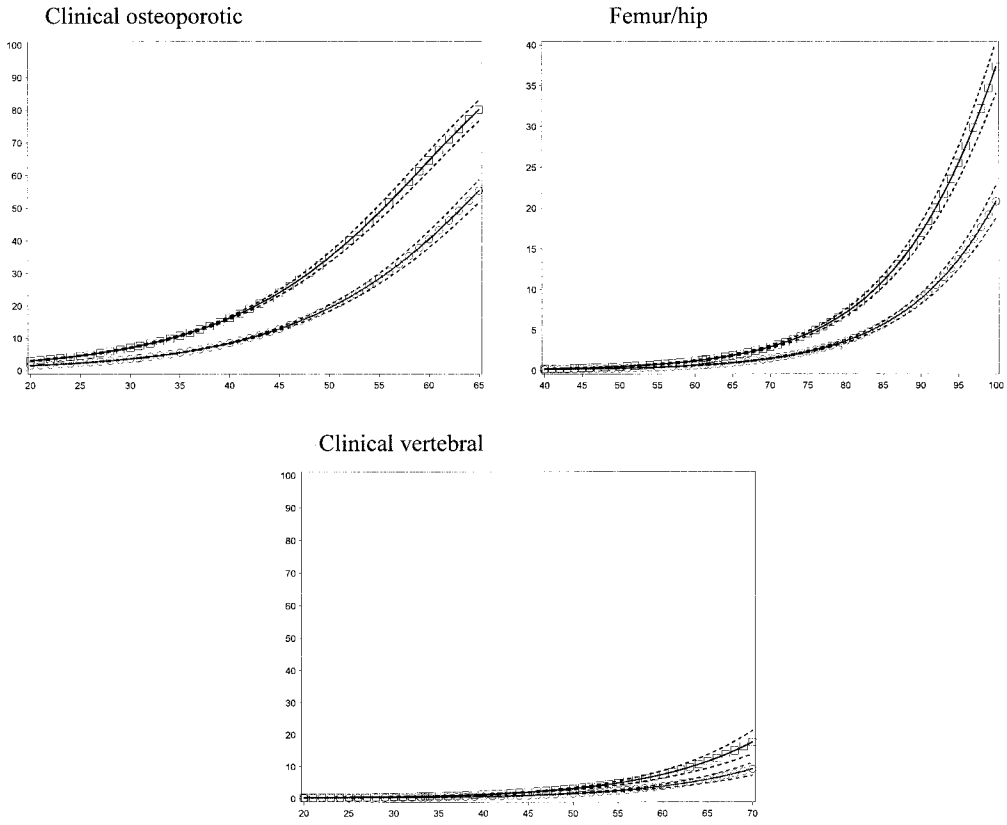

Figure 2. Risk of fracture (percentage) in relation to risk score (scale 0–100) over the 5-year (○) and 10-year (□) periods of followup in patients with rheumatoid arthritis. The dotted lines indicate 95% confidence intervals.

ical osteoporotic fracture 1.5 [95% CI 1.4–1.6], RR for hip fracture 2.0 [95% CI 1.8–2.3]). Including in the regression analyses duration of data collection prior to the index date did not change the results.

DISCUSSION

The results of this study suggest that patients with RA are at a substantially increased risk of fractures at the hip, pelvis, vertebrae, humerus, and tibia/fibula,

Table 4. Five-year fracture risks in patients with rheumatoid arthritis, by sex and age categories, at the 5th, 50th, and 95th percentiles of fracture risk scores*

	Clinical osteoporotic fracture			Femur/hip fracture			Clinical vertebral fracture		
Sex, age in years	5th	50th	95th	5th	50th	95th	5th	50th	95th
Women									
40–49	1.4 (19)	2.1 (24)	4.7 (33)	0.1 (40)	0.2 (48)	0.5 (59)	0.1 (21)	0.2 (27)	0.8 (42)
50–59	2.1 (24)	3.3 (29)	7.2 (38)	0.2 (49)	0.4 (56)	1.2 (68)	0.2 (25)	0.3 (32)	1.3 (48)
60–69	3.3 (29)	5.5 (35)	12.9 (45)	0.5 (58)	1.1 (67)	4.0 (81)	0.3 (30)	0.5 (38)	2.7 (56)
70–79	5.1 (34)	9.2 (41)	22.6 (52)	1.2 (68)	3.0 (78)	10.6 (92)	0.4 (36)	1.0 (45)	5.0 (63)
80+	8.5 (40)	15.2 (47)	35.3 (58)	3.3 (79)	8.1 (89)	24.5 (102)	0.6 (40)	1.7 (51)	7.8 (68)
Men									
40–49	0.7 (12)	1.1 (16)	2.1 (24)	0.1 (34)	0.1 (41)	0.3 (51)	0.1 (16)	0.1 (22)	0.4 (36)
50–59	1.2 (17)	1.6 (21)	3.9 (31)	0.1 (43)	0.2 (50)	0.7 (62)	0.1 (21)	0.2 (28)	0.9 (44)
60–69	1.6 (21)	2.8 (27)	6.6 (37)	0.3 (52)	0.6 (60)	1.8 (72)	0.2 (26)	0.4 (34)	1.7 (51)
70–79	2.8 (27)	4.7 (33)	10.9 (43)	0.7 (61)	1.5 (70)	4.3 (82)	0.3 (31)	0.6 (40)	3.2 (58)
80+	3.9 (31)	7.2 (38)	16.5 (48)	1.6 (71)	3.6 (80)	10.6 (92)	0.4 (35)	1.1 (46)	5.0 (63)

* Values are the fracture risk percentage (median fracture risk score).

whereas they have a lower risk of radius/ulna fractures. The increases in the risks of fracture were larger in patients with longstanding disease and a lower BMI. Moreover, the increases in the risks of fracture were apparent not only in RA patients who had been treated with oral glucocorticoids, but also in patients who had not taken oral glucocorticoids.

Although several studies have examined the risk of hip fracture in patients with RA, the relative contributions of oral glucocorticoids and the underlying disease process to this increased risk remain unclear. Of the 2 largest studies, the study by Huusko et al did not evaluate the effects of oral glucocorticoids in patients with RA (3). In a Southampton, UK case–control study, the effects of RA and oral glucocorticoids were found to be largely independent of each other; patients with RA who were not receiving oral glucocorticoids had a doubled risk of hip fracture, although this did not reach statistical significance (1). Our findings are consistent with the findings of the UK study, in suggesting that active disease is associated with increases in the risk of fracture. In our study, one-quarter of the RA patients were taking oral glucocorticoids; this is in accordance with other estimates from Europe (24), whereas in other parts of the world (such as the US), up to 75% of RA patients may take oral glucocorticoids (25). The use of disease-modifying antirheumatic drugs was low in our population (with data collected from 1987 to 2002), but this prevalence has changed considerably with calendar time (26). We found that RA patients who were not taking oral glucocorticoids also had increased risks of fracture. This indicates that the underlying disease process in RA may also contribute to the fracture risk.

RA is a systemic disease that results in joint inflammation with associated joint destruction. The inflammation results in bone loss adjacent to the affected joints (27). Generalized axial and appendicular bone loss at sites distant from the affected joints has also been demonstrated in several studies (28–30). This may be related to systemic effects of rheumatoid inflammation, immobility, nutritional problems, and weight loss (31). This is consistent with our finding that fracture rates were elevated at sites not typically affected by joint inflammation in RA.

The RA definition used in our study was based on the general practitioner's diagnosis and recording. We did not apply commonly used criteria for the diagnosis of RA, such as the American College of Rheumatology (formerly, American Rheumatism Association) criteria (32). The reason for this is that such information is not routinely recorded for all patients, since the diagnosis can be made in secondary care, with the general practitioner being informed only about the diagnosis and treatment plan. Therefore, for this study, it is likely that we imposed a relatively sensitive, but nonspecific, diagnosis of RA, with a corresponding underestimate of its clinical effects. However, our results did not change when the analyses were restricted to RA patients who had received drug treatment or when a more restrictive list of RA diagnoses was used. The frequency of utilization of bone-sparing agents such as bisphosphonates was too low among the patients with RA to provide adequate power for an exploration of any benefits that they might confer.

In this study, we developed a risk score that provides an easily applicable clinical method of estimating a patient's individual risk of fracture. The data used for this risk score are routinely recorded in the general practitioner medical records, and therefore the general practitioner could estimate the long-term risk of fracture using this standard information. Individuals with a risk score of 25 would have a 10-year risk of any osteoporotic fracture of ~5%, in contrast with those scoring 50, whose risk would rise to ~30%. Our findings suggest that the long-term risk of fracture can be substantial in RA patients. In postmenopausal osteoporosis, intervention thresholds are currently determined by a combination of clinical risk factors and assessment of BMD. However, fracture probability varies substantially with age at any given level of BMD. Older people have much higher fracture risks than younger people, even when their BMD is similar (17). Treatment decisions for osteoporosis should therefore be based primarily on absolute long-term risks of fracture (17,18,33).

The risk estimates in this study were based on retrospective data, and therefore need to be validated in prospective studies, particularly because populations and circumstances are continuously changing (34). Furthermore, these risk estimates may not be easily generalized to other populations. It would be more appropriate to view these estimates as a tool to improve the prediction of fracture in RA patients, rather than as definitive risk estimates applicable to every patient.

This study has several limitations. Although it is the first large, population-based study to examine fracture risk and major risk factors in patients with RA, there were no data on some possible etiologic factors, such as malabsorption. The evaluation of various contributing factors, including vitamin D levels and physical activity, was also limited.

Second, the GPRD does not permit easy identification of the date of onset of RA, but rather permits capture of data from a specific period of observation following the diagnosis of RA. It is likely, therefore, that our estimates of disease duration are lower than the true values, but it seems unlikely that this would systematically bias our assessment of fracture risk in patients with RA as compared with controls.

Third, fractures that are completely dealt with in an emergency room setting (such as wrist fractures) may be less completely captured than those resulting in in-patient care. This would explain the attenuated risk estimates for wrist fracture that we observed. An additional explanation might lie in the type of fall sustained by patients with RA, who might selectively avoid stretching their arm and thereby sustain direct injury to the axial, rather than appendicular, skeleton.

Fourth, the predictor variables available for the study were chosen opportunistically as indirect markers of disease severity; they are subject to measurement error and, for some variables, there was the possibility of incomplete ascertainment. Again, these limitations are conservative biases and would have been unlikely to spuriously elevate the risk estimates observed.

Fifth, medications prescribed only in hospitals, such as anti–tumor necrosis factor treatment, would not be recorded. Finally, the assessment of vertebral fracture is likely to be incomplete in the GPRD. A previous validation study showed that the vertebral fractures identified in the GPRD tended to be clinically symptomatic fractures confirmed on a radiograph (21,24). Systematic morphometry of vertebral fractures is not routinely performed by primary care physicians in the UK. Moreover, RA disease severity was evaluated only through the use of indirect markers. The long-term prediction of fracture could likely improve with more detailed information on RA disease severity.

Thus, the present study demonstrates that patients with RA have an increased risk of fractures at the hip, pelvis, vertebrae, humerus, and tibia/fibula; this risk was accentuated in patients with longstanding disease, in patients with a low BMI, and in those taking oral glucocorticoids. The increased risk is attributable to a combination of disease activity and use of oral glucocorticoids, with each having a similar magnitude of effect. The long-term risks of fracture can be substantial, and further investigations, such as those involving bone densitometry, might be conveniently targeted to patients with higher absolute long-term fracture risk.

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