RHEUMATOLOGY

Rheumatology 2022;61:1448–1458
doi:10.1093/rheumatology/keab548
Advance Access publication 13 July 2021

Original article

Low-dose oral glucocorticoid therapy and risk of osteoporotic fractures in patients with rheumatoid arthritis: a cohort study using the Clinical Practice Research Datalink

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Abstract

Objectives. Clinical trials have shown that low-dose glucocorticoid therapy in patients with RA reduces bone loss in hands or hip, but the effect on osteoporotic fractures is not yet clear. Therefore, we investigated the use of low-dose oral glucocorticoids and risk of osteoporotic fractures among patients with RA.

Methods. This was a cohort study including patients with RA aged 50+ years from the Clinical Practice Research Datalink between 1997 and 2017. Exposure to oral glucocorticoids was stratified by the most recent prescription in current (<6 months), recent (7–12 months) and past (>1 year) use, and average daily and cumulative doses. Risk of incident osteoporotic fractures (including hip, vertebrae, humerus, forearm, pelvis and ribs) was estimated by time-dependent Cox proportional-hazards models, adjusted for lifestyle parameters, comorbidities and comedications. Secondary analyses assessed osteoporotic fracture risk with a combination of average daily and cumulative doses of oral glucocorticoids.

Results. Among 15 123 patients with RA (mean age 68.8 years, 68% females), 1640 osteoporotic fractures occurred. Current low-dose oral glucocorticoid therapy (≤7.5 mg prednisolone equivalent dose/day) in patients with RA was not associated with overall risk of osteoporotic fractures (adjusted hazard ratio 1.14, 95% CI 0.98, 1.33) compared with past glucocorticoid use, but was associated with an increased risk of clinical vertebral fracture (adjusted hazard ratio 1.59, 95% CI 1.11, 2.29). Results remained unchanged regardless of a short-term or a long-term use of oral glucocorticoids.

Conclusion. Clinicians should be aware that even in RA patients who receive low daily glucocorticoid doses, the risk of clinical vertebral fracture is increased.

Key words: osteoporotic fractures, RA, glucocorticoids, BMD

CLINICAL SCIENCE

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Submitted 5 March 2021; accepted 27 June 2021

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Rheumatology key messages

- Low-dose oral glucocorticoid use (≤7.5mg prednisolone equivalent dose/day) incurred a 59% increased risk of clinical vertebral fracture in RA patients.
- There was no association between non-vertebral fracture risk and low daily doses of oral glucocorticoids in RA.
- The results remained unchanged regardless of a short- or a long-term oral glucocorticoid use.

Introduction

Osteoporotic (OP) fractures are a major complication among patients with RA [1–3]. The reason for this increased susceptibility of OP fractures in RA is the underlying chronic inflammation of the disease, and the pharmacotherapy that patients with RA receive, most importantly oral glucocorticoids (GCs). Short-term GC therapy is part of the EULAR recommendations 2019 update for RA management, and around a quarter of RA patients are treated with GCs in the UK [1, 4]. GC therapy leads to decreased BMD and increased fracture risk from early in the treatment course, by mediating a reduction in bone formation and an increase in bone resorption [5–8].

Low-dose GC therapy, especially in chronic inflammatory diseases, could also have positive effects on bone loss, where it suppresses the underlying deleterious inflammation and improves the functional status of patient [9–14]. The randomised controlled trial (RCT) by Haugeberg *et al.* reported a statistically significant reduced bone loss in hands after 1 and 2 years in RA patients who were taking 7.5 mg prednisolone once daily compared with placebo [9]. However, extrapolation of this local beneficial effect in hands to the generalised bone loss in RA and the resulting risk of OP fracture is questionable. On the other hand, observational studies have reported higher fracture rates with low-dose oral GC use [i.e. ≤7.5 mg prednisolone equivalent dose (PED) per day] in RA compared with non-use [13, 15, 16], although these findings may be confounded by indication or disease severity. Additionally, the results of a review by an EULAR task force regarding the risk of harm (including osteoporosis and OP fractures) of long-term GC therapy in RA was inconclusive for dosages between 5 and 10 mg PED/day [17]. These conflicting findings and the uncertainty over any possible beneficial effect of low daily doses of oral GCs on fracture risk in RA justifies a more detailed examination of this association using real-world data. Thus, the objective of this study was to investigate the use of low-dose oral GCs and risk of OP fractures among patients with RA.

Methods

Database

This is a retrospective cohort study using data from the Clinical Practice Research Datalink, GOLD (CPRD; www.cprd.com). CPRD is one of the world's largest primary care databases. It contained medical records of 674 practices in the UK in 2013, representing 4.4 million active patients that equalled to 6.9% of the total population [18]. It includes data on patient demographics, lifestyle parameters, clinical diagnoses, prescription details, laboratory test results, specialist referrals and major outcomes since 1987, with continuing data collection. The CPRD has been well validated for a wide range of diseases, including hip and vertebral fractures [19, 20].

Study population

The study population comprised all adults aged 50+ years diagnosed with RA in the CPRD between 1 January 1997 and 31 December 2017. We used a validated algorithm that detected 86% of the true RA cases among people with an RA Read code in the CPRD (supplementary Table S1, available at *Rheumatology* online) [21, 22]. The date of the first RA diagnosis during the period of valid data collection (considering up to standard time of the CPRD practice) defined the index date (i.e. start of follow-up). Each patient was then followed from the index date until the occurrence of the intended outcome, the end of study period, moving out of the practice area, death or last data collection date of the CPRD practice, whichever came first. Follow-up time was broken down into 30-day periods. Patients with a history of oral GC use during the 1 year before the index date, and those with an OP fracture prior to the index date were excluded.

Exposure and outcome

The exposure of interest was the use of oral GCs, which was assessed time-dependently in 30-day periods. At the start of each 30-day period, we identified prescribing of oral GCs in a retrospective manner. A period was defined as current, recent or past use when the most recent prescription of oral GCs was issued within 6 months before, 7–12 months before and >12 months before, respectively [6, 23]. Non-use was defined as all other follow-up time without a history of oral GC exposure.

Current GC use was further broken down into subcategories based on average daily and cumulative dose. All oral GC prescriptions were retrieved, and the prescribed quantity was extracted and converted into PED, using the World Health Organisation Anatomical Therapeutic Chemical classification system of defined daily doses (ATC/DDD) [24]. Values for missing data on

prescribed quantity were assigned the median value of all prescriptions. The cumulative amount of the drug prescribed in each follow-up period was estimated by summing all consecutive prescriptions since the index date. The average daily dose in each follow-up period was calculated by dividing the cumulative amount prescribed by the treatment time (i.e. the time between the first oral GC prescription and the start date of a period of current use). The composite outcome in this study was the occurrence of a first OP fracture in patients with RA after the index date, including the hip, clinically symptomatic vertebral, humerus, forearm, pelvic and rib fractures, through relevant Read codes [1, 16, 19, 23, 25, 26].

Potential confounders

Sex, BMI, smoking status and alcohol use were assessed at the index date. During follow-up, we determined age, and a history of asthma, chronic obstructive pulmonary disease, ischaemic heart disease (including myocardial infarction), cerebrovascular disease, congestive heart failure, anaemia, peripheral arterial disease, gastroesophageal reflux disease, peptic ulcer disease, IBD (Crohn's disease and ulcerative colitis), coeliac disease, hyperthyroidism, hypothyroidism, type 1 and 2 diabetes mellitus, osteomalacia, hypopituitarism, Cushing's disease, bilateral orchidectomy or oophorectomy, chronic renal failure, AS, muscular dystrophy, dementia, Parkinson's disease, spinal cord injury, anorexia nervosa, major infections (i.e. sepsis, meningitis, upper and lower respiratory tract infections), malignant neoplasms (excluding non-melanoma skin cancers), and organ transplantation [27]. Falls were determined in the 7–12 months before each period. The use of comedications in 6 months prior was determined and included antihypertensives, anticoagulants, proton pump inhibitors, calcium/vitamin D, bisphosphonates, HRT, anticonvulsants, hypnotics/anxiolytics, antidepressants and antipsychotics. The following medications were measured at the same time-windows and were considered as indicators of the underlying severity of RA: non-selective NSAIDs, cyclooxygenase-2 selective inhibitors, paracetamol, tramadol, opioids (stronger than tramadol), and conventional synthetic DMARDs (csDMARDs).

Statistical analysis

Time-dependent Cox proportional-hazards models estimated the risk of OP fracture in RA patients with current use of low-dose oral GCs [average daily dose $\leq$7.5 mg PED/day (based on EULAR definitions [4])] *vs* past use. We selected past use as the reference category—instead of non-use—to have the most comparable control group and to reduce confounding by indication. Also, medium and high average daily use of oral GCs (7.6–14.9 mg PED/day and $\geq$15.0 mg PED/day, respectively) were compared with past use. All these exposure subcategories under current GC use were statistically compared with a Wald test. Additionally, separate analyses were conducted for various OP fracture sites. Any of the potential confounders were incorporated in the model if they changed the beta-coefficient of the association >5% or based on literature following authors' assessment. Collinearity between potential confounders was assessed.

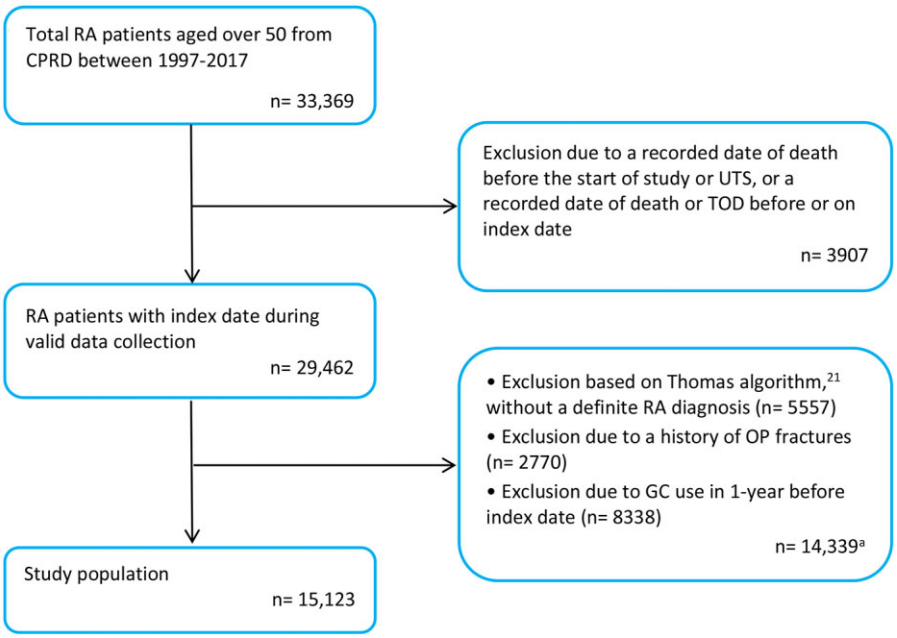
In secondary analyses, cumulative use of oral GCs and its combination with average daily doses of oral GCs in RA patients were compared with past use. Furthermore, four sensitivity analyses were conducted. First, OP fracture risk in RA was assessed in various other cut-offs for low GC use (i.e. $\leq$5.0 mg PED/day and $\leq$2.5 mg PED/day). Second, we repeated a Cox model to estimate the risk of OP fracture with low-dose oral GC use by removing csDMARDs as confounder, since we thought csDMARDs, as a measure of RA disease severity, might lie in the causal pathway of this association [4, 28]. In the third sensitivity analysis, we repeated the main model, only after excluding those patients with a prior OP fracture in the 1 year before the index date. Fourthly, we ran a Cox model by comparing current use of low-dose oral GCs to non-use of GCs. Finally, a *post hoc* analysis was performed to evaluate the association between a GC daily dose of 5.1–7.5 mg PED/day and OP fractures in patients with RA. Data were analysed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). This study was approved by the Independent Scientific Advisory Committee for Medicines and Healthcare products Regulatory Agency database research (protocol 19_201).

Results

The study population consisted of 15 123 RA patients aged 50+ years (Fig. 1). Table 1 shows a mean follow-up time of 8.1 years for GC users (N = 7039) and 6.2 years for non-users (N = 8084). The average duration of GC use was 3.7 years. The mean age of GC users at the index date was 68.4 years and of non-users was 69.1 years. Females constituted 67% of GC users and 70% of non-users. Around one-third of both exposure groups had a normal-range BMI (25–30 kg/m^2). While 23% of GC users were current smokers, only 19% of non-users were smokers at the index date. The most frequent comorbidities among GC users were major infections and asthma, and major infections and anaemia among non-users. Around 30% of GC users and >35% of non-users were concomitantly taking csDMARDs at the index date.

Current use of low-dose oral GCs ($\leq$7.5 mg PED/day) was not associated with overall risk of OP fractures among patients with RA compared with past GC use [adjusted hazard ratio (aHR) 1.14, 95% CI 0.98, 1.33] (Table 2). However, current use of higher daily dosages of oral GCs incurred a 38% increased (aHR 1.38, 95% CI 1.11, 1.73 for 7.6–14.9 mg PED/day) or an 84% increased risk (aHR 1.84, 95% CI 1.23, 2.74 for $\geq$15.0 mg PED/day) of OP fractures. The increased fracture risk with high-dose oral GCs was statistically

Fig. 1 Flowchart on establishment of patient population



UTS: up to standard time (i.e. date at which the practice data is deemed to be of research quality); TOD: transfer out of database date (i.e. date the patient transferred out of the practice); OP: osteoporotic; GC: glucocorticoid; CPRD: Clinical Practice Research Datalink. [a]The numbers for specific exclusion criteria would not add up to the total excluded number as there was some overlap between the exclusion categories.

different from low-dose oral GC use (Wald test, $P < 0.05$). Sensitivity analyses showed that current use of lower dosages of oral GCs shifted the association further towards null, yielding an aHR of 1.07 (95% CI 0.89, 1.29) for an average daily dose ≤5.0 mg PED/day, and an aHR of 1.00 (95% CI 0.77, 1.31) for an average daily dose ≤2.5 mg PED/day for OP fracture risk (supplementary Table S2, available at *Rheumatology* online).

Table 3 shows that treatment with low daily doses of oral GCs in patients with RA was associated with a 59% increased risk of clinical vertebral fracture, compared with past GC use (aHR 1.59, 95% CI 1.11, 2.29). Nonetheless, the risk of other individual OP fracture sites, i.e. hip, humerus, forearm, pelvic and rib fractures, was not associated with low-dose oral GC use *vs* past use.

Patients with RA who were current users of low-dose oral GCs had no increased risk of OP fracture, regardless of a short-term (≤1.0 g PED) or a long-term (>1.0 g PED) use (Table 4). In contrast, high-dose (≥7.5 mg PED/day) long-term oral GC users had a 1.5-fold increased risk of OP fracture compared with patients who had stopped taking oral GCs for >1 year, yielding an aHR of 1.52 (95% CI 1.22, 1.89).

When csDMARDs were removed from the Cox model as confounder, we observed similar estimates of OP fracture risk with the various daily doses of oral GCs (supplementary Table S3, available at *Rheumatology* online). However, exclusion of patients with a prior fracture only in 1 year before the index date ($N = 16\,450$) resulted in associations shifting away from the null (supplementary Table S4, available at *Rheumatology* online). Furthermore, a comparison of current use of oral GCs to non-use, instead of past GC use, resulted in a statistically significant 21% increased risk of OP fracture with low-dose oral GC use (aHR 1.21, 95% CI 1.05, 1.39) (data not shown). Finally, 136 OP fractures occurred among those RA patients who used a GC daily dose of 5.1–7.5 mg PED/day, with an incidence rate of 23.2 per 1000 person years. Current use of oral GCs with a dose of 5.1–7.5 mg PED/day in RA incurred a 24% increased risk of OP fractures (aHR 1.24, 95% CI 1.02, 1.51), compared with past GC use.

Discussion

We found that current low-dose oral GC use (≤7.5 mg PED/day) in patients with RA was not associated with an increased risk of OP fractures compared with past GC use. Similar findings were revealed for lower daily doses, i.e. ≤5.0 mg PED/day and ≤2.5 mg PED/day. Nevertheless, low-dose oral GC therapy was associated with an increased risk of clinical vertebral fracture, while the risk of other individual OP fracture sites was not increased. Additionally, the main results remained unchanged regardless of a short-term or a long-term use.

There is evidence from RCTs reporting that GC therapy in RA especially in low doses might have local protective effects on bone health, probably by suppressing

Table 1 Baseline characteristics of patients with RA, stratified by oral GC therapy status during follow-up ($N = 15\,123$).

	Oral GC users ($N = 7039$)[a]		Non-users ($N = 8084$)	
	N	%	*N*	%
Mean duration of follow-up (years, S.D.)	8.1 (4.9)		6.2 (4.7)	
Age (years)[b]				
Mean (S.D.)	68.4 (8.6)		69.1 (8.7)	
50–59	1150	16.3	1211	15.0
60–69	2842	40.4	3052	37.8
70–79	2312	32.8	2817	34.8
80+	735	10.4	1004	12.4
Number of females	4687	66.6	5654	69.9
BMI (kg/m^2)[b]				
Mean (S.D.)	26.5 (5.2)		26.3 (5.2)	
<20.0	481	6.8	568	7.0
20.0–24.9	2279	32.4	2642	32.7
25.0–29.9	2432	34.6	2687	33.2
30.0–34.9	1003	14.2	1039	12.9
≥35.0	394	5.6	435	5.4
Missing	450	6.4	713	8.8
Smoking status[b]				
Non	2488	35.3	3132	38.7
Current	1609	22.9	1557	19.3
Past	2856	40.6	3183	39.4
Missing	86	1.2	212	2.6
Alcohol use[b]				
No	2058	29.2	2205	27.3
Yes	4464	63.4	5125	63.4
Missing	517	7.3	754	9.3
History of comorbidities[b]				
Asthma	942	13.4	536	6.6
COPD	544	7.7	263	3.3
Ischemic heart disease (including myocardial infarction)	940	13.4	987	12.2
Cerebrovascular disease	399	5.7	470	5.8
Congestive heart failure	192	2.7	254	3.1
Anaemia	923	13.1	1126	13.9
Peripheral arterial disease	364	5.2	416	5.1
Gastroesophageal reflux disease	585	8.3	596	7.4
Peptic ulcer disease	66	0.9	64	0.8
Coeliac disease	22	0.3	26	0.3
IBD (Crohn's disease and ulcerative colitis)	75	1.1	66	0.8
Hyperthyroidism	48	0.7	46	0.6
Hypothyroidism	558	7.9	619	7.7
Diabetes mellitus type 1	51	0.7	54	0.7
Diabetes mellitus type 2	425	6.0	560	6.9
Chronic renal failure	363	5.2	394	4.9
AS	9	0.1	18	0.2
Dementia	34	0.5	65	0.8
Parkinson's disease	14	0.2	47	0.6
Major infections[c]	1437	20.4	1414	17.5
Malignant neoplasms (excluding non-melanoma skin cancers)	651	9.2	747	9.2
Falls (7–12 months before)	47	0.7	71	0.9
Comedications use (6 months before)[b]				
Antihypertensives	2597	36.9	3141	38.9

(continued)

Table 1 Continued

	Oral GC users (*N* = 7039)[a]		Non-users (*N* = 8084)	
	N	%	*N*	%
Anticoagulants	218	3.1	237	2.9
Proton pump inhibitors	1756	24.9	2006	24.8
Calcium/vitamin D	380	5.4	574	7.1
Bisphosphonates	280	4.0	385	4.8
HRT	233	3.3	231	2.9
Anticonvulsants	118	1.7	159	2.0
Hypnotics/anxiolytics	647	9.2	589	7.3
Antidepressants	916	13.0	967	12.0
Antipsychotics	67	1.0	77	1.0
Disease severity indicators				
Non-selective NSAIDs	4057	57.6	4344	53.7
COX-2 selective inhibitors	711	10.1	669	8.3
Paracetamol	3603	51.2	3811	47.1
Tramadol	541	7.7	513	6.3
Opioids (stronger than tramadol)	430	6.1	392	4.8
csDMARDs	2104	29.9	2849	35.2

Data on the history of osteomalacia, hypopituitarism, Cushing's disease, bilateral orchidectomy/oophorectomy, muscular dystrophy, spinal cord injury, anorexia nervosa and organ transplantation are not shown due to a small number of patients in both cohorts. [a]Oral GC users are patients who had at least one prescription of an oral GC during follow-up. [b]At the index date (and start of follow-up). [c]Major infections included sepsis, meningitis, upper and lower respiratory tract infections. COPD: chronic obstructive pulmonary disease; COX-2: cyclooxygenase-2; csDMARDs: conventional synthetic DMARDs; GC: glucocorticoid.

Table 2 Use of oral GCs and risk of OP fracture in patients with RA, by average daily dose

Oral GC use By recency of use	OP fractures (*N* = 1640)[a]	IR per 1000 PYs	Age/sex adjusted HR (95% CI)	Fully adjusted HR[b] (95% CI)
Current use[c]	428	21.3	**1.36 (1.18, 1.56)**	**1.22 (1.06, 1.40)**
Mean daily dose ≤7.5 mg PED/day	301	20.3	**1.26 (1.08, 1.46)**	1.14 (0.98, 1.33)
Mean daily dose 7.6–14.9 mg PED/day	101	23.3	**1.60 (1.29, 2.00)**	**1.38 (1.11, 1.73)**
Mean daily dose ≥15.0 mg PED/day	26	27.9	**2.09 (1.40, 3.11)**	**1.84 (1.23, 2.74)**[d]
Recent use[c]	36	11.1	0.76 (0.54, 1.06)	0.71 (0.51, 1.00)
Past use[c]	375	15.7	Reference	Reference
Non-use	801	12.6	0.90 (0.80, 1.02)	0.94 (0.83, 1.07)

Statistically significant hazard ratios are shown in bold. [a]There were 1640 OP fracture events among all included patients. [b]Adjusted at baseline for sex, BMI, smoking status and alcohol use, and during follow-up for age, a history of AS, chronic obstructive pulmonary disease, dementia, falls (in the past 7–12 months), IBD, and the use in the past 6-months of antidepressants, antihypertensives, proton pump inhibitors, paracetamol, non-selective NSAIDs, cyclooxygenase-2 selective inhibitors, tramadol, opioids (stronger than tramadol), and conventional synthetic DMARDs. [c]Current, recent and past use refer to the last prescription within 6 months, 7–12 months and >12 months before a period, respectively. [d]Statistically different from low daily GC use (≤7.5 mg PED/day), Wald test $P < 0.05$. OP: osteoporotic; GC: glucocorticoid; HR: hazard ratio; IR: incidence rate; PYs: person years; PED: prednisolone equivalent dose.

the inflammatory process of the disease [9, 10]. Apart from the reduced hand bone loss in RA by once daily 7.5 mg prednisolone reported by Haugeberg *et al.* [9], another RCT from the Better Anti-Rheumatic FarmacOTherapy (BARFOT) study group showed conservation of BMD at the hip, but not in the spine, by taking 7.5 mg prednisolone daily for 2 years in patients with active RA compared with no prednisolone treatment [10]. However, there was no statistically significant difference in BMD changes at the hip or lumbar spine

Table 3 Use of oral GCs and risk of osteoporotic fracture in patients with RA, by fracture type and average daily dose

	Hip (*N* = 642)		Clinical vertebral (*N* = 267)		Humerus (*N* = 426)		Forearm (*N* = 340)		Pelvis (*N* = 135)		Rib (*N* = 92)	
Oral GC use By recency of use	**IR per 1000 PYs**	**Fully adjusted HR[a] (95% CI)**	**IR per 1000 PYs**	**Fully adjusted HR[b] (95% CI)**	**IR per 1000 PYs**	**Fully adjusted HR[a] (95% CI)**	**IR per 1000 PYs**	**Fully adjusted HR[c] (95% CI)**	**IR per 1000 PYs**	**Fully adjusted HR[d] (95% CI)**	**IR per 1000 PYs**	**Fully adjusted HR[e] (95% CI)**
Current use[f]	8.4	1.20 (0.96, 1.50)	4.5	**1.75 (1.25, 2.45)**	4.4	1.00 (0.76, 1.34)	3.1	0.94 (0.68, 1.30)	2.0	**1.78 (1.08, 2.94)**	1.2	1.07 (0.62, 1.86)
Mean daily dose ≤7.5mg PED/day	8.1	1.14 (0.90, 1.45)	4.1	**1.59 (1.11, 2.29)**	4.5	1.01 (0.75, 1.38)	2.9	0.84 (0.58, 1.21)	1.8	1.59 (0.93, 2.73)	1.1	1.08 (0.59, 1.98)
Mean daily dose 7.6–14.9mg PED/day	9.1	1.34 (0.95, 1.90)	5.4	**2.15 (1.33, 3.48)**	4.1	0.96 (0.59, 1.58)	3.4	1.17 (0.68, 2.01)	2.3	**2.22 (1.08, 4.55)**	1.7	1.50 (0.67, 3.34)[g]
Mean daily dose ≥15.0mg PED/day	9.3	1.62 (0.82, 3.18)	6.1	**2.68 (1.15, 6.26)**	4.1	1.06 (0.39, 2.89)	5.1	1.89 (0.76, 4.67)	3.1	**3.57 (1.07, 11.89)**	–	NA
Recent use[f]	5.3	0.92 (0.56, 1.50)	1.2	0.53 (0.19, 1.46)	1.8	0.44 (0.19, 1.00)	2.9	0.85 (0.44, 1.65)	1.4	1.53 (0.58, 3.99)	0.6	0.59 (0.14, 2.48)
Past use[f]	6.0	Reference	2.2	Reference	4.0	Reference	3.3	Reference	1.0	Reference	1.0	Reference
Non-use	4.5	0.89 (0.73, 1.09)	1.7	1.02 (0.73, 1.41)	3.4	0.96 (0.75, 1.22)	2.7	0.98 (0.74, 1.28)	0.9	1.29 (0.81, 2.07)	0.6	0.61 (0.37, 1.01)

Statistically significant hazard ratios are shown in bold. [a]Adjusted at baseline for sex, BMI, smoking status and alcohol use, and during follow-up for age, a history of AS, COPD, dementia, falls (in the past 7–12 months), IBD, and use in the past 6 months of antidepressants, antihypertensives, PPIs, paracetamol, NSAIDs, COX-2 selective inhibitors, tramadol, OPIs and csDMARDs. [b]Adjusted at baseline for sex, BMI, smoking status and alcohol use, and during follow-up for age, a history of COPD, dementia, falls (in the past 7–12 months), IBD, and use in the past 6 months of antidepressants, antihypertensives, hypnotics/anxiolytics, PPIs, paracetamol, non-selective NSAIDs, COX-2 selective inhibitors, tramadol, OPIs and csDMARDs. [c]Adjusted at baseline for sex, BMI, smoking status and alcohol use, and during follow-up for age, a history of asthma, COPD, dementia, falls (in the past 7–12 months), IBD, and use in the past 6 months of antidepressants, antihypertensives, anticoagulants, anticonvulsants, hypnotics/anxiolytics, PPIs, paracetamol, non-selective NSAIDs, COX-2 selective inhibitors, tramadol, OPIs and csDMARDs. [d]Adjusted at baseline for sex, and during follow-up for age, and use in the past 6 months of antidepressants, antihypertensives, PPIs, paracetamol, tramadol, OPIs and csDMARDs. [e]Adjusted at baseline for sex, and during follow-up for age, and use in the past 6 months of PPIs and paracetamol. [f]Current, recent and past use refer to the last prescription within 6 months, 7–12 months and >12 months before a period, respectively. [g]Due to no rib fracture in the high daily GC use (≥15.0 mg PED/day) group, this group was lumped together with users of medium oral GCs. Together it represents a mean daily dose >7.5 mg/day. COPD: chronic obstructive pulmonary disease; COX-2: cyclooxygenase-2; csDMARDs: conventional synthetic DMARDs; HR: hazard ratio; IR: incidence rate; NA: not available; OPIs: opioids stronger than tramadol; PPIs: proton pump inhibitors; PYs: person years; GC: glucocorticoid; PED: prednisolone equivalent dose.

TABLE 4 Use of oral GCs and risk of OP fracture in patients with RA, by cumulative and average daily dose

Oral GC use By recency of use	OP fractures (N = 1640)[a]	IR per 1000 PYs	Age/sex adjusted HR (95% CI)	Fully adjusted HR[b] (95% CI)
Current use[c]	428	21.3	**1.36 (1.18, 1.56)**	**1.22 (1.06, 1.40)**
Cumulative use ≤1.0 g PED	70	17.4	1.20 (0.93, 1.55)	1.11 (0.86, 1.44)
Mean daily dose ≤7.5 mg PED/day	53	17.2	1.18 (0.88, 1.57)	1.10 (0.83, 1.47)
Mean daily dose >7.5 mg PED/day	17	18.0	1.27 (0.78, 2.06)	1.15 (0.71, 1.87)
Cumulative use >1.0 g PED	358	22.3	**1.39 (1.21, 1.61)**	**1.24 (1.07, 1.44)**
Mean daily dose ≤7.5 mg PED/day	248	21.2	**1.27 (1.09, 1.50)**	1.15 (0.98, 1.35)
Mean daily dose >7.5 mg PED/day	110	25.5	**1.77 (1.43, 2.20)**	**1.52 (1.22, 1.89)**[d]
Past use[c]	375	15.7	Reference	Reference
Non-use	801	12.6	0.90 (0.80, 1.02)	0.94 (0.83, 1.07)

Statistically significant hazard ratios are shown in bold. [a]There were 1640 osteoporotic fracture events among all included patients. [b]Adjusted at baseline for sex, BMI, smoking status and alcohol use, and during follow-up for age, a history of AS, chronic obstructive pulmonary disease, dementia, falls (in the past 7–12 months), IBD, and use in the past 6 months of antidepressants, antihypertensives, proton pump inhibitors, paracetamol, non-selective NSAIDs, cyclooxygenase-2 selective inhibitors, tramadol, opioids (stronger than tramadol), conventional synthetic DMARDs, and recent use of oral GCs. [c]Current, recent and past use refer to the last prescription within 6 months, 7–12 months and >12 months before a period, respectively. [d]Statistically different from low daily GC use (≤7.5 mg PED/day) within the same stratum of cumulative use, Wald test P <0.05. GC: glucocorticoid; HR: hazard ratio; OP: osteoporotic; IR: incidence rate; PYs: person years, PED: prednisolone equivalent dose.

between the treatment groups in the latter study [10]. Our findings of no higher risk of non-vertebral OP fractures with an average daily dose of ≤7.5 mg/day was to some extent comparable to the findings of these RCTs. The only fracture in our study with an observed increased risk with low daily GC use was the clinical vertebral (aHR 1.59). We know that vertebral fracture risk is markedly increased in RA [1, 29], and it is well-known that GC therapy in particular affects trabecular bone, which is abundantly present in lumbar vertebrae [5]. Therefore, we can hypothesise that the beneficial effect of low-dose GC therapy on suppressing the background inflammation of RA could probably be enough to offset its negative effect on bone synthesis in most fracture sites but not in vertebrae.

When comparing our findings to those of RCTs several points need further clarification. First, BMD changes associated with GC therapy cannot be directly translated into changes in fracture risk. A meta-analysis of observational studies showed that the increase in hip and vertebral fractures after GC use is higher than the rate estimated based on BMD decrease alone [5]. This may be due to GC-induced micro-architectural changes at specific active sites in bone, which were not reflected by the lowered BMD [8]. Second, the choice of past users as the comparator in our study might not fully mimic the placebo group in the RCTs [9, 10], as past users could have already reduced levels of disease activity, hence an improved bone health and a reduced fracture risk. Moreover, as any possible beneficial effect of GCs on bone is thought to be through reduction of RA's background inflammation, adjusting for csDMARDs in analyses (which was intended to minimise confounding) might have annihilated this beneficial effect through overadjustment [4, 28]. However, removing csDMARDs from the Cox model produced similar estimates compared with the main model (supplementary Table S3, available at *Rheumatology* online). This shows that csDMARD use was not perhaps a strong indicator of the disease severity and the background inflammation.

Conflicting results have been reported from observational studies. Our findings were partly in line with those from a recently conducted study that used the same data source, but with a different study design and underlying hypothesis [16]. Robinson and colleagues found no increased OP fracture risk in RA patients taking an average daily dose up to 5.0 mg PED/day, but increased risks with daily doses ≥5.0 mg PED/day compared with non-users [16]. Our *post hoc* analysis showed conformity with these findings, as we observed an increased risk of OP fractures with a GC dose of 5.1–7.5 mg PED/day, and comparable incidence rates of OP fracture between this daily dose group (23.2 per 1000 person years) and that of the next stratum, i.e. 7.6–14.9 mg PED/day (23.3 per 1000 person years). While we both studied cohorts of RA patients in CPRD, the age limit of included patients (50+ years in our study *vs* 18+ years in Robinson *et al.* [16]) and the comparator group (past use *vs* non-use) were different.

Higher fracture rates with low-dose GC therapy (<7.5 mg/day) were also found in two other studies that compared current GC users with non-users. These included US patients who had a mix of autoimmune diseases including RA and Danish patients from the general population [15, 30]. The choice of non-users as the comparator group without adjustment for additional indicators of RA severity in these studies could have possibly introduced confounding by indication. This might have led to an overestimation of the associations between GC use and OP fractures in these studies and

the observed discrepancy to our main findings in Table 2. The statistically significant association between low daily GC use and OP fracture risk only against non-use in our study and not against past GC use supports such a hypothesis. We observed no increased OP fracture risk with cumulative GC use $\leq$1.0 g PED, even for doses $>$7.5 mg PED/day. This is in line with the results from a paper that used older data from the same data source (1987–1997) and reported no increased OP fracture rates in patients with arthropathy with a cumulative GC use $\leq$1.0 g and an average daily dose $\geq$15.0 mg/day compared with past use [23]. This suggests that short-term intermittent high-dose GC therapy had no considerable effect on fracture risk.

Our study had several strengths. We used data from CPRD, which is one of the world's largest primary care databases. Validated definitions of RA were used in this study by means of a previously verified algorithm [21, 22]. Moreover, an on-treatment study design was utilised, allowing for relatively fair and flexible assessment of changes in onset and offset of oral GC exposure, which also helped to avoid time-related biases. Also, by complying with the new-user design, we could tackle biases that would arise from inclusion of prevalent users [31]. Furthermore, we statistically adjusted for a wide range of potential confounders including well-established risk factors of fractures.

This study had also limitations. Disease severity indicators of RA, such as the DAS in 28 joints (DAS-28) [32] and the use of biological drugs, were not available from the CPRD. This may have resulted in confounding by disease severity. Patients with a more severe RA have higher odds of receiving GCs and are at higher risk of having an OP fracture [1, 16]. Also, the 1.9-year difference in follow-up time between GC users and non-users could be due to inclusion of more patients with a shorter follow-up and less severe RA. However, we incorporated five analgesics and csDMARDs into the Cox model to also consider the effect of RA disease severity on the observed association. Another limitation was a potential misclassification of exposure with oral GCs, as we had only prescribing information from the CPRD, which is roughly two steps behind actual drug use by patients [33]. Non-adherence with medication and an 'as needed' order for oral GCs might lead to overestimation of drug use by patients and underestimation of the association between oral GCs and fracture risk in our study. However, an average duration of GC use of 3.7 years was an indication of actual use. On the other hand, as our primary care data was not linked to Hospital Episodes Statistics, covering outpatient and admitted patient care by specialist teams at hospitals, we might have missed information on some short episodes of GC therapy during hospitalisations. Furthermore, detection bias might explain at least part of the finding of an increased risk of clinical vertebral fracture in our study [33]. In contrast to other fracture types, about two-thirds of all vertebral fractures remain undetected in clinical practice as asymptomatic fractures, and hence their incidence rates would be underestimated when using large databases [34–36]. Patients who have more frequent visits to medical doctors, e.g. because of complaints that require prescriptions of oral GCs, may discuss complaints of back pain more often and may have higher odds of being referred for further diagnosis.

In conclusion, we found an increased risk of clinical vertebral fracture with low-dose GC therapy in RA patients compared with past GC use, while the risk of non-vertebral OP fractures was not increased. Our results are partly in line with findings from RCTs reporting a local beneficial effect of low-dose GC therapy on BMD in various anatomical sites. Clinicians should be aware that even in RA patients who receive low daily GC doses, the risk of clinical vertebral fracture is increased.

S.A., A.M.B., A.B. and F.d.V. contributed to intellectual concept and design of the research. J.H.M.D. and P.C.S. carried out the data acquisition. S.A. and J.H.M.D. conducted the data analysis. All authors contributed to data interpretation. S.A. wrote the manuscript. All authors were involved in editing or quality control. All authors are accountable for their own contribution, in addition to all aspects of the manuscript. All authors have approved the (re)submitted version of the manuscript.

Acknowledgement

The authors would like to acknowledge Keele University's Prognosis and Consultation Epidemiology Research Group, who have given us permission to utilise the morbidity definitions/categorisations lists (©2014). The copyright of the morbidity definitions/categorisations lists (©2014) used in this paper is owned by Keele University, the development of which was supported by the Primary Care Research Consortium. For access/details relating to the morbidity definitions/categorisation lists (©2014) please go to www.keele.ac.uk/mrr.

Funding: No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

Disclosure statement: A.B. received grants from AbbVie and Celgene, and fees for lectures or advisory board meetings from UCB, Eli Lilly and Galapagos, all paid to her department, not related to the current study. J.P.v.B. reports grants from UCB and Amgen, outside the submitted work. F.d.V. supervises three PhD students who are employed with F. Hoffmann La Roche Ltd, (Basel, Switzerland/Welwyn Garden City, UK). He has not received any fees or reimbursements for this, and the topics of their PhD theses are not related to the current study proposal. The other authors have declared no conflicts of interest.

Data availability statement

We used anonymised patient data from the Clinical Practice Research Datalink under licence. These data

are not openly available and are not distributable. No additional data available.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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