EPIDEMIOLOGICAL SCIENCE

Concomitant use of oral glucocorticoids and proton pump inhibitors and risk of osteoporotic fractures among patients with rheumatoid arthritis: a population-based cohort study

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ABSTRACT

Background Patients with rheumatoid arthritis (RA) commonly use oral glucocorticoids (GCs) and proton pump inhibitors (PPIs), both associated with osteoporotic fractures. We investigated the association between concomitant use of oral GCs and PPIs and the 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 GCs and PPIs was stratified by the most recent prescription as current use (<6 months), recent use (7–12 months) and past use (>1 year); average daily and cumulative dose; and duration of use. The risk of incident osteoporotic fractures (including hip, vertebrae, humerus, forearm, pelvis and ribs) was estimated by time-dependent Cox proportional-hazards models, statistically adjusted for lifestyle parameters, comorbidities and comedications.

Results Among 12 351 patients with RA (mean age of 68 years, 69% women), 1411 osteoporotic fractures occurred. Concomitant current use of oral GCs and PPIs was associated with a 1.6-fold increased risk of osteoporotic fractures compared with non-use (adjusted HR: 1.60, 95% CI: 1.35 to 1.89). This was statistically different from a 1.2-fold increased osteoporotic fracture risk associated with oral GC or PPI use alone. Most individual fracture sites were significantly associated with concomitant use of oral GCs and PPIs. Among concomitant users, fracture risk did not increase with higher daily dose or duration of PPI use.

Conclusions There was an interaction in the risk of osteoporotic fractures with concomitant use of oral GCs and PPIs. Fracture risk assessment could be considered when a patient with RA is co-prescribed oral GCs and PPIs.

Key messages

What is already known about this subject?

- Oral glucocorticoids (GCs) and proton pump inhibitors (PPIs) are among the commonly prescribed medications for patients with rheumatoid arthritis (RA).
- Oral GCs increase the risk of osteoporotic fractures by well-established biological mechanisms, including effects on bone, muscle strength and vision.
- The association between PPIs and fracture risk is less well established, although biological mechanisms such as hypochlorhydria and reduced calcium absorption have been proposed.

What does this study add?

- This is the first study to evaluate the association between concomitant use of oral GCs and PPIs and the risk of osteoporotic fractures in patients with RA, using a large primary care database.

How might this impact on clinical practice or future developments?

- As we observed a 1.6-fold increased risk of osteoporotic fractures with concomitant use of oral GCs and PPIs in patients with RA, fracture risk assessment could be considered for these patients.

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INTRODUCTION

Rheumatoid arthritis (RA) is a common chronic musculoskeletal inflammatory disease with many complications, including an elevated risk of osteoporotic (OP) fractures.[1–3] The contributors to increased fracture risk include the inflammatory process of RA and the pharmacological treatment of the disease, most importantly oral glucocorticoids (GCs). About one-quarter of patients with RA in the UK are current users of oral GCs.[1] Patients with RA taking oral GCs have reduced bone mineral density (BMD) at the hip and vertebrae and up to a 35% increased 5-year fracture risk.[1 4] This higher fracture risk with GCs is independent of the disease process and by known mechanisms, such as decreased bone formation, elevated bone resorption and ultimately reduced bone density.[5–9]

Apart from GCs, patients with RA frequently use other medications that could also be associated with fragility fractures. Non-steroidal anti-inflammatory drugs (NSAIDs) are routinely prescribed for patients with RA as analgesics, and proton pump inhibitors (PPIs) may be co-prescribed to reduce the gastrointestinal side effects. A randomised, double-blind,

crossover trial showed that fractional ^{45}calcium absorption was significantly decreased among elderly women using omeprazole (3.5%) versus placebo (9.1%), possibly because of hypochlorhydria.[10] Observational studies have reported conflicting results. Some reported an increased risk of hip and vertebral fractures with PPI use, suggesting a causal effect,[11–15] whereas others could not match the shape of the hazard function of PPI-induced fracture risk to calcium absorption hypothesis.[16 17] Other mechanisms such as an increased fall risk due to hypomagnesaemia or explanations such as unmeasured confounding were also proposed to explain this association.[16–20]

A population-based study reported a 2.4-fold increased risk of hip fracture among concomitant users of both PPIs and high-dose oral GCs (≥15 mg prednisolone equivalent dose (PED)).[16] But, to our knowledge, no studies have evaluated the effects of simultaneous use of both drugs on fracture risk in patients with RA, particularly in elderly patients who are regular users of PPIs.[21 22] Thus, we sought to investigate the association between concomitant use of oral GCs and PPIs and the risk of OP fractures among patients with RA.

METHODS

Data source

This was a retrospective cohort study based on the Clinical Practice Research Datalink (CPRD) GOLD database (http://www.cprd.com). The CPRD is one of the largest databases of primary care data in the world, which contained medical records of 674 practices in the UK in 2013, representing 4.4 million active patients, which equalled 6.9% of the total population.[23] It includes data on patient demographics, 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.[24 25]

Study population

The study cohort included adults aged 50+ years and diagnosed with RA between 1 January 1997 and 31 December 2017. We used a validated algorithm to identify definite RA cases in the CPRD, which can detect 86% of the true RA cases (online supplementary table 1).[26 27] The date of the first RA diagnosis during valid data collection defined the index date. Patients were followed until the occurrence of the outcome, the end of the study period, a patient's transfer out of practice, death or the end of data collection, whichever came first. Following a new-user design, patients with a history of GC/PPI 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

Oral GCs and PPIs were the exposures of interest. From the RA index date, follow-up was divided into consecutive 30-day periods and exposure status was assessed time-dependently at the start of each period. A period was defined as current, recent or past use when the most recent prescription of oral GCs/PPIs was issued within 6 months, 7–12 months and >12 months before a period, respectively.[7 11 12 16 28] Follow-up time was defined as non-use if no oral GC/PPI had ever been prescribed. Patients were allowed to move between exposure states during follow-up. Once a non-user had taken oral GCs/PPIs, he could never become a non-user again.

To evaluate a dose–response relationship and to replicate previous similar studies,[11 17 28] current use of both drugs was further stratified in average daily and cumulative dose, and duration of treatment. All oral GC and PPI prescriptions were retrieved, and the prescribed quantity was extracted and converted into PED for GCs and omeprazole equivalent dose (OED) for PPIs using the WHO Anatomical Therapeutic Chemical classification system .[29] 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 (ie, the time between the first oral GC/PPI prescription and the start date of a period of current use). Continuous duration of PPI use was determined at each period of current use using the prescribed quantity and written dosage information, allowing a gap of 30 days after the expected end date of a prescription.[30] The outcome in this study was a first OP fracture after the RA index date, which included hip, clinically symptomatic vertebral, humerus, forearm, pelvic and rib fractures.[1 28 31 32]

Potential confounders

Body mass index (BMI), smoking status and alcohol use were determined at the index date. Age and history of comorbidities and comedications were determined time-dependently. Comorbidities included asthma, chronic obstructive pulmonary disease, ischaemic heart disease (including myocardial infarction), cerebrovascular disease, congestive heart failure, anaemia, peripheral vascular disease, gastro-oesophageal reflux disease, peptic ulcer disease, inflammatory bowel diseases (Crohn's disease and ulcerative colitis), coeliac disease, hyperthyroidism, hypothyroidism, type 1 and 2 diabetes mellitus, chronic renal failure, ankylosing spondylitis, dementia, Parkinson's disease, major infections (ie, sepsis, meningitis, and upper and lower respiratory tract infections) and malignant neoplasms (excluding non-melanoma skin cancers).[33] Falls were measured in the 7–12 months prior to a period. Use of comedications in the 6 months prior included antihypertensives, anticoagulants, calcium/vitamin D, bisphosphonates, hormone replacement therapy, anticonvulsants, hypnotics/anxiolytics, antidepressants and antipsychotics. The following proxy indicators of RA severity were included: use of non-selective NSAIDs, cyclo-oxygenase-2 selective inhibitors, paracetamol, tramadol, opioids (stronger than tramadol) or conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) in the past 6 months.

Statistical analysis

Time-dependent Cox proportional-hazards models estimated the risk of OP fracture in patients with RA with concomitant current use of oral GCs and PPIs versus non-use. Also, the use of oral GCs alone and PPIs alone, and the recent and past use of oral GCs and PPIs (regardless of the use of the other drug) were compared with non-use. Individual exposure categories were statistically compared with a Wald test to detect between-group significance. Stratified analyses were conducted for various OP fracture sites. Potential confounders were incorporated into the model if the beta coefficient of the association changed by >5% or based on expert opinion.

Secondary analyses focused on average daily and cumulative dose of current GC use in relation to average daily dose and continuous duration of PPI use. Furthermore, three sensitivity analyses were performed. First, calcium/vitamin D and bisphosphonates were added to the model as confounders. They were not

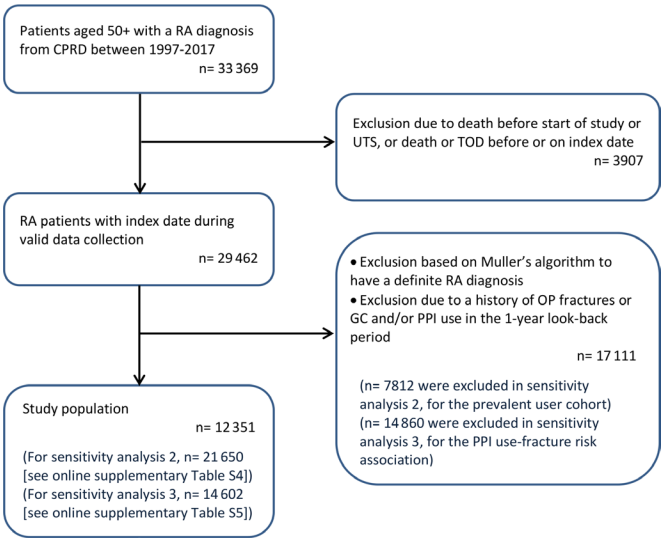

Figure 1 Flowchart on establishment of patient population. CPRD, Clinical Practice Research Datalink; GC, glucocorticoid; OP,osteoporotic; PPI, proton pump inhibitor; RA, rheumatoid arthritis; TOD, transfer out of database date (ie, date the patient was transferred out of the practice); UTS, up to standard time (ie, date at which the practice data are deemed to be of research quality).

considered in the main analysis because of the accompaniment of their prescriptions with those of oral GCs and as we expected them to lie in the causal pathway of the intended association as mediators.[34–36] Second, the main association was re-evaluated by including the prevalent users of GCs and PPIs. Finally, the association between PPI use and OP fractures was assessed among the primary cohort of patients with RA, by excluding only those with PPI use during the 1 year before the index date. Data were analysed using SAS V.9.4 (SAS Institute).

RESULTS

The study population included 12 351 patients with RA (figure 1). The mean age of concomitant users of oral GCs and PPIs at the index date was 67.5 years, 1.5 years younger than non-users (table 1). The mean duration of follow-up was 9.1 years for concomitant users and 5.1 years for non-users. About two-thirds of patients with RA were women (concomitant users: 67%; non-users: 70%). More than one-third of concomitant users were overweight, whereas 34% of non-users had a normal BMI. In the 6 months before the index date, 54% of concomitant users and 48% of non-users had taken non-selective NSAIDs. The average duration of drug use was 3.3 years for concomitant and single GC users, and 4.1 years for single PPI users.

Concomitant current use of oral GCs and PPIs in patients with RA was associated with a 1.6-fold increased risk of OP fractures compared with non-use of both drugs (adjusted HR (adj. HR): 1.60, 95% CI: 1.35 to 1.89; table 2). Both oral GC and PPI use alone had a 1.2-fold increased risk of OP fracture (adj. HR: 1.23, 95% CI: 1.03 to 1.47 (oral GC use alone); adj. HR: 1.22, 95% CI: 1.05 to 1.42 (PPI use alone)). The OP fracture risk associated with the current use of oral GCs or PPIs alone was statistically different from concomitant use. There was no significant increase in OP fracture risk in those patients who had stopped taking oral GCs or PPIs for more than 6 months (recent and past users) versus non-use. Considering calcium/vitamin D and bisphosphonates as confounders reduced the association to a 1.4-fold increased fracture risk for concomitant users and to a statistically non-significant risk for oral GC use alone versus non-use (online supplementary table 3).

Table 3 shows that among patients with RA, most OP fracture sites were statistically significantly associated with concomitant current use of oral GCs and PPIs versus non-use. With concomitant current use of oral GCs and PPIs, we observed a 1.5-fold increased risk of hip fracture, a 2.8-fold increased risk of clinical vertebral fracture, a 2.5-fold increased risk of pelvic fracture and a 4-fold increased risk of rib fracture. Risks of fracture of the humerus or forearm were not increased.

Table 4 shows the stratification of concomitant oral GC and PPI use by average daily doses of GCs and then substratification by average daily doses and continuous duration of PPI use. There was no increased fracture risk with increasing PPI daily doses. Under all strata of GC use, short-term PPI use (≤1 year) was associated with higher fracture risk, but there was no association between long-term PPI use (>1 year) and OP fractures. When concomitant use of GCs and PPIs was stratified by cumulative GC use and then substratified by PPI use, similar associations were observed (online supplementary table 2).

The second sensitivity analysis including prevalent users of GCs and PPIs (N=21 650) resulted in similar estimates to the main analyses (online supplementary table 4). In the third sensitivity analysis (N=14 602), current PPI use was associated with a 1.3-fold increased risk of OP fractures (adj. HR: 1.30, 95% CI: 1.15 to 1.47) versus non-use (online supplementary table 5).

DISCUSSION

Concomitant use of oral GCs and PPIs was associated with an increased risk of OP fractures compared with non-use in patients with RA. This was significantly higher when compared with the single use of oral GCs or PPIs. Increased fracture risk associated with concomitant GC and PPI use was observed for fractures of the hip, clinical vertebrae, pelvis and ribs, but not for those of the humerus or forearm. Among concomitant users, there was no increased OP fracture risk with higher daily dose or longer duration of PPI use.

This is the first study, to our knowledge, that looked into the association between concomitant use of GCs and PPIs and the risk of OP fracture in patients with RA . A Dutch population-based study found a 1.3-fold to 2.4-fold increased risk of hip/femur fracture with concomitant use of PPIs and various daily doses of oral GCs.[16] This is in line with our finding for the concomitant current use of GCs and PPIs (adj. HR: 1.60) and most of the strata of concomitant use in table 4. However, their reference group was different and limited to never PPI users. Moreover, they focused on 18+ general population, whereas we included patients with RA aged 50+ years with higher baseline fracture risks.

Our results regarding the higher fracture risk with PPI use are partly in line with several previous observational studies.[11 12 15–17] A meta-analysis of observational studies in non-RA patients reported increased risk of hip and spine fracture with PPI use (relative risks of 1.30 and 1.56, respectively),[14] which is comparable with adj. HR of 1.30 for current PPI use and OP fractures in our study. However, a recent study in patients with RA did not reveal a higher risk of OP fractures with PPI use, which was attributed to higher use of bisphosphonates among PPI users.[22] Previous studies found stronger associations with higher daily doses of PPIs[11] or with 7 years of PPI use and fracture risk,[12] whereas another older study that used the same data source but a different reference group did not report any dose–response or duration–response relationships at all.[17] Our findings (ie, no

Table 1 Baseline characteristics of study population at index date, stratified by oral GC and PPI therapy status during follow-up (N=12 351)

	Concomitant users of oral GCs and PPIs* (N=4254)		Users of oral GCs alone† (N=2136)		Users of PPIs alone‡ (N=2823)		Non-users (N=3138)	
	N	%	N	%	N	%	N	%
Mean duration of follow-up (years, SD)	9.1	5.0	7.5	4.9	8.4	5.0	5.1	4.3
Age (years)§								
Mean, SD	67.5	8.4	68.3	8.8	67.5	8.5	69.0	9.2
50–59	802	18.9	390	18.3	540	19.1	550	17.5
60–69	1763	41.4	813	38.1	1190	42.2	1102	35.1
70–79	1328	31.2	699	32.7	842	29.8	1055	33.6
80+	361	8.5	234	11.0	251	8.9	431	13.7
Number of women	2837	66.7	1443	67.6	2003	71.0	2190	69.8
BMI (kg/m^2)§								
Mean, SD	26.4	5.1	26.2	5.0	26.2	5.1	25.9	5.1
<20.0	304	7.1	146	6.8	200	7.1	222	7.1
20.0–24.9	1384	32.5	735	34.4	937	33.2	1079	34.4
25.0–29.9	1482	34.8	698	32.7	981	34.8	965	30.8
30.0–34.9	586	13.8	279	13.1	377	13.4	328	10.5
≥35.0	234	5.5	109	5.1	142	5.0	151	4.8
Missing	264	6.2	169	7.9	186	6.6	393	12.5
Smoking status§								
Non	1560	36.7	805	37.7	1158	41.0	1252	39.9
Current	988	23.2	522	24.4	571	20.2	646	20.6
Past	1670	39.3	770	36.0	1058	37.5	1104	35.2
Missing	36	0.8	39	1.8	36	1.3	136	4.3
Alcohol use§								
No	1249	29.4	559	26.2	780	27.6	795	25.3
Yes	2720	63.9	1380	64.6	1819	64.4	1969	62.7
Missing	285	6.7	197	9.2	224	7.9	374	11.9
History of comorbidities								
Asthma	573	13.5	277	13.0	170	6.0	207	6.6
COPD	321	7.5	161	7.5	65	2.3	102	3.3
Ischaemic heart disease (including myocardial infarction)	503	11.8	234	11.0	278	9.8	323	10.3
Cerebrovascular disease	234	5.5	109	5.1	139	4.9	152	4.8
Congestive heart failure	98	2.3	70	3.3	61	2.2	115	3.7
Anaemia	520	12.2	262	12.3	338	12.0	399	12.7
Peripheral arterial disease	200	4.7	103	4.8	132	4.7	139	4.4
Gastro-oesophageal reflux disease	198	4.7	94	4.4	130	4.6	110	3.5
Peptic ulcer disease	38	0.9	15	0.7	21	0.7	15	0.5
Coeliac disease	10	0.2	5	0.2	9	0.3	6	0.2
Inflammatory bowel disease (Crohn's disease and ulcerative colitis)	45	1.1	19	0.9	28	1.0	19	0.6
Hyperthyroidism	24	0.6	13	0.6	16	0.6	15	0.5
Hypothyroidism	289	6.8	149	7.0	206	7.3	213	6.8
Type 1 diabetes mellitus	25	0.6	17	0.8	17	0.6	15	0.5
Type 2 diabetes mellitus	230	5.4	101	4.7	164	5.8	172	5.5
Chronic renal failure	144	3.4	68	3.2	81	2.9	110	3.5
Ankylosing spondylitis	6	0.1	<5	<0.3	5	0.2	7	0.2
Dementia	17	0.4	11	0.5	19	0.7	28	0.9
Parkinson's disease	10	0.2	4	0.2	9	0.3	20	0.6
Malignant neoplasms (excluding non-melanoma skin cancers)	371	8.7	173	8.1	248	8.8	244	7.8
Major infections¶	812	19.1	397	18.6	468	16.6	452	14.4
Falls (in the past 7–12 months)	38	0.9	10	0.5	16	0.6	21	0.7
Comedication use (in the past 6 months)								
Antihypertensives	1383	32.5	718	33.6	905	32.1	1117	35.6
Anticoagulants	118	2.8	70	3.3	45	1.6	104	3.3
Calcium/vitamin D	290	6.8	105	4.9	133	4.7	190	6.1
Bisphosphonates	260	6.1	87	4.1	108	3.8	119	3.8

Continued

Table 1 Continued

	Concomitant users of oral GCs and PPIs* (N=4254)		Users of oral GCs alone† (N=2136)		Users of PPIs alone‡ (N=2823)		Non-users (N=3138)	
	N	%	N	%	N	%	N	%
Hormone replacement therapy	184	4.3	65	3.0	107	3.8	81	2.6
Anticonvulsants	51	1.2	29	1.4	37	1.3	46	1.5
Hypnotics/anxiolytics	356	8.4	168	7.9	184	6.5	189	6.0
Antidepressants	498	11.7	237	11.1	275	9.7	290	9.2
Antipsychotics	36	0.8	19	0.9	17	0.6	40	1.3
Disease severity indicators								
Non-selective NSAIDs	2309	54.3	1202	56.3	1514	53.6	1518	48.4
COX-2 selective inhibitors	409	9.6	205	9.6	255	9.0	191	6.1
Paracetamol	2117	49.8	987	46.2	1147	40.6	1328	42.3
Tramadol	263	6.2	113	5.3	148	5.2	138	4.4
Opioids (stronger than tramadol)	241	5.7	105	4.9	114	4.0	118	3.8
csDMARDs	1323	31.1	637	29.8	915	32.4	1091	34.8

*Concomitant users of oral GCs and PPIs are patients who had at least one co-prescription of an oral GC and PPI during follow-up.
†Users of oral GCs alone are patients who had at least one prescription of an oral GC during follow-up without having prescribed PPI and excluding concomitant users.
‡Users of PPIs alone are patients who had at least one prescription of a PPI during follow-up without having prescribed oral GCs and excluding concomitant users and users of oral GCs alone.
§At index date.
¶Major infections included sepsis, meningitis, and upper and lower respiratory tract infections.
BMI, body mass index; COPD, chronic obstructive pulmonary disease; COX-2, cyclo-oxygenase-2; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; GCs, glucocorticoids; NSAIDs, non-steroidal anti-inflammatory drugs; PPIs, proton pump inhibitors.

specific trend with longer duration or higher daily doses of PPI use) are comparable to the latter study.

Our findings in the single GC use group were generally consistent with the literature. Previous observational studies have reported increased OP fracture risks in patients with RA with current GC use between 43% and 70%, higher than the 23% increased risk that we found.[1 31] We used a different reference group (non-users of both GCs and PPIs), which may also explain the unexpected lack of statistical significance for a higher risk of clinical vertebral fracture with current GC use alone.

The magnitude of the association between concomitant GC and PPI use and the risk of OP fracture may indicate an additive effect of the individual drugs rather than a synergistic effect. This was suggested by a significantly higher fracture risk with concomitant GC and PPI use compared with monotherapy with either drug and as the observed HRs seem to be additive. This may be related to different biological mechanisms of GCs and PPIs acting on osteoporosis or falling. The effect of GCs on bone is mostly via decreased bone formation and interference with active bone remodelling sites.[1 6 8 9] But additionally, GCs might increase the fracture risk by inducing muscle atrophy or cataract especially with higher doses and in long-term use.[37–39] Previous studies have shown that the onset and offset of the effects of GCs on fracture risk are rather rapid, which is supported by our results.[7 31 40] Similar to GCs, the positive association of fracture risk with PPI use quickly subsided when the patient discontinued

Table 2 OP fracture risk by concomitant use of oral GCs and PPIs in patients with rheumatoid arthritis

By recency of use	Number of OP fractures (N=1411)*	IR per 1000 Pys	Age/sex-adjusted HR (95% CI)	Fully adjusted HR† (95% CI)
Non-use of GCs and PPIs	325	10.5	Reference	Reference
Current use‡				
GCs and PPIs concomitantly	264	24.4	**1.93 (1.65 to 2.27)**	**1.60 (1.35 to 1.89)**
GCs alone	178	15.5	**1.34 (1.12 to 1.59)**	**1.23 (1.03 to 1.47)**§
PPIs alone	324	16.7	**1.32 (1.14 to 1.54)**	**1.22 (1.05 to 1.42)**§
Recent GC use‡ ¶	34	11.0	0.87 (0.62 to 1.23)	0.82 (0.58 to 1.16)
Recent PPI use‡¶	49	16.0	1.21 (0.90 to 1.62)	1.17 (0.87 to 1.57)
Past GC use‡ ¶	339	15.6	**1.16 (1.01 to 1.33)**	1.13 (0.98 to 1.29)
Past PPI use‡ ¶	219	13.5	0.96 (0.82 to 1.13)	0.94 (0.80 to 1.10)

Statistically significantly increased HRs are shown in bold.
*1411 OP fracture events among all included patients with RA. The number of events in exposure groups do not sum to this total due to the overlap between recent and past use of GCs and PPIs.
†Adjusted at baseline for sex, body mass index, smoking status and alcohol use; during follow-up for age, a history of ankylosing spondylitis, chronic obstructive pulmonary disease, dementia, falls (in the past 7–12 months) and inflammatory bowel disease; and use in the past 6 months of antidepressants, paracetamol, non-selective non-steroidal anti-inflammatory drugs, cyclo-oxygenase-2 selective inhibitors, tramadol, opioids and conventional synthetic disease-modifying antirheumatic drugs.
‡Current, recent and past use refer to the last prescription within 6 months, 7–12 months and >12 months before a period, respectively.
§Statistically different from concomitant GC and PPI use, Wald test p<0.05.
¶Regardless of the use of the other drug.
GCs, glucocorticoids; IR, incidence rate; OP, osteoporotic; PPIs, proton pump inhibitors; Pys, person years.

Table 3 OP fracture risk by concomitant use of oral GCs and PPIs in patients with rheumatoid arthritis, stratified by fracture type

	Hip (N=541)		Clinical vertebral (N=224)		Humerus (N=372)		Forearm (N=302)		Pelvis (N=116)		Rib (N=90)	
By recency of use	IR per 1000 Pys	Fully adjusted HR* (95% CI)	IR per 1000 Pys	Fully adjusted HR† (95% CI)	IR per 1000 Pys	Fully adjusted HR‡ (95% CI)	IR per 1000 Pys	Fully adjusted HR§ (95% CI)	IR per 1000 Pys	Fully adjusted HR¶ (95% CI)	IR per 1000 ys	Fully adjusted HR** (95% CI)
Non-use of GCs and PPIs	3.8	Reference	1.0	Reference	2.9	Reference	2.5	Reference	0.6	Reference	0.6	Reference
Current use††												
GCs and PPIs concomitantly	9.0	**1.45 (1.11 to 1.91)**	5.4	**2.84 (1.87 to 4.32)**	5.8	1.29 (0.93 to 1.78)	2.9	0.87 (0.57 to 1.32)	2.9	**2.47 (1.41 to 4.34)**	1.7	**4.03 (2.13 to 7.63)**
GCs alone	6.0	1.26 (0.95 to 1.66)	1.8	1.31 (0.79 to 2.16)‡‡	3.3	0.99 (0.69 to 1.43)	3.2	1.17 (0.81 to 1.70)	0.9	1.07 (0.54 to 2.14)‡‡	1.2	**2.28 (1.17 to 4.46)**
PPIs alone	5.9	1.10 (0.86 to 1.41)	3.1	**1.78 (1.20 to 2.65)**‡‡	4.5	1.17 (0.88 to 1.55)	3.3	0.98 (0.71 to 1.37)	1.6	**1.93 (1.11 to 3.34)**	0.8	1.24 (0.66 to 2.34)‡‡
Recent GC use†† §§	5.9	1.25 (0.78 to 2.01)	1.2	0.59 (0.22 to 1.63)	1.5	0.42 (0.17 to 1.03)	3.1	1.00 (0.52 to 1.91)	1.2	0.97 (0.35 to 2.72)	0.6	1.21 (0.29 to 5.14)
Recent PPI use†† §§	5.3	1.00 (0.60 to 1.65)	2.8	1.73 (0.85 to 3.54)	3.4	0.93 (0.50 to 1.72)	3.7	1.09 (0.60 to 2.00)	0.9	1.16 (0.35 to 3.87)	1.5	2.17 (0.83 to 5.62)
Past GC use†† §§	5.5	1.08 (0.86 to 1.35)	2.4	1.12 (0.78 to 1.59)	3.7	0.98 (0.75 to 1.27)	3.6	1.19 (0.90 to 1.58)	0.8	0.64 (0.37 to 1.11)	1.2	**2.43 (1.39 to 4.22)**
Past PPI use†† §§	5.4	0.98 (0.76 to 1.27)	1.9	1.11 (0.71 to 1.74)	2.7	0.72 (0.51 to 1.01)	3.0	0.86 (0.61 to 1.21)	0.9	1.17 (0.62 to 2.20)	0.6	0.86 (0.43 to 1.75)

Statistically significantly increased HRs are shown in bold.
*Adjusted at baseline for sex, BMI, smoking status and alcohol use; during follow-up for age, a history of anaemia, AS, COPD, dementia, falls (in the past 7–12 months) and IBD; and use in the past 6 months of antidepressants, hypnotics/anxiolytics, paracetamol, non-selective NSAIDs, COX-2 selective inhibitors, tramadol, opioids and csDMARDs.
†Adjusted at baseline for sex, BMI, smoking status and alcohol use; during follow-up for age, a history of COPD, falls (in the past 7–12 months) and IBD; and use in the past 6 months of antidepressants, anticonvulsants, paracetamol, non-selective NSAIDs, COX-2 selective inhibitors, tramadol, opioids and csDMARDs.
‡Adjusted at baseline for sex, BMI, smoking status and alcohol use; during follow-up for age, a history of anaemia, AS, COPD, dementia, falls (in the past 7–12 months) and IBD; and use in the past 6 months of antidepressants, paracetamol, non-selective NSAIDs, COX-2 selective inhibitors, tramadol, opioids and csDMARDs.
§Adjusted at baseline for sex, BMI, smoking status and alcohol use; during follow-up for age, a history of anaemia, type 2 diabetes mellitus, COPD, dementia, falls (in the past 7–12 months), gastro-oesophageal reflux disease and IBD; and use in the past 6 months of antidepressants, anticoagulants, anticonvulsants, antihypertensives, paracetamol, non-selective NSAIDs, COX-2 selective inhibitors, tramadol, opioids and csDMARDs.
¶Adjusted at baseline for sex, during follow-up for age and use in the past 6 months of antidepressants, paracetamol and opioids.
**Adjusted at baseline for sex and during follow-up for age.
††Current, recent and past use refer to the last prescription within 6 months, 7–12 months and >12 months before a period, respectively.
‡‡Statistically different from concomitant GC and PPI use within the same fracture type, Wald test p<0.05.
§§Regardless of the use of the other drug.
AS, ankylosing spondylitis; BMI, body mass index; COPD, chronic obstructive pulmonary disease; COX-2, cyclo-oxygenase-2; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; GCs, glucocorticoids; ; IBD, inflammatory bowel disease; IR, incidence rate; NSAIDs, non-steroidal anti-inflammatory drugs; OP, Osteoporotic; PPIs, proton pump inhibitors; Pys, person years.

Table 4 OP fracture risk by average daily dose of oral GC use in patients with rheumatoid arthritis, stratified by average daily dose and continuous duration of PPI use

By recency of use	OP fractures (N=1411)*	IR per 1000 Pys	Age/sex-adjusted HR (95% CI)	Fully adjusted HR† (95% CI)
Non-use of GCs and PPIs	325	10.5	Reference	Reference
Current use of GCs and PPIs concomitantly‡	264	24.4	**1.93 (1.65 to 2.27)**	**1.60 (1.35 to 1.89)**
❶*Low GC use (DD ≤7.5 mg PED/day)*				
+ Low-dose PPI use (DD <20 mg OEDs/day)	142	23.2	**1.75 (1.44 to 2.13)**	**1.42 (1.16 to 1.74)**
+ Medium-dose PPI use (DD 20–35 mg OEDs/day)	39	24.9	**1.93 (1.39 to 2.69)**	**1.54 (1.10 to 2.16)**
+ High-dose PPI use (DD >35 mg OEDs/day)	8	34.2	**2.72 (1.35 to 5.47)**	**2.10 (1.04 to 4.24)**
+ Short-term continuous PPI use (≤1 year)	89	25.7	**2.00 (1.59 to 2.52)**	**1.60 (1.26 to 2.04)**
+ Long-term continuous PPI use (>1 year)	71	20.3	**1.49 (1.15 to 1.93)**	1.18 (0.91 to 1.53)
+ No continuous duration of PPI§	29	30.4	**2.36 (1.62 to 3.45)**	**2.00 (1.36 to 2.93)¶**
❷*Medium GC use (DD 7.6–14.9 mg PED/day)*				
+ Low-dose PPI use (DD <20 mg OEDs/day)	43	25.0	**2.22 (1.62 to 3.04)**	**1.76 (1.27 to 2.43)**
+ Medium-dose PPI use (DD 20–35 mg OEDs/day)	19	27.7	**2.41 (1.52 to 3.82)**	**1.92 (1.20 to 3.05)**
+ High-dose PPI use (DD >35 mg OEDs/day)	<5	17.2	1.46 (0.36 to 5.86)	1.26 (0.31 to 5.07)
+ Short-term continuous PPI use (≤1 year)	36	30.2	**2.70 (1.92 to 3.80)**	**2.20 (1.55 to 3.11)**
+ Long-term continuous PPI use (>1 year)	23	20.9	**1.78 (1.17 to 2.72)**	1.37 (0.89 to 2.10)
+ No continuous duration of PPI§	5	22.3	2.00 (0.83 to 4.84)	1.67 (0.69 to 4.03)
❸*High GC use (DD ≥15.0 mg PED/day)*				
+ Low-dose PPI use (DD <20 mg OEDs/day)	5	21.1	1.92 (0.79 to 4.64)	1.58 (0.65 to 3.81)
+ Medium-dose PPI use (DD 20–35 mg OEDs/day)	<5	38.8	**3.77 (1.41 to 10.09)**	**3.05 (1.13 to 8.18)**
+ High-dose PPI use (DD >35 mg OEDs/day)	<5	41.1	3.83 (0.95 to 15.37)	3.30 (0.82 to 13.26)
+ Short-term continuous PPI use (≤1 year)	9	34.1	**3.21 (1.66 to 6.21)**	**2.72 (1.40 to 5.27)**
+ Long-term continuous PPI use (>1 year)	<5	11.3	0.99 (0.14 to 7.08)	0.72 (0.10 to 5.15)
+ No continuous duration of PPI§	<5	27.1	2.65 (0.37 to 18.90)	2.38 (0.33 to 16.97)

Statistically significantly increased HRs are shown in bold.
*1411 OP fracture events among all included patients with RA. The number of fractures in exposure groups do not sum to this total due to not reporting the current only use and recent and past use of GCs and PPIs.
†Adjusted at baseline for sex, body mass index, smoking status and alcohol use; during follow-up for age, a history of anaemia, ankylosing spondylitis, chronic obstructive pulmonary disease, dementia, falls (in the past 7–12 months) and inflammatory bowel disease; use in the past 6 months of antidepressants, paracetamol, non-selective non-steroidal anti-inflammatory drugs, cyclo-oxygenase-2 selective inhibitors, tramadol, opioids and conventional synthetic disease-modifying antirheumatic drugs; and current only use and recent and past use of oral GCs and PPIs.
‡Concomitant current use refers to the most recent prescription of both oral GCs and PPIs in the 6 months before the start of a period.
§This represents fracture events that happened during a current period of PPI use but not eligible for a continuous duration of use calculation (ie, up to 6 months after the last PPI prescription, but after 1-month threshold gap of our definition for the continuous duration of PPI use).
¶Statistically different from long-term continuous PPI use within the same category, Wald test p<0.05.
DD, average daily dose; GCs, glucocorticoids; IR, incidence rate; OED, omeprazole equivalent dose; OP, osteoporotic; PED, prednisolone equivalent dose; PPIs, proton pump inhibitors; Pys, person years.

the treatment (after 6 months). But for PPIs, underlying pharmacological effects on fracture are not well understood.[41 42] The US Food and Drug Administration published a drug safety communication for a possible increased fracture risk with PPI use in 2011, which remained unchanged to date and was based on evidence from observational studies.[43] This was later criticised for not being supported by a clear biological mechanism.[44]

Various pharmacological mechanisms have been proposed to explain the PPI use and fracture risk association. Reduced intestinal absorption of calcium was previously suggested due to induced hypochlorhydria by PPI therapy and the effect on bone quality.[10] However, a more recent trial found no BMD changes after 52 weeks and non-significant changes in bone turnover markers after 26 weeks with dexlansoprazole or esomeprazole use.[45] An alternative mechanism is an increased falling risk due to muscle weakness and drowsiness, caused by malabsorption of magnesium or vitamin B12.[18–20 46 47] Long-term PPI therapy (≥1 year) in elderly women was shown to significantly reduce serum vitamin B12 levels and double the 5-year risk of injurious falling-related and fracture-related hospitalisation.[46] But the design of this study did not consider proper timing of the exposure and outcome, which limits its interpretation. A third mechanism is effects on osteoclasts to increase bone resorption by PPIs.[48] Finally, methodological explanations for the observed associations include selection bias and/or unknown confounding.[16 17 44] Significant association only with short-term PPI use and no specific trend with increasing daily doses do not fit into any of the proposed mechanisms mentioned above. As we used different strategies in design and analysis to avoid potential sources of bias and to adjust for confounding, and when the GC findings are supported by previous literature with well-known biological mechanisms, the mere explanation of the PPI results by unmeasured confounding would be difficult. Hence, more research is recommended to elaborate on the exact biological mechanism of PPIs on bone.

This study had several strengths. We used data from the CPRD, which is one of the world's largest primary care databases. Our study had a substantial mean duration of follow-up (9.1 years for concomitant users). To bring more insight into the observed association, we stratified GC and PPI use by recency of use, average daily and cumulative dose, and duration of treatment. Furthermore, all analyses were performed time-dependently, incorporating all follow-up times, to avoid time-related biases. There were also several limitations. Biological

therapies, especially during hospitalisation, and some RA severity indices (eg, the disease activity score using 28 joints (DAS-28)) were not adequately captured in the CPRD as a general practice database, which might have introduced confounding by indication or disease severity. Patients with higher disease activity may have an elevated risk of fracture and be more prone to receive oral GCs/PPIs. Also, an improved clinical status might have led to both discontinuation of drug(s) and lower fracture rates. To partly overcome this, we statistically adjusted our analyses for six indicators of RA severity, including analgesics and csDMARDs. We cannot confirm the actual use of medications as we only had prescribing information, and GCs and PPIs are often prescribed on an as-needed basis. The over-the-counter use of PPIs was also not captured. However, with an average duration of use of >3 years, repeated prescriptions are indicators of actual use. Finally, the number of vertebral fractures might be underestimated, as some of them might not immediately come into clinical attention.[49 50] This might virtually increase the HRs for vertebral fractures due to detection bias.[35]

In conclusion, there was an interaction in the risk of OP fracture with concomitant use of oral GCs and PPIs. This increased risk seems to emerge from separate mechanisms of action of GCs and PPIs on bone or falling risk. Considering the increasing life expectancies and high consumption of PPIs among elderly patients, fracture risk assessment could be considered when a patient with RA is co-prescribed oral GCs and PPIs.

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