## SUPPLEMENTARY MATERIAL

**Table S1.** Criteria from Thomas et al. algorithm to detect true cases of rheumatoid arthritis in the General Practice Research Database, also used in the updated version by Muller et al.[26,27]

| | |
|---|---|
| Criteria 1 | At least one diagnostic Read code for RA and at least one appropriate prescription of a DMARD with no alternative indication for the DMARD; |
| OR | |
| Criteria 2 | all three of the following:<br>a) two or more diagnostic Read codes for RA (on different dates);<br>b) no alternative diagnosis after the final RA code;<br>c) RA code in group 1 (seropositive or erosive RA) or group 2 ('rheumatoid arthritis' codes e.g. RA of knee), opposed to only group 3 (systemic manifestations of RA) or group 4 (seronegative RA or other weak evidence of RA). |
| Abbreviation: RA, rheumatoid arthritis; DMARD, disease modifying antirheumatic drugs. | |

**Table S2.** Osteoporotic fracture risk by cumulative use of oral glucocorticoids in rheumatoid arthritis patients, stratified by average daily dose and duration of use of proton pump inhibitors.

| By recency of use | OP fractures (N=1411)* | IR per 1,000 Pys | Age/Sex adjusted Hazard Ratio (95% CI) | Fully adjusted Hazard Ratio† (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 (1.65-2.27)** | **1.60 (1.35-1.89)** |
| ❶ *Low GC use (CD ≤1.0g PED)* | | | | |
| + Low-dose PPI use (DD <20mg OEDs/day) | 21 | 25.4 | **2.10 (1.36-3.27)** | **1.79 (1.15-2.79)** |
| + Medium-dose PPI use (DD 20-35mg OEDs/day) | <5 | 15.3 | 1.33 (0.50-3.56) | 1.10 (0.41-2.96) |
| + High-dose PPI use (DD >35mg OEDs/day) | <5 | 22.7 | 1.86 (0.46-7.46) | 1.61 (0.40-6.47) |
| + Short-term continuous PPI use (≤1 year) | 18 | 26.4 | **2.22 (1.38-3.56)** | **1.89 (1.17-3.03)** |
| + Long-term continuous PPI use (>1 year) | <5 | 7.7 | 0.62 (0.15-2.47) | 0.50 (0.12-2.01) |
| + No continuous duration of PPI§ | 7 | 29.9 | **2.54 (1.20-5.37)** | **2.25 (1.06-4.75)** |
| ❷ *Medium GC use (CD 1.1-4.9g PED)* | | | | |
| + Low-dose PPI use (DD <20mg OEDs/day) | 61 | 29.5 | **2.34 (1.79-3.07)** | **1.95 (1.48-2.57)** |
| + Medium-dose PPI use (DD 20-35mg OEDs/day) | 19 | 27.0 | **2.22 (1.40-3.52)** | **1.82 (1.15-2.90)** |
| + High-dose PPI use (DD >35mg OEDs/day) | <5 | 28.5 | 2.32 (0.87-6.22) | 1.85 (0.69-4.97) |
| + Short-term continuous PPI use (≤1 year) | 50 | 30.8 | **2.53 (1.89-3.40)** | **2.11 (1.57-2.84)** |
| + Long-term continuous PPI use (>1 year) | 21 | 23.2 | **1.75 (1.12-2.71)** | 1.41 (0.91-2.20) |
| + No continuous duration of PPI§ | 13 | 34.1 | **2.78 (1.60-4.84)** | **2.40 (1.38-4.17)** |
| ❸ *High GC use (CD ≥5.0g PED)* | | | | |
| + Low-dose PPI use (DD <20mg OEDs/day) | 108 | 20.8 | **1.61 (1.30-2.00)** | **1.26 (1.01-1.58)** |
| + Medium-dose PPI use (DD 20-35mg OEDs/day) | 39 | 28.0 | **2.22 (1.59-3.09)** | **1.72 (1.23-2.41)** |
| + High-dose PPI use (DD >35mg OEDs/day) | 6 | 35.1 | **2.94 (1.31-6.59)** | **2.28 (1.01-5.12)** |
| + Short-term continuous PPI use (≤1 year) | 66 | 25.3 | **2.01 (1.54-2.62)** | **1.56 (1.19-2.05)** |
| + Long-term continuous PPI use (>1 year) | 72 | 20.4 | **1.55 (1.20-2.01)** | 1.20 (0.92-1.56) |
| + No continuous duration of PPI§ | 15 | 25.0 | **1.93 (1.15-3.24)** | 1.59 (0.95-2.67) |

Abbreviations: OP, osteoporotic; IR, Incidence rate; Pys, person years; CI, confidence interval; GCs, glucocorticoids; PPIs, proton pump inhibitors; CD, cumulative dose; DD, average daily dose; PED, Prednisolone equivalent dose; OED, Omeprazole equivalent dose. Statistically significantly increased hazard ratios are shown in bold. None of the Wald tests comparing exposure states within the same category were statistically significant.

* 1411 osteoporotic fracture events among all included RA patients. 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, and during follow-up for age, a history of anaemia, ankylosing spondylitis, chronic obstructive pulmonary disease, dementia, falls (in the past 7-12 months), inflammatory bowel disease, and the use in the past 6-months of antidepressants, paracetamol, non-selective non-steroidal anti-inflammatory drugs, cyclooxygenase-2 selective inhibitors, tramadol, opioids,

conventional synthetic disease modifying antirheumatic drugs, and current only use and recent and past use of oral glucocorticoids and proton pump inhibitors.

‡ Concomitant use refers to the most recent prescription of both oral GCs and PPIs within 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 (i.e. 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).

**Table S3.** Sensitivity analysis 1, the association between concomitant use of oral glucocorticoids and proton pump inhibitors and osteoporotic fracture risk after adding calcium/vitamin D and bisphosphonates as confounders to the Cox model.

| By recency of use | **Number of OP fractures (N=1411)*** | **IR per 1,000 Pys** | **Age/Sex adjusted Hazard Ratio (95% CI)** | **Fully adjusted Hazard Ratio† (95% CI)** |
|---|---|---|---|---|
| Non-use of GCs and PPIs | 325 | 10.5 | Reference | Reference |
| Current use‡ | | | | |
| GCs and PPIs concomitantly | 264 | 24.4 | **1.93 (1.65-2.27)** | **1.39 (1.16-1.66)** |
| GCs alone | 178 | 15.5 | **1.34 (1.12-1.59)** | 1.11 (0.92-1.33)§ |
| PPIs alone | 324 | 16.7 | **1.32 (1.14-1.54)** | **1.20 (1.03-1.40)**§ |
| Recent GC use‡ ‖ | 34 | 11.0 | 0.87 (0.62-1.23) | 0.79 (0.56-1.12) |
| Recent PPI use‡ ‖ | 49 | 16.0 | 1.21 (0.90-1.62) | 1.16 (0.86-1.56) |
| Past GC use‡ ‖ | 339 | 15.6 | **1.16 (1.01-1.33)** | 1.10 (0.96-1.27) |
| Past PPI use‡ ‖ | 219 | 13.5 | 0.96 (0.82-1.13) | 0.93 (0.79-1.10) |

Abbreviation: OP, osteoporotic; IR, incidence rate; Pys, person years; CI, confidence interval; GCs, glucocorticoids; PPIs, proton pump inhibitors. Statistically significantly increased hazard ratios are shown in bold.

* 1411 osteoporotic fracture events among all included RA patients. The number of events in exposure groups do not sum to this total due to overlap between recent and past use of GCs and PPIs.

† Adjusted at baseline for sex, body mass index, smoking status and alcohol use, and during follow-up for age, a history of ankylosing spondylitis, chronic obstructive pulmonary disease, dementia, falls (in the past 7-12 months), inflammatory bowel disease, and the use in the past 6-months of calcium/vitamin D supplements, bisphosphonates, antidepressants, paracetamol, non-selective non-steroidal anti-inflammatory drugs, cyclooxygenase-2 selective inhibitors, tramadol, opioids, 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.

**Table S4.** Sensitivity analysis 2, evaluating a prevalent user cohort instead of a new-user cohort (Table 2). Osteoporotic fracture risk by concomitant use of oral glucocorticoids and proton pump inhibitors in patients with rheumatoid arthritis (N=21,650).

| By recency of use | **OP fractures (N=2384)*** | **IR per 1,000 Pys** | **Age/Sex adjusted Hazard Ratio (95% CI)** | **Fully adjusted Hazard Ratio† (95% CI)** |
|---|---|---|---|---|
| Non-use of GCs and PPIs | 325 | 10.5 | Reference | Reference |
| Current use‡ | | | | |
| GCs and PPIs concomitantly | 613 | 25.0 | **2.00 (1.76-2.26)** | **1.63 (1.43-1.85)** |
| GCs alone | 363 | 16.8 | **1.33 (1.17-1.52)** | **1.21 (1.06-1.38)**§ |
| PPIs alone | 622 | 16.5 | **1.34 (1.19-1.51)** | **1.21 (1.07-1.37)**§ |
| Recent GC use‡ ‖ | 66 | 11.7 | 0.85 (0.66-1.10) | 0.81 (0.63-1.05) |
| Recent PPI use‡ ‖ | 93 | 17.3 | **1.30 (1.04-1.62)** | **1.24 (1.00-1.55)** |
| Past GC use‡ ‖ | 541 | 15.3 | 1.07 (0.96-1.20) | 1.05 (0.94-1.17) |
| Past PPI use‡ ‖ | 376 | 14.4 | 1.04 (0.91-1.18) | 1.00 (0.88-1.14) |

Abbreviation: OP, osteoporotic; IR, incidence rate; Pys, person years; CI, confidence interval; GCs, glucocorticoids; PPIs, proton pump inhibitors. Statistically significantly increased hazard ratios are shown in bold.

* 2384 osteoporotic fracture events among all included RA patients. The number of events in exposure groups do not sum to this total due to overlap between recent and past use of GCs and PPIs.

† Adjusted at baseline for sex, body mass index, smoking status and alcohol use, and during follow-up for age, a history of ankylosing spondylitis, chronic obstructive pulmonary disease, dementia, falls (in the past 7-12 months), inflammatory bowel disease, and the use in the past 6-months of antidepressants, paracetamol, non-selective non-steroidal anti-inflammatory drugs, cyclooxygenase-2 selective inhibitors, tramadol, opioids, 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.

**Table S5.** Sensitivity analysis 3, osteoporotic fracture risk by use of proton pump inhibitors in patients with rheumatoid arthritis (N=14,602).

| By recency of use | **OP fractures (N=1629)*** | **IR per 1,000 Pys** | **Age/Sex adjusted Hazard Ratio (95% CI)** | **Fully adjusted Hazard Ratio† (95% CI)** |
|---|---|---|---|---|
| Non-use of PPIs | 680 | 11.9 | Reference | Reference |
| Current PPI use‡ | 626 | 19.8 | **1.52 (1.35-1.70)** | **1.30 (1.15-1.47)** |
| Recent PPI use‡ | 58 | 17.0 | **1.31 (1.00-1.72)** | 1.23 (0.94-1.61) |
| Past PPI use‡ | 265 | 14.1 | 1.04 (0.90-1.21) | 1.00 (0.86-1.16) |

Abbreviation: OP, osteoporotic; IR, incidence rate; Pys, person years; CI, confidence interval; PPIs, proton pump inhibitors. Statistically significantly increased hazard ratios are shown in bold.

* 1629 osteoporotic fracture events among all included RA patients.

† Adjusted at baseline for sex, body mass index, smoking status and alcohol use, and during follow-up for age, a history of ankylosing spondylitis, chronic obstructive pulmonary disease, dementia, falls (in the past 7-12 months), inflammatory bowel disease, and the use in the past 6-months of oral glucocorticoids, antidepressants, paracetamol, non-selective non-steroidal anti-inflammatory drugs, cyclooxygenase-2 selective inhibitors, tramadol, opioids, 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.