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Fragility fracture risk and bone mineral density testing in long-term versus short-term users of proton pump inhibitors and potassium-competitive acid blockers: a retrospective cohort study using Japanese municipal claims data

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Abstract

Background

Proton pump inhibitors (PPIs) and potassium-competitive acid blockers (P-CABs) are widely used to treat acid-related disorders and are often continued beyond the recommended treatment duration. Long-term PPI use has been associated with an increased risk of fragility fractures in several meta-analyses, but evidence on fracture risk with P-CABs is limited, and little is known about bone mineral density (BMD) testing among patients receiving these agents long term.

Methods

We conducted a retrospective cohort study using municipal National Health Insurance claims data in Japan (January 2016 to March 2025). New users of PPIs or P-CABs aged 18–74 years were included. Using a landmark approach, patients were classified as long-term (≥ 56 days) or short-term (< 56 days; reference) users based on cumulative days supplied during the 90-day landmark period. Follow-up began at the landmark. The primary outcome was fragility fracture, identified using a predefined claims-based list of standardised fracture diagnoses; associations were analysed with Cox proportional hazards models using overlap weighting. The secondary outcome was BMD testing; associated factors were assessed using logistic regression.

Results

Among 9,399 patients (long-term 4,673; short-term 4,726), 184 fragility fractures occurred. Long-term use was associated with fragility fracture (overlap-weighted hazard ratio [HR] **1.70**, 95% confidence interval [CI] 1.23–2.35), and fracture risk increased across cumulative exposure categories (P for trend < 0.001). **In the P-CAB subgroup, the HR for fragility fracture was 1.75 (95% CI 0.95–3.22).** BMD testing was performed in 994 patients (10.6%; men 2.9%, women 18.1%) and was most strongly associated with female sex and prior osteoporosis diagnosis or anti-osteoporosis treatment. Neither long-term PPI/P-CAB use (adjusted odds ratio 1.14, 95% CI 0.97–1.33) nor cumulative days supplied was significantly associated with BMD testing.

Conclusions

Long-term PPI/P-CAB use was associated with fragility fracture but was not significantly associated with BMD testing after multivariable adjustment. These findings suggest a divergence between fracture risk associated with long-term PPI/P-CAB use and patterns of BMD testing in real-world practice.

Background

Fragility fractures due to osteoporosis are an important health problem associated with loss of independence and increased mortality. In Japan, the number of patients with osteoporosis is approximately 12.8 million, and 150,000 to 200,000 hip fractures occur annually; prevention and early risk assessment are therefore essential [1–3]. Several drugs are known to increase fracture risk [4–7]. Among them, proton pump inhibitors (PPIs) have been consistently associated with an increased risk of fragility fractures in multiple meta-analyses [8–11] and subsequent observational studies [12–14]. In addition to treating acid-related disorders, PPIs are frequently co-prescribed to prevent gastrointestinal injury from nonsteroidal anti-inflammatory drugs (NSAIDs) used for chronic pain or musculoskeletal disease. This practice may further contribute to long-term use. In Japan, the recommended treatment duration for the acute phase of reflux oesophagitis is 8 weeks (56 days), yet co-prescription of PPIs with NSAIDs may contribute to continued use in some patients. Potassium-competitive acid blockers (P-CABs; vonoprazan), which are widely used in Japan, provide potent acid suppression comparable with that of PPIs, but real-world evidence on their associated fracture risk is limited, and studies evaluating both PPIs and P-CABs are scarce.

Although the association between long-term PPI use and fracture risk is well described, no established recommendation exists for bone mineral density (BMD) testing in patients receiving PPIs. The Japanese guidelines for the prevention and treatment of osteoporosis (2025) list adults receiving drugs that lower BMD as candidates for BMD measurement, but the role of long-term PPI/P-CAB use is not explicitly addressed [15]. Consequently, how often BMD testing is performed in routine care among patients receiving long-term PPI/P-CAB therapy remains unknown. Insufficient screening of patients with drug-related fracture risk has been reported previously [16]; for example, BMD testing was performed in only 1.46% of patients receiving long-term systemic corticosteroid therapy overall, and rates were even lower among men and primary-care patients [17]. To our knowledge, however, few studies have used Japanese claims data to examine BMD testing among patients receiving long-term PPI/P-CAB therapy. Addressing these questions requires a data source that can longitudinally capture prescriptions, diagnoses, fragility fractures, and BMD testing across healthcare providers within a defined population.

Whereas large-scale claims databases are valuable for identifying broad population-level trends, municipal claims data enable region-specific evaluation and may inform responses tailored to local healthcare needs [18]. Kodaira City, the Kodaira Pharmacists Association, and Musashino University have established a formal tripartite collaboration agreement covering analyses of medication use and healthcare claims data. This framework allows research findings to be shared directly with local healthcare professionals and used to inform community-based medication safety initiatives.

We therefore used municipal National Health Insurance claims data to examine the association between long-term (≥ 56 days) PPI/P-CAB use and fragility fracture risk and, in the same cohort, the association between long-term use and BMD testing in routine clinical practice.

Methods

Study design and data source

We conducted a retrospective cohort study using National Health Insurance claims data from Kodaira City, Japan, covering January 2016 to March 2025. The data include prescription, diagnosis, and procedure information for insured residents. Eligible individuals were National Health Insurance enrollees aged 18–74 years. Individuals aged 75 years or older were excluded because they are transferred to the Late-Stage Elderly Healthcare System and are therefore not captured in these data. We report the study in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement and its REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) extension for studies using routinely collected health data.

Because PPIs/P-CABs are prescribed for acid-related disorders, comparison with non-users would be subject to substantial confounding by indication. We therefore restricted the cohort to new users of PPIs/P-CABs and compared long-term users with short-term users using a landmark design.

Study population

Patients with no PPI/P-CAB prescription during the 12 months before their first observed PPI/P-CAB prescription were defined as new users, and this first prescription date was defined as the index date. The exclusion criteria were (i) age under 18 or 75 years or older; (ii) no continuous National Health Insurance enrolment during the 12 months before the index date; and (iii) any record of fragility fracture before the index date (identified from the start of data availability in January 2016 to the index date). We excluded 48 patients who developed a fragility fracture before the landmark (90 days after the index date), leaving 10,080 patients. We further excluded 681 patients who could not be followed to the landmark because of death or loss of insurance eligibility, leaving a final analytical cohort of 9,399 patients (Fig. 1).

Patient selection among new PPI/P-CAB users and stratification by cumulative days supplied during the landmark period. The landmark period was 90 days after the index date: cumulative days supplied of 56 days or more defined long-term use, and fewer than 56 days defined short-term use. After excluding 48 patients who developed a fragility fracture before the landmark and 681 patients who could not be followed to the landmark, the final analytical cohort was 9,399. PPI, proton pump inhibitor; P-CAB, potassium-competitive acid blocker.

Exposure

The main exposure was cumulative days supplied for PPIs/P-CABs during the 90-day landmark period after the index date. Patients with a cumulative supply of 56 days or more were classified as long-term users and those with fewer than 56 days as short-term users (reference). The 56-day threshold corresponds to the standard 8-week treatment period for reflux oesophagitis in the Japanese label.

Cumulative days supplied were calculated by summing the supply durations of all PPI/P-CAB prescriptions issued during the 90-day landmark period for each patient. To avoid immortal time bias, a landmark approach was used: follow-up began at the landmark, and patients who developed a fracture before the landmark or who did not reach the landmark because of death or loss of eligibility were excluded, thereby separating the exposure-ascertainment window from the follow-up period.

Outcomes

Follow-up for all outcomes began at the landmark and continued for a maximum of 730 days. Follow-up was censored at the earliest occurrence of the outcome, loss of National Health Insurance eligibility, end of data availability (31 March 2025), or 730 days.

The primary outcome was fragility fracture, defined using a predefined list of standardised disease names covering four skeletal regions (vertebra, femur, distal radius, and proximal humerus), together with osteoporotic pathological fracture diagnoses, including those without a specified site (Additional file 1: Supplementary Table 1). Because the mechanism of injury cannot be reliably ascertained from claims data, traumatic fractures could not be completely excluded. The diagnosis date recorded on the claim was used as the event date.

The secondary outcome was BMD testing, defined using procedure codes (160091310, 160147310, 160170410, 160226050). Patients with at least one record of any of these procedure codes from the landmark to the end of follow-up were classified as having undergone BMD testing. This outcome was used to describe testing status in the cohort and not to evaluate the appropriateness of testing.

Covariates

Covariates were selected on the basis of established fracture risk factors. Age at the index date (continuous) and sex were included. Exposure windows for drug covariates were defined according to their presumed mechanisms of action. Current use, defined as at least one prescription within the 3 months before the index date, was defined for NSAIDs, selective serotonin reuptake inhibitors (SSRIs), and benzodiazepines/Z-drugs, whereas ever use (any prescription on or before the index date) was defined for anti-osteoporosis medications and oral corticosteroids. Disease covariates comprised gastro-oesophageal reflux disease (GERD)-related diagnoses **(**any confirmed diagnosis on or before the index date**)**, a history of osteoporosis (within the 12 months before the index date), the Charlson comorbidity index (calculated using the Quan algorithm for the International Classification of Diseases, 10th Revision [ICD-10], from diagnoses in the 12 months before the index date), and musculoskeletal disease (confirmed diagnoses in the 12 months before the index date, excluding fracture and osteoporosis).

Polypharmacy was defined as six or more oral medications meeting the exposure definition. Drug counts were based on generic names and included oral medications supplied for 28 days or more during the 90

days before the index date, excluding the index PPI/P-CAB. Use of a P-CAB at the index date was included as a covariate. Drug, disease, and procedure code lists are provided in Additional file 1 (Supplementary Tables 1–6). All drugs are listed by generic name; brand names are not used.

Statistical analysis

Continuous variables were summarised as means ± standard deviations (SDs), and categorical variables as frequencies (%). Balance in baseline factors was assessed using the standardised mean difference (SMD), with |SMD| < 0.1 indicating adequate balance.

Fragility fracture was analysed using Cox proportional hazards models to estimate the hazard ratio (HR) and 95% confidence interval (CI) for long-term versus short-term use, with follow-up starting at the landmark (maximum 730 days). In the primary analysis, a propensity score for long-term use was estimated from the 13 covariates by logistic regression, and overlap weighting was applied to estimate the average treatment effect in the overlap population (ATO) using a weighted Cox model. Post-weighting balance was assessed by SMD, and the proportional hazards assumption was examined using Schoenfeld residuals. Overlap weights were estimated using the WeightIt package and covariate balance was assessed with the cobalt package. Sensitivity analyses included (1) a multivariable Cox model with the same covariates entered directly and (2) analyses using alternative definitions of musculoskeletal disease (broad and narrow). Cumulative days supplied were also categorised into four groups and analysed with a multivariable Cox model using < 28 days as the reference. Trend was assessed by entering the ordinal category as a continuous variable.

Kaplan–Meier curves were constructed for the four categories of cumulative days supplied and compared using the log-rank test.

Subgroup analyses were performed by age (18–64 and 65–74 years), sex, and index-date drug (PPI, P-CAB), with interactions assessed by including the corresponding interaction term in each model. Fragility fracture incidence was also described by age stratum (18–49, 50–64, and 65–74 years), and BMD testing rates were described by age and sex. Factors associated with BMD testing were assessed by a logistic regression model with the same covariates, yielding odds ratios (ORs) and 95% CIs. Because BMD testing was infrequent among those aged 18–49 years, an analysis of BMD testing restricted to patients aged 50 years or older was also performed. Stratified and subgroup analyses were considered exploratory, with no correction for multiple comparisons. Analyses used R version 4.6, with a two-sided significance level of 5%.

Ethics

This observational study was conducted using anonymised National Health Insurance claims data and was approved by the Musashino University Research Ethics Committee (approval number: R8-14).

Use of generative artificial intelligence

During the preparation of this manuscript, the authors used ChatGPT (**GPT-6.1**, OpenAI) to assist with statistical code development. The authors reviewed and verified all artificial intelligence-assisted outputs and take full responsibility for the content of the manuscript.

Results

Baseline characteristics

The study cohort comprised 9,399 patients (short-term 4,726; long-term 4,673) (Table 1). Compared with short-term users, long-term users were older (mean age 64.77 vs 58.43 years; SMD 0.498) and less likely to be female (44.3% vs 56.5%; SMD 0.245). GERD-related diagnoses (80.5% vs 64.4%; SMD 0.366) and polypharmacy (27.3% vs 12.4%; SMD 0.380) were more frequent among long-term users. In contrast, NSAID use was less frequent among long-term users (17.2% vs 24.4%; SMD 0.179). The proportion of patients with an index P-CAB prescription was higher among short-term users (31.7% vs 19.3%; SMD 0.288). Differences in SSRI use, benzodiazepine/Z-drug use, oral corticosteroid use, osteoporosis diagnosis history, musculoskeletal disease, and the Charlson comorbidity index were small (SMD < 0.1). After overlap weighting, all 13 primary covariates had |SMD| < 0.001, indicating good balance.

Overlap-weighted effective sample sizes were 3,979 (84.2% of the original sample) among short-term users and 4,045 (86.6%) among long-term users.

Table 1
Patient characteristics before and after overlap weighting

Characteristic	Before weighting: Short-term users, n = 4726	Before weighting: Long-term users, n = 4673	SMD	After weighting: Short-term users	After weighting: Long-term users	SMD
Age, years	58.43 (14.90)	64.77 (10.13)	0.498	62.63 (12.24)	62.63 (11.60)	< 0.001
Female sex	2668 (56.5)	2069 (44.3)	0.245	50.6	50.6	< 0.001
NSAIDs	1152 (24.4)	802 (17.2)	0.179	20.5	20.5	< 0.001
SSRIs	93 (2.0)	100 (2.1)	0.012	2.1	2.1	< 0.001
Benzodiazepines/Z-drugs	657 (13.9)	806 (17.2)	0.092	16.1	16.1	< 0.001
Oral corticosteroids	693 (14.7)	554 (11.9)	0.083	13.2	13.2	< 0.001
Anti-osteoporosis medication history	215 (4.5)	321 (6.9)	0.100	6.0	6.0	< 0.001
Osteoporosis diagnosis history	174 (3.7)	251 (5.4)	0.081	4.7	4.7	< 0.001
GERD-related diagnosis	3043 (64.4)	3761 (80.5)	0.366	73.3	73.3	< 0.001
Polypharmacy	587 (12.4)	1277 (27.3)	0.380	18.4	18.4	< 0.001
Musculoskeletal disease (broad)	1252 (26.5)	1114 (23.8)	0.061	26.0	26.0	< 0.001
Charlson comorbidity index	1.69 (2.09)	1.82 (2.43)	0.058	1.85 (2.17)	1.85 (2.45)	< 0.001
P-CAB as the index drug	1497 (31.7)	900 (19.3)	0.288	24.8	24.8	< 0.001

Values before weighting are presented as n (%) or mean (SD). After weighting, binary variables are presented as weighted percentages and continuous variables as weighted means (SDs). An absolute standardised mean difference (SMD) < 0.1 was considered indicative of adequate balance. Overlap weights were estimated using a propensity score based on the 13 covariates included in the primary analysis. After weighting, all 13 covariates had an absolute SMD of < 0.001. Medication characteristics represented patients who met the prespecified definition of use during the covariate assessment period.

NSAID, nonsteroidal anti-inflammatory drug; SSRI, selective serotonin reuptake inhibitor; GERD, gastro-oesophageal reflux disease; SD, standard deviation; SMD, standardised mean difference; P-CAB, potassium-competitive acid blocker.

Fragility fracture

During follow-up, 184 fragility fractures occurred: 62 (1.3%) among short-term users and 122 (2.6%) among long-term users. In the primary overlap-weighted Cox model, long-term use was associated with a higher risk of fragility fracture (HR 1.70, 95% CI 1.23–2.35), and the proportional hazards assumption was met. Results were consistent across sensitivity analyses, including the multivariable Cox model and the sensitivity analysis using the narrow definition of musculoskeletal disease.

In subgroup analyses (Table 2), no interaction between long-term use and age or index-date drug was observed (*P* for interaction = 0.112 and 0.892, respectively). An interaction between long-term use and sex was observed (*P* for interaction < 0.001): the HR was 2.71 (95% CI 1.79–4.12) in women and 0.94 (95% CI 0.58–1.53) in men. Among women, the proportion of patients with fragility fracture was higher in long-term users than in short-term users (3.9% vs 1.2%), whereas the corresponding proportions among men were 1.6% and 1.4%, respectively. The index drug was not significantly associated with fracture risk (P-CAB vs PPI: adjusted HR 1.08, 95% CI 0.76–1.52).

Table 2
Subgroup analyses of the association between long-term PPI/P-CAB use and fragility fracture

Subgroup	Events/N	HR (95% CI)	*P* for interaction
Overall	184/9399	1.70 (1.23–2.35)	—
Age			0.112
18–64 years	44/4089	2.92 (1.55–5.50)	
65–74 years	140/5310	1.64 (1.14–2.35)	
Sex			< 0.001
Male	70/4662	0.94 (0.58–1.53)	
Female	114/4737	2.71 (1.79–4.12)	
Index drug			0.892
PPI	141/7002	1.83 (1.26–2.67)	
P-CAB	43/2397	1.75 (0.95–3.22)	

HRs and 95% CIs compare long-term with short-term use within each subgroup and were estimated using overlap-weighted Cox proportional hazards models. *P* values for interaction were obtained by including the interaction term between long-term use and the corresponding subgroup variable. Long-

term use was defined as a cumulative supply of ≥ 56 days during the 90-day landmark period. HR, hazard ratio; CI, confidence interval; PPI, proton pump inhibitor; P-CAB, potassium-competitive acid blocker.

Factors associated with fragility fracture

In the multivariable Cox model, long-term PPI/P-CAB use, age, and female sex were associated with fragility fracture (Table 3). The adjusted HRs were 1.81 (95% CI 1.31–2.50) for long-term use, 1.64 (95% CI 1.35–2.00) per 10-year increase in age, and 1.75 (95% CI 1.28–2.39) for female sex. The HR was 1.07 (95% CI 0.74–1.55; *P* = 0.704) for NSAID use and 1.05 (95% CI 1.00–1.12; *P* = 0.068) per 1-point increase in the Charlson comorbidity index. No clear associations with fragility fracture were observed for the remaining covariates.

Table 3
Factors associated with fragility fracture in the multivariable Cox model

Characteristic	**HR**	**95% CI**	***P* value**
Long-term PPI/P-CAB use (vs short-term use)	1.81	1.31–2.50	< 0.001
Age, per 10-year increase	1.64	1.35–2.00	< 0.001
Female sex (vs male sex)	1.75	1.28–2.39	< 0.001
NSAIDs	1.07	0.74–1.55	0.704
SSRIs	1.69	0.73–3.95	0.224
Benzodiazepines/Z-drugs	1.22	0.84–1.77	0.285
Oral corticosteroids	1.35	0.90–2.03	0.142
Anti-osteoporosis medication history	1.00	0.59–1.70	0.992
Osteoporosis diagnosis history	1.17	0.66–2.07	0.590
GERD-related diagnosis	0.83	0.59–1.16	0.265
Polypharmacy	1.26	0.89–1.77	0.193
Musculoskeletal disease (broad)	1.25	0.90–1.75	0.184
Charlson comorbidity index, per point	1.05	1.00–1.12	0.068
P-CAB (vs PPI)	1.08	0.76–1.52	0.677

HRs and 95% CIs were estimated using a multivariable Cox proportional hazards model that simultaneously included all 13 covariates. Long-term use was defined as cumulative days supplied ≥ 56 days. For binary covariates, the reference categories were short-term use for long-term PPI/P-CAB use, male sex for female sex, PPI use for P-CAB use, and absence of the characteristic for all other binary covariates. HR, hazard ratio; CI, confidence interval; PPI, proton pump inhibitor; P-CAB, potassium-

competitive acid blocker; NSAID, nonsteroidal anti-inflammatory drug; SSRI, selective serotonin reuptake inhibitor; GERD, gastro-oesophageal reflux disease.

Cumulative days supplied and fracture risk

When cumulative days supplied during the 90-day landmark period were categorised into four groups, with < 28 days as the reference, the HRs were 0.93 (95% CI 0.55–1.59) for 28–55 days, 1.58 (95% CI 0.96–2.59) for 56–89 days, and 1.84 (95% CI 1.24–2.72) for ≥ 90 days. Fracture risk increased across categories of cumulative days supplied (HR 1.25 per category increase; *P* for trend < 0.001). The crude proportions of patients with fragility fracture were 1.30%, 1.34%, 2.19%, and 2.77%, respectively.

In the Kaplan–Meier analysis, the < 28-day and 28–55-day groups showed similar curves, whereas the 56–89-day and ≥ 90-day groups showed higher estimated cumulative incidence of fragility fracture (Fig. 2).

Kaplan-Meier estimates of cumulative fragility fracture incidence from the landmark, with patients grouped by cumulative days supplied during the landmark period (90 days after the index date). Groups were compared using the log-rank test (P < 0.001).

BMD testing

BMD testing was performed in 994 patients (10.6%) during follow-up (Table 4). Testing was more frequent among women (18.1%) than among men (2.9%) and increased across age groups (18–49 years, 2.4%; 50–64 years, 8.6%; and 65–74 years, 14.1%). Testing rates were higher among patients with musculoskeletal disease (16.3%) and those with a prior osteoporosis diagnosis (45.2%). Testing rates were 11.6% among long-term users and 9.6% among short-term users, and 11.0% among patients with a PPI index prescription versus 9.3% among those with a P-CAB index prescription.

Table 4
BMD testing according to patient characteristics

Characteristic	N	BMD testing, n (%)
Overall	9399	994 (10.6)
PPI/P-CAB use duration		
Short-term use	4726	453 (9.6)
Long-term use	4673	541 (11.6)
Sex		
Male	4662	135 (2.9)
Female	4737	859 (18.1)
Age, years		
18–49	1724	42 (2.4)
50–64	2365	204 (8.6)
65–74	5310	748 (14.1)
Index drug		
PPI	7002	770 (11.0)
P-CAB	2397	224 (9.3)
Musculoskeletal disease (broad)		
No	7033	609 (8.7)
Yes	2366	385 (16.3)
Osteoporosis diagnosis history		
No	8974	802 (8.9)
Yes	425	192 (45.2)

Values are presented as n (%). BMD, bone mineral density; PPI, proton pump inhibitor; P-CAB, potassium-competitive acid blocker.

By cumulative days supplied, BMD testing rates were 9.3% for < 28 days, 10.2% for 28–55 days, 12.0% for 56–89 days, and 11.4% for ≥ 90 days; testing did not increase consistently across categories. With < 28 days as the reference category, the adjusted ORs were 0.97 (95% CI 0.78–1.22) for 28–55 days, 1.26 (95% CI 0.99–1.59) for 56–89 days, and 1.07 (95% CI 0.89–1.30) for ≥ 90 days (Supplementary Table 7).

Factors associated with BMD testing

In the multivariable logistic regression including the same covariates as the fracture analysis, female sex, prior anti-osteoporosis medication use, prior osteoporosis diagnosis, age, and musculoskeletal disease were associated with BMD testing after adjustment (Table 5). No clear associations were observed for long-term PPI/P-CAB use (OR 1.14, 95% CI 0.97–1.33) or polypharmacy (OR 1.12, 95% CI 0.93–1.36). Figure 3 presents the HRs for fragility fracture and ORs for BMD testing for each factor. In the analysis restricted to patients aged 50 years or older (n = 7,675), no clear association was observed between long-term use and BMD testing (OR 1.07, 95% CI 0.91–1.25).

Table 5
Factors associated with BMD testing (multivariable logistic regression)

Characteristic	**OR (95% CI)**	***P* value**
Long-term PPI/P-CAB use (vs short-term use)	1.14 (0.97–1.33)	0.110
Age, per 10-year increase	1.56 (1.43–1.69)	< 0.001
Female sex (vs male sex)	5.86 (4.82–7.12)	< 0.001
NSAIDs	1.03 (0.86–1.24)	0.759
SSRIs	1.24 (0.73–2.10)	0.427
Benzodiazepines/Z-drugs	1.02 (0.84–1.25)	0.819
Oral corticosteroids	0.93 (0.75–1.16)	0.529
Anti-osteoporosis medication history	5.07 (4.10–6.28)	< 0.001
Osteoporosis diagnosis history	2.38 (1.85–3.05)	< 0.001
GERD-related diagnosis	1.13 (0.94–1.34)	0.187
Polypharmacy	1.12 (0.93–1.36)	0.225
Musculoskeletal disease (broad)	1.31 (1.11–1.55)	0.001
Charlson comorbidity index, per point	1.02 (0.99–1.06)	0.158
P-CAB (vs PPI)	0.90 (0.76–1.08)	0.259

ORs and 95% CIs were estimated using a multivariable logistic regression model that simultaneously included all 13 covariates. For binary covariates, the reference categories were short-term use for long-term PPI/P-CAB use, male sex for female sex, PPI use for P-CAB use, and absence of the characteristic for all other binary covariates. BMD, bone mineral density; OR, odds ratio; CI, confidence interval; PPI, proton pump inhibitor; P-CAB, potassium-competitive acid blocker; NSAID, nonsteroidal anti-inflammatory drug; SSRI, selective serotonin reuptake inhibitor; GERD, gastro-oesophageal reflux disease.

For each factor, the hazard ratio for fragility fracture (multivariable Cox model) and the odds ratio for BMD testing (multivariable logistic regression) are shown side-by-side, with both models adjusted for the

same 13 variables. The horizontal axis is on a logarithmic scale, the error bars represent 95% CIs, and the dashed line indicates the reference (ratio = 1). Age was expressed per 10 years. HR, hazard ratio; OR, odds ratio; CI, confidence interval; BMD, bone mineral density; P-CAB, potassium-competitive acid blocker.

Discussion

In this cohort, long-term PPI/P-CAB use was associated with fragility fracture, with fracture risk increasing across categories of cumulative days supplied. In contrast, BMD testing was associated with female sex and a prior osteoporosis diagnosis or anti-osteoporosis treatment, whereas no clear association was observed with long-term PPI/P-CAB use.

Long-term use and fragility fracture

The association between PPI use and fragility fracture has been reported in multiple meta-analyses [8–11], and our findings are consistent with these previous reports. Two important methodological features were the use of short-term users of the same drug class, rather than non-users, as the reference group and a landmark approach that separated the exposure-ascertainment window from follow-up. The former mitigated confounding by indication for acid-related disorders, whereas the latter reduced immortal time bias. The observed association was directionally consistent with prior reports. Fracture risk increased across categories of cumulative days supplied, and the trend test was significant, supporting an association between longer exposure and fragility fracture.

Real-world data on fracture risk with P-CABs are limited. Among the 2,397 patients whose index drug was a P-CAB, the **point estimate of the** HR for long-term use was similar to that for PPIs; however, the number of events was limited (43), and no clear difference in fracture risk was observed between the drugs. **These findings suggest that long-term P-CAB use may be similarly associated with fragility fracture as long-term PPI use.** The overall association between long-term PPI/P-CAB use and fragility fracture was somewhat stronger than in some prior reports and should be interpreted with caution. Nevertheless, the findings suggest that fracture risk may warrant attention in patients receiving long-term P-CAB therapy as well as in those receiving long-term PPI therapy.

The association between long-term use and fragility fracture also differed by sex, with an association observed in women but not in men. However, because the subgroup analyses were exploratory, were not adjusted for multiple comparisons, and included a limited number of events, this finding should be interpreted cautiously and warrants confirmation in other populations.

BMD testing and the divergence from fracture risk

In this cohort, BMD testing appeared to reflect the existing framework of osteoporosis diagnosis and management more closely than long-term PPI/P-CAB exposure. Testing was performed in 45.2% of patients with a prior osteoporosis diagnosis but only 8.9% of patients without one, and rates were also

higher among patients with musculoskeletal disease, suggesting that BMD testing may be more closely linked to established osteoporosis-related clinical pathways. By contrast, no clear association was observed between long-term PPI/P-CAB use and BMD testing, either in the overall cohort or among patients aged 50 years or older, and testing rates did not increase consistently across categories of cumulative days supplied (**Supplementary Table 7**).

Current BMD measurement guidance may partly explain this pattern. The Japanese osteoporosis guidelines (2025) recommend BMD measurement based on age and established clinical risk factors, but do not explicitly identify long-term PPI/P-CAB use as an indication for BMD measurement [15]. In addition, specific recommendations for fracture risk assessment and bone health management have been established for patients receiving systemic glucocorticoids [19]. Similarly, the UK osteoporosis guideline recognises PPI use as a factor associated with increased fracture risk but notes uncertainty regarding causality and makes no specific recommendation for patients receiving PPIs [20]. Although the US Food and Drug Administration issued a warning regarding PPI use and fracture risk in 2010, the 2022 American College of Gastroenterology guideline does not recommend routine BMD monitoring for patients with GERD receiving PPIs who have no other risk factors for bone disease [21]. Thus, the observed pattern may reflect the current clinical guidance, in which PPI use alone is not regarded as an indication for BMD testing.

The patterns of association with fragility fracture and BMD testing differed across factors (Fig. 3). Age and female sex were associated with both outcomes, consistent with BMD testing being more common among patients with established fracture risk factors. In contrast, long-term PPI/P-CAB use was associated with fragility fracture but showed no clear association with BMD testing. These findings indicate a divergence between fracture risk associated with long-term PPI/P-CAB use and the factors associated with BMD testing in routine clinical practice.

These findings do not imply that routine BMD testing is warranted for all patients receiving long-term PPI/P-CAB therapy. Rather, they suggest that long-term PPI/P-CAB exposure may be relevant when considering overall fracture risk, although further studies are needed to determine whether and how this information should be incorporated into clinical risk assessment.

Limitations

Some limitations should be considered. First, fragility fractures were identified using diagnosis codes without requiring confirmatory procedure codes. The mechanism of injury cannot be ascertained from claims data; therefore, some traumatic fractures may have been included. Conversely, asymptomatic vertebral fractures that did not result in a medical visit may have been missed, leading to underascertainment.

Second, exposure was classified according to cumulative days supplied, and patients with longer exposure may have differed in underlying disease severity or other clinical characteristics associated with treatment duration. Although using short-term users as the reference group reduces confounding by

indication relative to using non-users, residual confounding cannot be fully excluded. In addition, days supplied reflect prescriptions rather than actual medication use, and adherence could not be assessed.

Third, the cohort was limited to individuals aged 18–74 years; therefore, the findings may not be generalisable to individuals aged 75 years or older, who are at higher risk of fracture. The claims data also did not capture access to BMD testing; therefore, observed differences in testing may partly reflect patterns of care, health-seeking behaviour, or healthcare access rather than clinical decision-making alone. In addition, this study was based on data from a single municipality, and healthcare utilisation and prescribing patterns may differ across regions; therefore, caution is warranted when generalising the findings to the broader Japanese population. Fourth, claims data lack important clinical information related to fracture risk, including smoking, alcohol use, body mass index, history of falls, and BMD; therefore, residual confounding by these factors cannot be excluded.

Fifth, subgroup analyses were exploratory and were not adjusted for multiple comparisons; therefore, the subgroup findings should be considered hypothesis-generating and require confirmation in future studies.

Conclusions

In this cohort, long-term PPI/P-CAB use was associated with fragility fracture, with an estimate in the same direction as, but somewhat larger than, those in prior reports. BMD testing, however, was strongly associated with prior osteoporosis diagnosis or anti-osteoporosis treatment and female sex and showed no clear association with long-term PPI/P-CAB use. Thus, fracture risk associated with long-term PPI/P-CAB use diverged from the factors associated with BMD testing in routine clinical practice. Whether and how long-term PPI/P-CAB exposure should be incorporated into fracture risk assessment requires further investigation.

Abbreviations

PPI
proton pump inhibitor
P-CAB
potassium-competitive acid blocker
BMD
bone mineral density
ICD-10
International Classification of Diseases, 10th Revision
NSAID
nonsteroidal anti-inflammatory drug
SSRI
selective serotonin reuptake inhibitor

GERD
gastro-oesophageal reflux disease
HR
hazard ratio
OR
odds ratio
CI
confidence interval
SD
standard deviation
SMD
standardised mean difference
ATO
average treatment effect in the overlap population
STROBE
Strengthening the Reporting of Observational Studies in Epidemiology
RECORD
REporting of studies Conducted using Observational Routinely-collected health Data.

Declarations

Clinical trial number: not applicable.

Ethics approval and consent to participate

This study was approved by the Musashino University Research Ethics Committee (approval number: R8-14). Because the study used only pre-existing, anonymised National Health Insurance claims data, the requirement for informed consent was waived.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Author Contribution

Y.F. conceived and designed the study, performed the data analysis, and drafted the manuscript. T.H. contributed to the study design and interpretation of the results. K.M. provided overall scientific supervision and critically reviewed the manuscript. All authors reviewed and approved the final manuscript.

Acknowledgement

Not applicable.

Data Availability

The data that support the findings of this study were provided by Kodaira City and are not publicly available because of restrictions imposed by the data provider and the conditions governing their use. Any request for access to the data would require consultation with and approval from Kodaira City.

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Figures

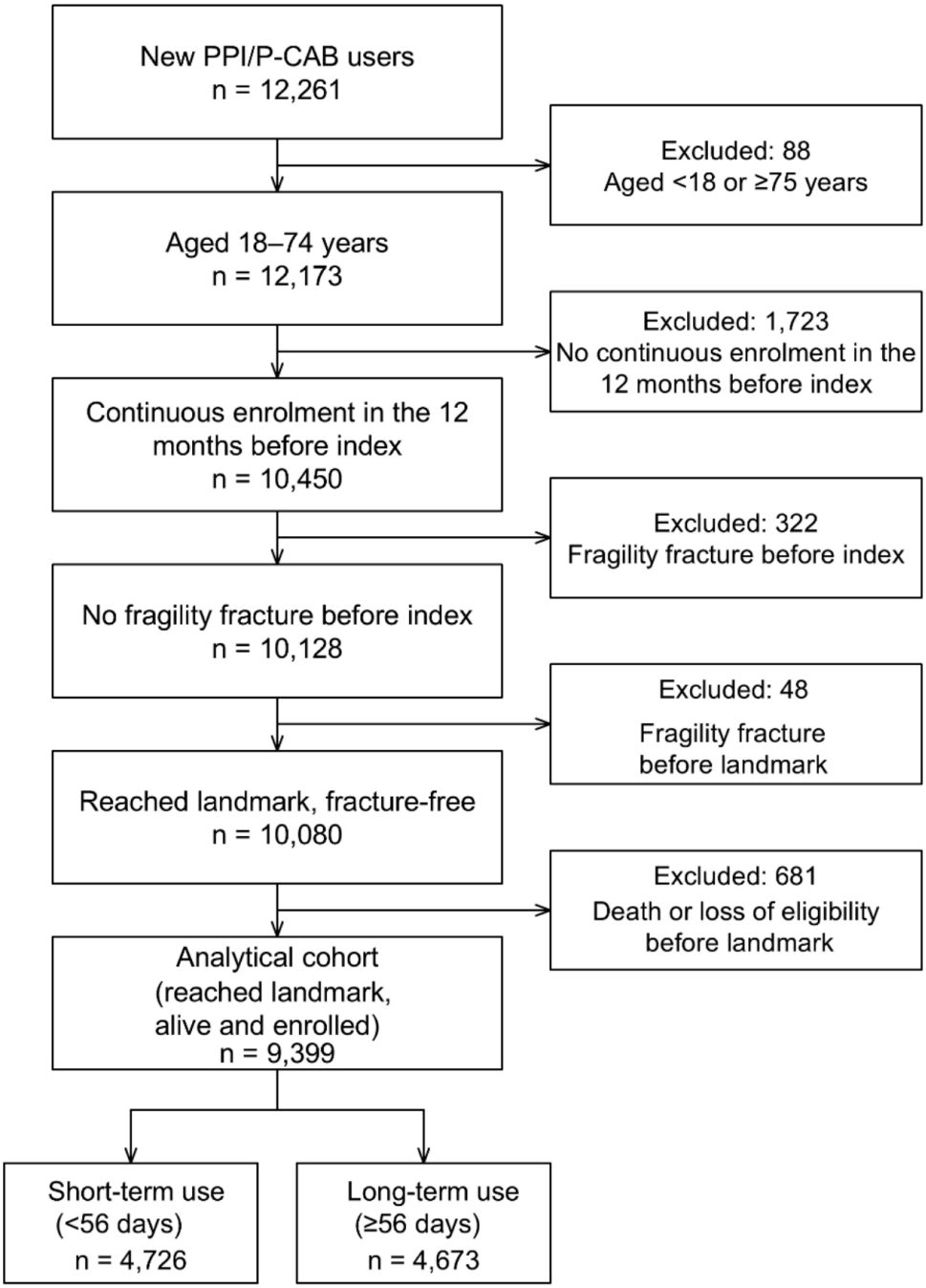


Figure 1

Study flowchart of patient selection and landmark stratification.

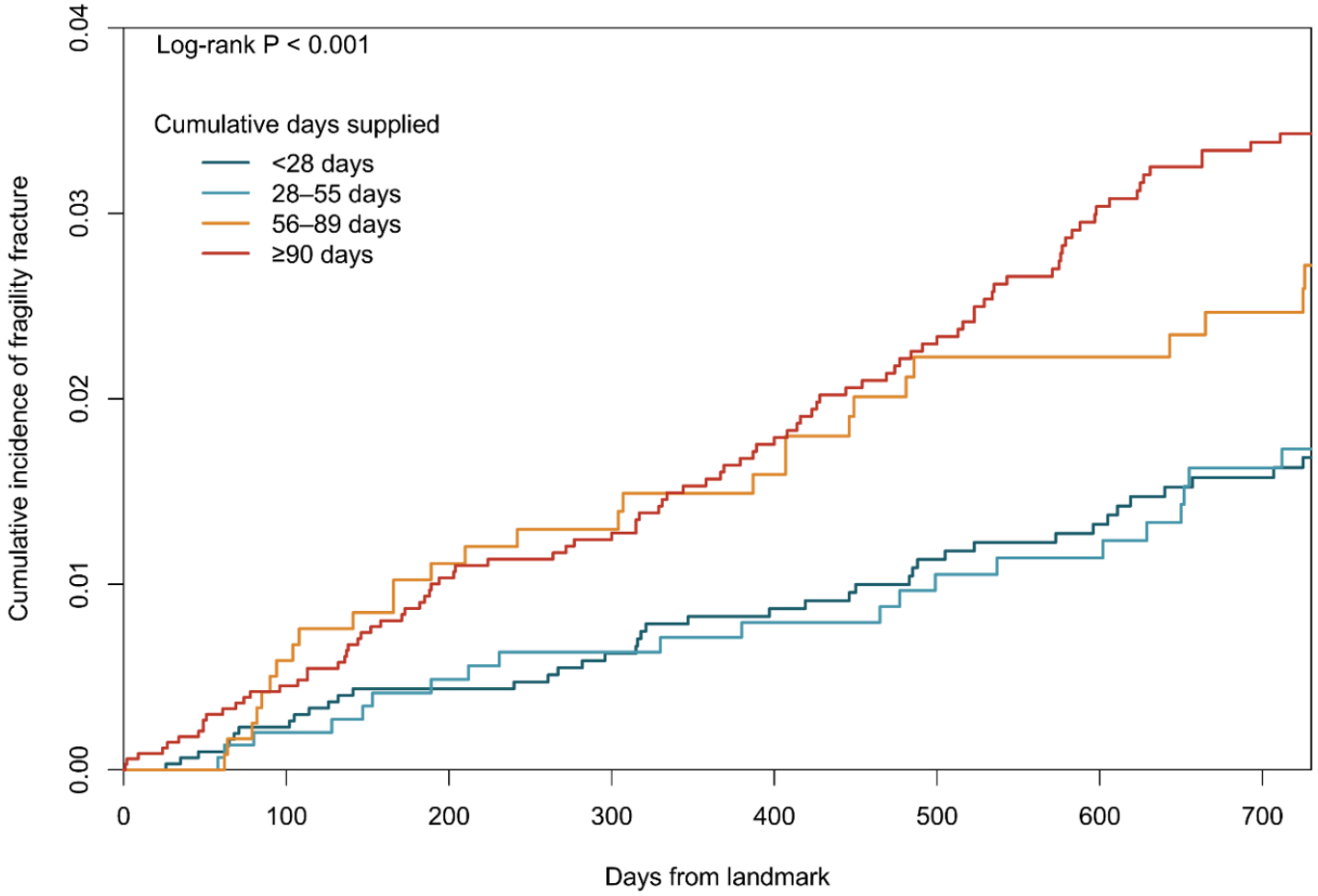


Figure 2

Cumulative incidence of fragility fracture by cumulative days supplied.

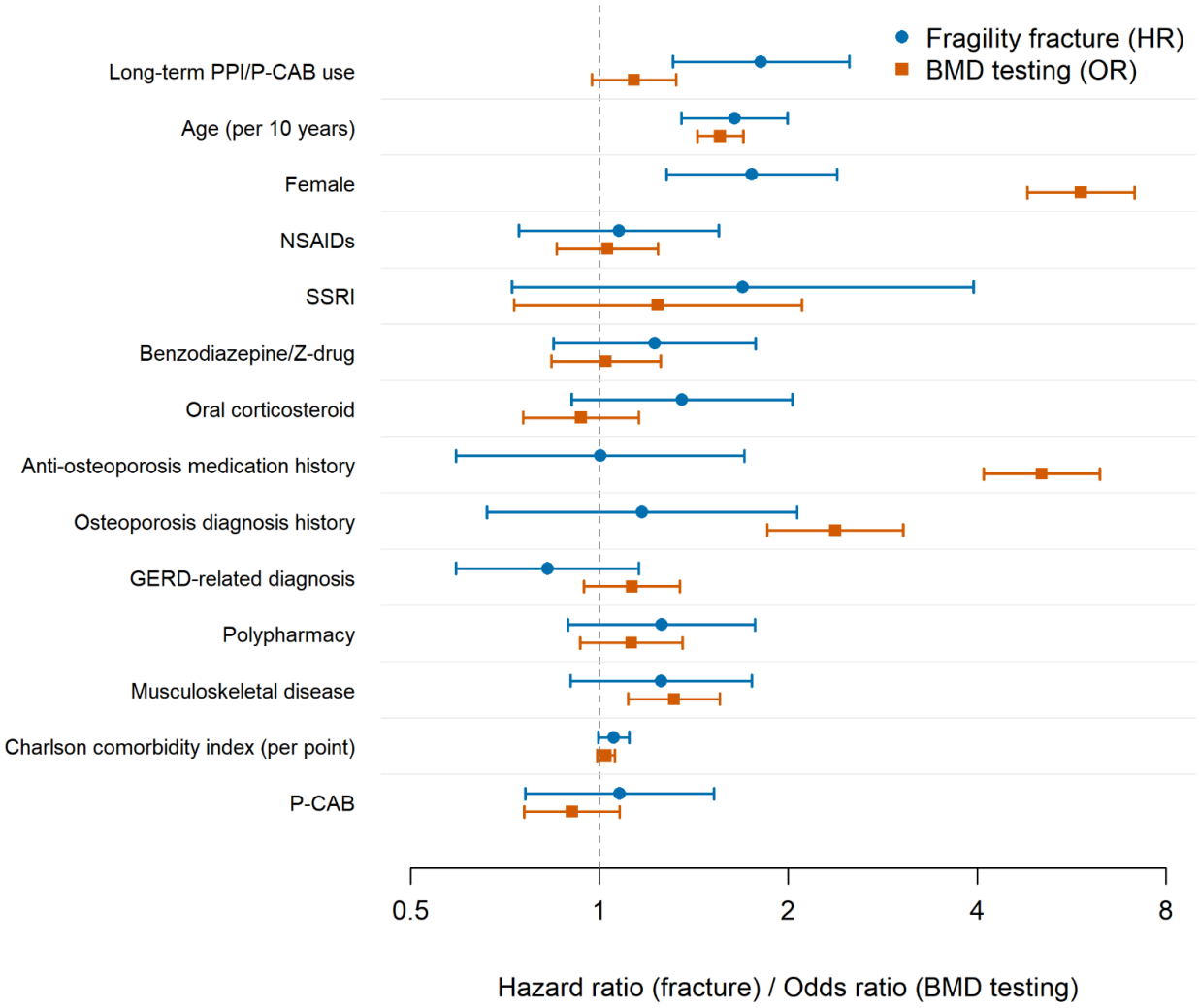


Figure 3

Hazard ratios for fragility fracture versus odds ratios for BMD testing.

Supplementary Files

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- Supplementarymaterial.docx