# Association of Gastrointestinal Events and Osteoporosis Treatment Initiation Among Newly Diagnosed Osteoporotic Israeli Women

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## Abstract

**Objectives:** To examine the association of gastrointestinal (GI) events and osteoporosis (OP) therapy initiation patterns among postmenopausal women following a diagnosis of OP from a large health plan in Israel.

**Methods:** Women aged ≥55 years were included in the analysis if they had ≥1 OP diagnosis (ICD-9 733.0X) (date for 1st OP diagnosis was index date), no estrogen use, no diagnosis of Paget's disease or malignant neoplasm. OP treatment initiation was defined as use of OP therapy: bisphosphonates (BIS) (alendronate, risedronate, zolendronic acid) and non-BIS (raloxifene, calcitonin, and teriparatide), during 12 months post-index. GI events (diagnosis of GI conditions) were reported for 12 months pre-index and post-index (from index to treatment initiation or end of 1 year post-index, whichever occurred first). The association of post-index GI events (yes/no) and initiation of OP treatment (yes/no), and the type of therapy initiated (i.e., BIS vs non-BIS) were examined with logistic regression and also Cox proportional hazard regression as sensitivity analysis.

**Results:** Among 30,788 eligible patients, aged 65.0 ± 7.6 (mean ± standard deviation [SD]) years, 17.5% had pre-index GI event, and 13.0% had post-index GI event. 70.6% of patients didn't receive OP therapy in the year following OP diagnosis, 25.1% received BIS, and 4.2% received non-BIS. The logistic regression showed that post-index GI events were associated with lower odds of OP medication initiation by approximately 51%-57% (p<0.001), and upon treatment initiation, post-index GI was not significantly associated with type of therapy initiated (BIS vs. non-BIS), controlling for baseline GI and patient characteristics.

**Conclusions:** Among newly diagnosed osteoporotic women from a large health plan in Israel, 70.6% did not receive pharmacological OP treatment within 1 year of OP diagnosis. Patients with post-index GI events were about 51-57% less likely to initiate OP treatment.

## Background

- Approximately 200 million women are estimated to be diagnosed with osteoporosis worldwide.[1,2] The prevalence of osteoporosis among Israeli women, as diagnosed by a physician, has been reported to be approximately 14%, which is similar to the rate among women in the United States (US).[3]
- Patients with osteoporosis remain under-diagnosed or untreated. Substantial under-treatment has been shown among patients diagnosed with osteoporosis.[4]
- Gastrointestinal events are highly prevalent among elderly women[5] Presence of comorbid gastrointestinal (GI) events among diagnosed osteoporosis patients may impact the initiation and the selection of pharmacological treatment in osteoporosis management.

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## Study Objectives

- The objective of the study was to examine the association of GI events after osteoporosis diagnosis and osteoporosis treatment initiation patterns among postmenopausal women following a diagnosis of osteoporosis from a large health plan in Israel.

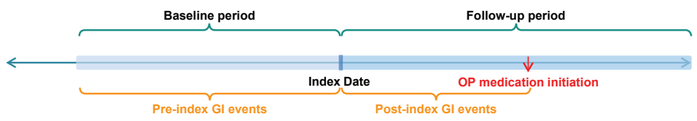
## Methods

### Data source

- Data for this analysis were obtained from the Maccabbi Healthcare Services (MHS) database, which comprises the electronic medical records (EMR) of all patients from the MHS health maintenance organization (HMO) in Israel. The Maccabi database, which originated in 1998, contains records of approximately 2.7 million Israeli members, approximately 2 million of whom are active members.

### Study design

- This was a retrospective analysis of the Maccabbi database between 1/1/2000 and 11/27/2012.
- The study population was defined using the following inclusion/exclusion criteria:
  1. ≥1 medical record with osteoporosis diagnosis (ICD-9 733.0X) – date of the first claim with osteoporosis diagnosis being the index date
  2. Female gender
  3. ≥55 years of age on index date
  4. Continuous enrollment in Maccabbi health plan during the year prior to and the year after index
  5. No estrogen use during the year before the index date
  6. No diagnosis of Paget's disease of the bone (ICD-9 731.0) or diagnosis of malignant neoplasm (ICD-9 140-171, 173-208, 230-239) throughout the data history
- **Index date:** 1st osteoporosis diagnosis in the computerized medical records (1998-2001)
- **Osteoporosis medication:** Drugs used to treat osteoporosis. They include:
  - Bisphosphonates (BIS) (alendronate, risedronate, zoledronic acid)
  - Non-bisphosphonate (non-BIS) (raloxifene, calcitonin, teriparatide)
    - All forms of drugs are included (i.e. oral, injectable, and infusion)
- **GI events**: Presence of either an ICD-9 code for GI diagnosis or a CPT code for GI procedures
  - Pre-index GI events assessed in the 1-year baseline period prior to the first OP
  - Post-index GI events assessed during the year after the index date, in relation to the timing of any OP treatment initiation; particularly,
    - The patient has post-index GI event if such event occurs after OP diagnosis and before the OP treatment initiation during the follow-up period
    - The patient had no post-index GI event if either GI event first occurs after the OP treatment initiation or does not occur at all during the follow-up period




### GI Event Definition

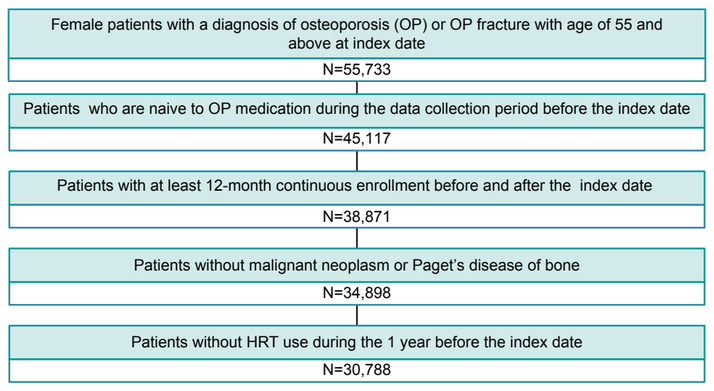
Diagnosis codes for selected GI events listed below:

- Esophagitis
- Ulcer of esophagus, with and without bleeding
- Esophageal reflux (GERD)
- Gastric ulcer
- Duodenal ulcer
- Peptic ulcer, site NOS
- Gastrojejunal ulcer

### Data Analysis

- Pre-index period: The presence of pre-index GI events, age group, baseline medication use (GPA: PPI, H2RA, cytoprotectant; NSAID; glucocorticoid), baseline Charlson-Deyo comorbidity index (CCI), and baseline OP-related comorbidities were assessed
- Post-index period: Comparisons were made between:
  - The occurrence of GI events before and after OP diagnosis
  - OP treatments for patients with and without post-diagnosis GI events
- Analytic models:
  1. Whether receiving any treatment within one year (yes/no): logistic regression (sensitivity analysis: cox hazard regression stratified by presence of pre-index GI) to address variant length of follow-up for capturing GI events among patients
  2. Among those who received any treatment, whether receiveing BIS or non-BIS: logistic regression (sensitivity analysis: discrete choice model with conditional logit)

### Sample Selection Flow Chart




## Results

### Table 1: Baseline Period Characteristics (N = 30,788)

| | N | % |
|---|---|---|
| Age at index | | |
| Mean, SD | 65 | 7.6 |
| 55-64 | 16350 | 53% |
| 64-74 | 10599 | 34% |
| 75-85 | 3433 | 11% |
| >85 | 406 | 1% |

| | | N | % |
|---|---|---|---|
| Medication use | Glucocorticoid for at least 3 consecutive months average 5 mg daily during 1 year before index | 189 | 0.6% |
| | Non OTC NSAID 1 year before index - for at least 3 consecutive months | 398 | 1.3% |
| | At least 3 consecutive months gastro-protective agents (i.e. PPI and H2RA) (some are OTC) 1 year before index | 2719 | 8.8% |
| Pre-index GI event | | 5386 | 17.5% |
| Charlson comorbidity Index (mean, SD) | | Mean 2.1 | SD 2.3 |

- Approximately 17.5% of women in the sample had GI events prior to first diagnosis of osteoporosis

### Table 2. Distribution of Patients by Pre- and Post-Index GI Events Within 1 Year of Follow-up (N = 30,788)

| | | Follow-up Period (N, %) | | |
|---|---|---|---|---|
| | | Absence of Post-index GI Events | Presence of Post-index GI Events | Total |
| Baseline Period | Absence of pre-index GI events | 24044<br>94.7% | 1358<br>5.3% | 25402<br>82.5% |
| | Presence of pre-index GI events | 4988<br>92.6% | 398<br>7.4% | 5386<br>17.5% |
| Total | | 29032<br>94.3% | 1756<br>5.7% | 30788<br>100% |

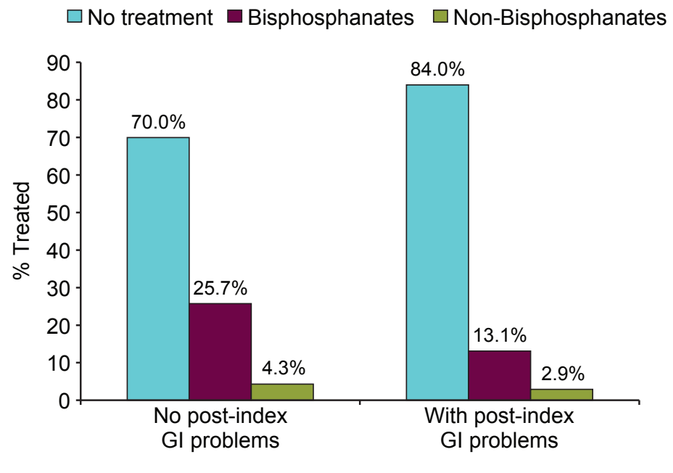
- Pre-Index GI: 17.5% of patients had GI events 1 year before index. Among these patients, 7.4% of them continued to have GI events from the index date to the end of 1-year follow-up or OP treatment initiation
- Post-Index GI: 5.7% of patients had GI events from the index date to the end of 1-year follow-up or OP treatment initiation

### Table 3. Distribution of Patients by Osteoporosis Treatment Type (N = 30,788)

| First Treatment Received Within 1-year Follow-up Period | N | % |
|---|---|---|
| Total | 30,788 | 100.00% |
| Bisphosphonates | 7,700 | 25.1% |
| Non-Bisphosphonates | 1,302 | 4.2% |
| No treatment | 21,786 | 70.7% |

- Bisphosphonates were the osteoporosis treatment within the 1-year follow-up period for 25% of patients
- Non-bisphosphonates were the OP treatment for 4% of patients
- 71% of osteoporosis patients received no treatment in the year after diagnosis

### Figure 1. Distribution of Osteoporosis Treatment by Post-Index GI Events (N=30,788)




### Summary of Findings

- Among the studied patient population, 70.7% did not receive any OP medication within 1 year of diagnosis
- In the study population, 17.5% had pre-index, and 5.7% had post-index GI events
- Compared to those without post-index GI events, patients who had post-index GI events were about 51-57% less likely to start OP treatment (p<0.001), controlling for baseline covariates

### Table 4. Logistic Regression Results for Post-Index GI and Treatment Initiation (N=30,788)

| Among Patients Without Pre-index GI | | | | |
|---|---|---|---|---|
| | Odds Ratio | 95% CI | | P-value |
| Post-index GI | 0.429 | 0.369 | 0.499 | <0.001 |
| Age 55-64 | 0.000 | | | <0.001 |
| Age 65-74 | 1.400 | 1.318 | 1.487 | <0.001 |
| Age 75-84 | 1.287 | 1.174 | 1.411 | <0.001 |
| Age 85+ | 0.582 | 0.440 | 0.770 | <0.001 |
| GPA | 1.182 | 1.060 | 1.318 | 0.003 |
| NSAIDs | 1.114 | 0.881 | 1.409 | 0.368 |
| GC | 1.971 | 1.407 | 2.760 | <0.001 |
| IBD | 1.145 | 0.955 | 1.374 | 0.144 |
| Chronic inflammatory joint | 1.071 | 0.997 | 1.150 | 0.062 |
| Celiac | 1.421 | 0.688 | 2.936 | 0.342 |
| Diabetes | 0.817 | 0.750 | 0.890 | <0.001 |
| Depression | 0.881 | 0.814 | 0.952 | 0.001 |
| Renal failure | 0.989 | 0.868 | 1.128 | 0.869 |
| Hypertension | 1.192 | 1.121 | 1.267 | <0.001 |
| Urination problems | 1.067 | 0.993 | 1.146 | 0.078 |
| Hyperparathyroidism | 1.328 | 1.023 | 1.725 | 0.033 |
| Vitamin D deficiency | 1.378 | 1.159 | 1.638 | <0.001 |
| Fatigue | 1.105 | 1.016 | 1.201 | 0.02 |
| Constant | 0.336 | | | <0.001 |

| Among Patients With Pre-index GI | | | | |
|---|---|---|---|---|
| | Odds Ratio | 95% CI | | P-value |
| Post-index GI | .486 | .373 | .634 | <0.001 |
| Age 55-64 | .000 | | | <0.001 |
| Age 65-74 | 1.348 | 1.184 | 1.534 | <0.001 |
| Age 75-84 | 1.131 | .924 | 1.383 | 0.233 |
| Age 85+ | .911 | .527 | 1.575 | 0.739 |
| GPA | 1.224 | 1.052 | 1.423 | 0.009 |
| NSAIDs | 1.184 | .717 | 1.956 | 0.51 |
| GC | 2.533 | 1.407 | 4.560 | 0.002 |
| IBD | .976 | .699 | 1.363 | 0.886 |
| Chronic inflammatory joint | .919 | .796 | 1.061 | 0.251 |
| Celiac | 1.293 | .369 | 4.534 | 0.688 |
| Diabetes | .698 | .584 | .834 | <0.001 |
| Depression | 1.004 | .864 | 1.168 | 0.954 |
| Renal failure | 1.014 | .787 | 1.307 | 0.915 |
| Hypertension | 1.210 | 1.064 | 1.377 | 0.004 |
| Urination problems | 1.240 | 1.082 | 1.420 | 0.002 |
| Hyperparathyrodism | 1.511 | .841 | 2.713 | 0.168 |
| Vitamin D deficiency | 1.436 | 1.023 | 2.016 | 0.036 |
| Fatigue | .854 | .717 | 1.018 | 0.078 |
| Constant | .358 | | | <0.001 |

### Table 5. Logistic Regression Results for Post-Index GI and Type of Treatment Initiated (N = 9,002)

| Among Patients Without Pre-index GI | | | | |
|---|---|---|---|---|
| | Odds Ratio | 95% CI | | P-value |
| Post-index GI | .798 | .552 | 1.153 | 0.229 |
| Age 55-64 | .000 | | | 0.219 |
| Age 65-74 | 1.154 | .995 | 1.338 | 0.058 |
| Age 75-84 | 1.172 | .935 | 1.470 | 0.169 |
| Age 85+ | .942 | .455 | 1.953 | 0.873 |
| GPA | .758 | .594 | .966 | 0.025 |
| NSAIDs | .846 | .503 | 1.423 | 0.529 |
| GC | 2.208 | .877 | 5.556 | 0.093 |
| IBD | 1.190 | .755 | 1.877 | 0.453 |
| Chronic inflammatory joint | .749 | .637 | .881 | <0.001 |
| Celiac | ---- | .000 | | 0.999 |
| Diabetes | 1.225 | .980 | 1.533 | 0.075 |
| Depression | .977 | .809 | 1.181 | 0.812 |
| Renal failure | 2.217 | 1.456 | 3.377 | <0.001 |
| Hypertension | 1.110 | .958 | 1.285 | 0.165 |
| Urination problems | 1.005 | .846 | 1.192 | 0.959 |
| Hyperparathyroidism | 1.356 | .676 | 2.723 | 0.391 |
| Vitamin D deficiency | 3.805 | 1.942 | 7.457 | <0.001 |
| Fatigue | .927 | .762 | 1.127 | 0.446 |
| Constant | 5.623 | | | <0.001 |

| Among Patients With Pre-index GI | | | | |
|---|---|---|---|---|
| | Odds Ratio | 95% CI | | P-value |
| Post-index GI | .808 | .448 | 1.459 | 0.48 |
| Age 55-64 | .000 | | | 0.515 |
| Age 65-74 | 1.017 | .765 | 1.352 | 0.909 |
| Age 75-84 | .834 | .543 | 1.281 | 0.408 |
| Age 85+ | 3.353 | .438 | 25.655 | 0.244 |
| GPA | .791 | .578 | 1.084 | 0.145 |
| NSAIDs | 1.179 | .397 | 3.501 | 0.767 |
| GC | 1.850 | .542 | 6.319 | 0.326 |
| IBD | .874 | .430 | 1.776 | 0.711 |
| Chronic inflammatory joint | .697 | .515 | .943 | 0.019 |
| Celiac | .599 | .060 | 5.995 | 0.663 |
| Diabetes | 1.231 | .800 | 1.894 | 0.344 |
| Depression | 1.039 | .746 | 1.449 | 0.82 |
| Renal failure | .791 | .465 | 1.348 | 0.389 |
| Hypertension | 1.409 | 1.062 | 1.870 | 0.017 |
| Urination problems | 1.021 | .761 | 1.371 | 0.889 |
| Hyperparathyroidism | ---- | .000 | | 0.998 |
| Vitamin D deficiency | 2.184 | .855 | 5.578 | 0.103 |
| Fatigue | .846 | .581 | 1.231 | 0.383 |
| Constant | 4.687 | | | <0.001 |

- Among patients who initiated treatment within 1 year, those with post-index GI were about 20% less likely to chose BIS vs. non-BIS

## Conclusions

- Among women enrolled in Maccabbi health plan who were newly diagnosed with OP and observed over a 1 year period:
  - Seven out of ten patients did not receive any pharmacological treatment for OP
  - 5.7% had GI events between OP diagnosis and treatment initiation
  - Occurrence of a GI event was associated with the likelihood of not being treated
    - Patients with a GI event were less likely to start osteoporosis treatment

**Conflict of Interest**

Jingbo Yu and Ankita Modi are employees of Merck & Co., Inc. and Ofer Sharon is an employee of MSD Israel. Inbal Goldshtein is an employee of Maccabbi Health Services, which received research fund from MSD Israel for conducting the analysis. Merck/MSD team provided scientific inputs into the data analysis and the poster preparation.