Association of gastrointestinal events with osteoporosis treatment initiation and treatment compliance in Germany: An observational study

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A B S T R A C T

Background: Gastrointestinal (GI) events are common in postmenopausal women treated for osteoporosis. The influence of GI events on treatment initiation and treatment compliance is the subject of ongoing research. 
Objective: The objectives of this study were (i) to determine the association of GI events with receipt of treatment in patients newly diagnosed with osteoporosis, and (ii) among treated patients, to determine the association of GI events with treatment compliance.

Methods: This was a retrospective analysis of claims data carried out in Germany using the Medipius database. Data were collected from January 1992 through December 2010. The dual-objective study design required two distinct cohorts. Cohort 1 comprised women aged ≥55 with a diagnosis of osteoporosis. GI events were recorded for the 12 month periods before and after the date of diagnosis. Time-varying Cox regression and discrete choice models were used, respectively, to assess the association of post-diagnosis GI events with the initiation of pharmacologic treatment (yes versus no) and the type of treatment initiated (bisphosphonates versus non-bisphosphonates). Cohort 2 comprised women aged ≥55 who initiated an oral bisphosphonate (alendronate, ibandronate, or risedronate). GI events were recorded for the 12 month periods before and after the date of bisphosphonate initiation, and a logistic regression model was employed to determine if pre-treatment or post-treatment GI events were associated with patient compliance, defined as a medication possession ratio (MPR) of ≥60%, with sensitivity analyses at MPR ≥60%.

Results: In cohort 1 (N = 18,813), 13.8% of patients had GI events in the pre-diagnosis period, and 14.8% had GI events in the post-diagnosis period. Among the patients with post-diagnosis GI events, 53.2% remained untreated during the post-index year, 6.2% were treated with bisphosphonates, and 0.6% received non-bisphosphonates. The respective percentages in patients without post-diagnosis GI events were 81.3%, 16.7%, and 1.9%. A post-diagnosis GI event decreased the likelihood of receiving any osteoporosis treatment (versus no treatment) by 83% (HR 0.17, 95% CI 0.14–0.20) and also decreased the likelihood of receiving a bisphosphonate (versus a non-bisphosphonate) by 39% (OR 0.61, 95% CI 0.54–0.68). In cohort 2 (N = 6040), 17.1% of patients had GI events in the year before treatment initiation, and 19.1% had GI events in the year after treatment initiation. At 12 months post-treatment initiation, GI events were more frequent in patients with pre-treatment GI events (53.2%) than in those without pre-treatment GI events (12.0%). Post-treatment GI events decreased the likelihood of attaining compliance defined as an MPR ≥60% (OR 0.84, 95% CI 0.73–0.97) but not an MPR ≥80% (OR 0.91, 95% CI 0.79–1.06).

Conclusions: In German women newly diagnosed with osteoporosis, GI events decreased the likelihood of receiving treatment and were associated with the choice of treatment. In women initiating oral bisphosphonates, post-treatment GI events were associated with reduced patient compliance.

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1. Introduction

Osteoporosis is present in an estimated 25% of women aged ≥50 in Germany (Gauthier et al., 2012). Findings from a national analysis of medical claims indicated that, among German patients being treated pharmacologically for osteoporosis, approximately half were prescribed oral bisphosphonates (Haussler et al., 2007).
Gastrointestinal (GI) symptoms (e.g., heartburn, reflux, nausea, vomiting) have been observed in up to 52% of German users of bisphosphonates (primarily women over age 45) (Ringe and Moller, 2009; Bauer et al., 2012), but GI symptoms are common among post-menopausal women (Freemante et al., 2010; Infantino, 2008), making it difficult to ascribe such symptoms to bisphosphonate use. Indeed, observational case-control studies have demonstrated that there is no significant relationship between bisphosphonate use and upper GI complications (Etminan et al., 2009; Vestergaard et al., 2010; Ghirardi et al., 2014). Nevertheless, GI adverse events (or the use of gastroprotective agents) have often been found to be associated with lower rates of compliance with osteoporosis therapy (Rossini et al., 2006; Penning-van Beest et al., 2008; Gallagher et al., 2008), and GI problems may affect the decision to treat osteoporosis (Colon-Emeric et al., 2007).

The impact of GI events on treatment decisions and patient compliance has not been studied in Germany. The objectives of this study were therefore (i) to determine whether GI events were associated with the decision to treat and the choice of treatment in female osteoporosis patients in Germany, and (ii) among treated patients, to estimate the association of GI events with compliance while on treatment.

2. Materials and methods

2.1. Data source and study design

Data for this analysis were abstracted from the Medipus database of Germany, a longitudinal physician-based database containing demographic, medical, pharmaceutical, and lab test results for patients. The database is representative of the German population with regard to the regional distribution of physicians, prescriptions, and diagnostic groups of patients.

Each objective required a distinct patient cohort and study design based on distinct index events. For objective 1, the index event was a diagnosis of osteoporosis, and subjects identified with this index event were defined as cohort 1. In this cohort, we observed GI events in the post-index period up until treatment initiation, for a maximum time of 12 months, and assessed the association of post-index GI events with the odds of treatment initiation and choice of treatment. For objective 2, the index event was the initiation of an oral bisphosphonate, and subjects identified with this event were defined as cohort 2. For this cohort, we estimated the proportion of patients with GI events at 3, 6, and 12 months following the index date and assessed the association of post-index GI events with patient compliance as of the 12-month time point.

2.2. Study samples and variables

All subjects in the analysis were women aged ≥55 years on the index date. Women who were diagnosed with a malignant neoplasm (International Classification of Diseases [ICD]-10 codes C00-C42, C44-C96, D00-D09, and D37-D49) or Paget’s disease (ICD-10 code M88) were excluded from this study.

In cohort 1, women were selected who: received a diagnosis of osteoporosis on an index date between January 1, 1993 and December 31, 2009; were naïve to osteoporosis medication any time prior to the index date and to estrogen for one year prior to the index date; and had ≥12 months of continuous eligibility before and after the index date. An osteoporosis diagnosis was defined by the presence of an ICD-10 code of M80 (osteoporosis with current pathological fracture) or M81 (osteoporosis without current pathological fracture). Osteoporosis medications were defined as either bisphosphonates or non-bisphosphonates and were identified in the data registry by their Anatomical Therapeutic Chemical codes. The bisphosphonates were alendronate, ibandronate, risedronate, and zoledronate, and the non-bisphosphonates were calcitonin, raloxifene, strontium ranelate, and teriparatide/parathyroid hormone. Both oral and injectable forms of all drugs were considered. GI events were identified by ICD-10 codes (see Supplementary Table S1) and included nausea/vomiting; dysphagia; esophagitis; gastroesophageal reflux disease; ulcer; stricture, perforation, or hemorrhage of the esophagus; gastric, duodenal, or peptic ulcers; acute gastritis; duodenitis; and GI hemorrhage. Pre-diagnosis GI events were assessed in the 1-year pre-index period. Post-diagnosis GI events were assessed from the index date until treatment initiation or the end of follow-up, whichever came first.

In cohort 2, women were selected who initiated a single oral bisphosphonate on an index date within the period 1996–2009, had ≥12 months of continuous eligibility before and after the index date, and were naïve to all osteoporosis medications in the year before the index prescription. Oral bisphosphonates of interest were alendronate, ibandronate, and risedronate, and GI events were the same as those listed for cohort 1. Compliance was defined as a medication possession ratio (MPR; the percentage of days in the post-index period on which patients were in possession of the prescribed medication) of ≥60%, with sensitivity analyses at MPR ≥80%.

2.3. Statistical analysis

Demographic and clinical characteristics (e.g., age; pre-index medication use (non-steroidal anti-inflammatory drugs [NSAIDs], gastroprotective agents, and glucocorticoids), fractures, and GI events; comorbidity profiles) were analyzed descriptively and are presented as numbers and percentages or means and standard deviations, as appropriate.

For cohort 1, the distribution of receipt of treatment and type of treatment was compared across the subgroups with and without GI events using a chi-square test. When quantifying the association of post-diagnosis GI events with treatment, a two-stage analysis accounted for the varying exposure time between the osteoporosis diagnosis and treatment initiation. In the first stage, a time-dependent Cox regression model was used to estimate the odds of receiving any treatment versus no treatment. In this model, patients were stratified according to the presence or absence of pre-diagnosis GI events. In the second stage, a discrete choice model with a conditional logit was used to estimate the odds of receiving bisphosphonates versus non-bisphosphonates. For both models, the independent variables included post-diagnosis GI events, age group, Deyo-Charlson comorbidity index (CCI) score, common comorbidities, and pre-diagnosis medication use. In the second model, pre-diagnosis GI events were added to the list of independent variables.

In cohort 2, the frequency of post-treatment GI events in patients with and without pre-treatment GI events was compared descriptively at 3, 6, and 12 months post-index. Logistic regression was used to estimate the odds of medication compliance. Independent variables included in this model were pre-treatment and post-treatment GI events, age group, pre-treatment medication use, pre-treatment osteoporosis-related fractures, and CCI score.

3. Results

3.1. Association of GI events with treatment for osteoporosis

A total of 18,813 women diagnosed with osteoporosis were included in cohort 1 (Table 1). The average age in this cohort was 71.4 years. During the pre-diagnosis period, 35.3% of the patients used NSAIDs and 16.9% used glucocorticoids, 18.1% used gastroprotective agents, and 13.8% experienced a GI event. The mean (SD) CCI score was 0.79 (1.11), and the most common comorbidity was hypertension (42.8%). Among patients diagnosed with osteoporosis, 3181 (16.9%) received pharmacotherapy in the year following the diagnosis (Table 2). Bisphosphonates were prescribed to 89.8% of treated patients and non-bisphosphonates to 10.2%. Alendronate was the most frequently prescribed treatment (Table 2). The bisphosphonates were prescribed to 89.8% of treated patients and non-bisphosphonates to 10.2%. Alendronate was the most frequently prescribed treatment (Table 2).
Table 1 Baseline characteristics of patients.

| Baseline characteristics | Cohort 1: Patients diagnosed with osteoporosisa (N = 18,813) | Cohort 2: Patients initiating bisphosphonatesa (N = 6040) |
|--------------------------|-----------------------------------------------------------|-------------------------------------------------------|
| Age at the index date, mean (SD)b 65–66 | 4751 (25.3) 1021 (16.9) | 733 (8.6) |
| Age at diagnosis            | 55–64 | 6902 (36.7) 2170 (35.9) |
|                          | 75–84 | 5578 (29.7) 2303 (38.1) |
|                          | 85+   | 1582 (8.4) 546 (9.0) |
| Pre-index medication useb  | Gastroprotective agents | 3408 (18.1) 1746 (28.9) |
|                          | Proton pump inhibitors | 2617 (13.9) 1500 (24.8) |
|                          | H2 receptor antagonists | 949 (5.0) 342 (5.7) |
|                          | Cytoprotectants | 54 (0.3) 18 (0.3) |
|                          | NSAIDs | 6644 (35.3) 2769 (45.8) |
|                          | Glucocorticoids | 3170 (16.9) 1399 (23.2) |
|                          | Estrogen | – 107 (1.8) |
|                          | Pre-index OP-related fracturesb | 2601 (13.8) 1033 (17.1) |
|                          | Pre-index OP-related fractures by site | 663 (3.5) 554 (9.2) |
|                          | Hip | 158 (0.8) 138 (2.3) |
|                          | Vertebral | 241 (1.3) 317 (5.3) |
|                          | Non-vertebral | 279 (1.5) 130 (2.2) |
|                          | Deyo-Charlson comorbidity index, mean (SD) | 0.79 (1.11) 0.87 (1.16) |
|                          | Common OP-related comorbiditiesc | Hypertension | 8053 (42.8) – |
|                          |                          | Depression | 2228 (11.8) – |
|                          |                          | Diabetes | 1335 (7.1) – |
|                          |                          | GI mucositis & urination problems | 687 (3.7) – |
|                          |                          | Chronic inflammatory joint disease | 546 (2.9) – |
|                          |                          | Fatigue | 328 (1.7) – |
|                          |                          | Chronic kidney disease | 119 (0.6) – |
|                          |                          | Chronic inflammatory bowel disease | 27 (0.1) – |
|                          |                          | Hyperparathyroidism | 6 (0.03) – |
|                          |                          | Vitamin D deficiency | 3 (0.02) – |
|                          |                          | Celiac disease | 3 (0.02) – |

Gl, gastrointestinal; NSAIDs, non-steroidal anti-inflammatory drugs; OP, osteoporosis; SD, standard deviation.

b Values are presented as N [%] unless indicated otherwise.

b The index date was the date of osteoporosis diagnosis for cohort 1 and the date of initiation of an oral bisphosphonate for cohort 2.

c Comorbidities were not collected for cohort 2.

prescribed bisphosphonate (63.4% of treated patients), followed by risedronate (22.9%), ibandronate (3.3%), and zoledronate (0.2%). Raloxifene was the most commonly prescribed non-bisphosphonate (5.7%). The average time from diagnosis to treatment was 47.1 days for bisphosphonates and 40.6 days for non-bisphosphonates.

The treatment distribution differed between patients with and without post-diagnosis GI events (P < 0.001; Fig. 1). Among the patients with post-diagnosis GI events (N = 2789, 14.8%), 93.2% remained untreated, 6.2% were treated with bisphosphonates, and 0.6% received non-bisphosphonates. The respective percentages in patients without post-diagnosis GI events (N = 16,024) were 81.3%, 16.7%, and 1.9%.

Post-diagnosis GI events were associated with an 83% lower likelihood of osteoporosis treatment (HR 0.17, 95% CI 0.14–0.20; Table 3). In contrast, use of gastroprotective agents in the pre-treatment period was predictive of treatment for osteoporosis (HR 1.62, 95% CI 1.48–1.77). Several individual comorbidities were associated with an increased likelihood of receiving treatment (HR 1.24 [95% CI 1.15–1.33] for hypertension, 1.18 [95% CI 1.02–1.35] for diabetes, and 1.27 [95% CI 1.06–1.53] for chronic inflammatory joint disease), but a higher CCI score was associated with lower likelihood of treatment (HR 0.94, 95% CI 0.91–0.98). Other factors significantly predictive of treatment for osteoporosis were older age (HR 1.27 [95% CI 1.16–1.40] for ages 65–74, 1.44 [95% CI 1.31–1.60] for ages 75–84, and 1.23 [95% CI 1.06–1.43] for ages ≥85, compared to the reference group aged 55–64), NSAID use (HR 1.29, 95% CI 1.20–1.38), and glucocorticoid use (HR 1.22, 95% CI 1.11–1.33).

Several factors were associated with a lower likelihood of receiving bisphosphonate versus non-bisphosphonate therapy (Table 3). These included pre- and post-diagnosis GI events (HR 0.85 [95% CI 0.78–0.94] and 0.61 [95% CI 0.54–0.68], respectively), ages 75–84 years (HR 0.79, 95% CI 0.71–0.87), and ≥85 years (HR 0.72, 95% CI 0.54–0.97; both versus age 55–64), and use of gastroprotective agents (HR 0.68, 95% CI 0.62–0.76).

3.2. Association of GI events with treatment compliance in patients initiating an oral bisphosphonate

A total of 6040 women who initiated an oral bisphosphonate were included in cohort 2 (Table 1). The mean age in this cohort was 73.3 years. During the pre-treatment period, 45.8% of women used NSAIDs, 23.2% used glucocorticoids, and 1.8% used estrogen. A total of 28.9% used gastroprotective agents, and 17.1% experienced a GI event. Post-treatment GI events occurred more frequently in patients with pre-treatment GI events (30.8%, 41.1%, and 53.2% at 3, 6, and 12 months, respectively) than in patients without pre-treatment GI events (4.4%, 5.0%, and 5.7% at 3, 6, and 12 months, respectively; Fig. 2). Overall, 19.1% of patients experienced GI events in the year after initiating an oral bisphosphonate.

Patients experiencing GI events post-treatment initiation were less likely than those not experiencing such events to exhibit compliance at MPR ≥ 60% (OR 0.84, 95% CI 0.73–0.97; Table 4). Use of NSAIDs and the occurrence of osteoporosis-related fractures in the pre-treatment period increased the odds of being compliant at MPR ≥ 60% (OR 1.15 [95% CI 1.04–1.27] for NSAIDs; OR 1.21 [95% CI 1.01–1.45] for fractures). In the sensitivity analyses, none of these variables were predictive of MPR ≥ 60% for the different treatment distributions of patients with and without post-diagnosis GI events.

![Fig. 1. Osteoporosis treatment in patients with and without post-diagnosis GI events.](https://example.com/fi.png)
postmenopausal German women hospitalized for a distal radius fracture in 2002–2003, 15.8% were receiving an anti-osteoporosis medication (Endres et al., 2007). Also like previous studies (Ziller et al., 2012; Duarte et al., 2007), we found that bisphosphonates were the most commonly prescribed pharmacotherapy in German osteoporosis patients.

The GI event rates in our cohort 1 (13.8% pre-diagnosis, 14.8% post-diagnosis) were on the low end of the range of GI events observed in previous studies of German osteoporosis patients (14.5%–51.6%) (Ringe and Moller, 2009; Bauer et al., 2012). Post-diagnosis GI events in cohort 1 were significantly predictive of non-treatment and of choosing non-bisphosphonates over bisphosphonates. The former result agrees with the findings of Colon-Emeric et al., who found that US nursing home residents with esophagitis, peptic ulcer disease, or dysphagia were less likely to receive treatment for osteoporosis (Colon-Emeric et al., 2007). The latter result differs from those of Foster et al., who found that diagnoses of peptic ulcer, dysphagia, reflux, or gastritis did not alter the odds of receiving raloxifene versus bisphosphonates in US women aged ≥45 insured commercially or via Medicare (Foster et al., 2008). Our findings that older age and glucocorticoid use were predictive of treatment in the year following an osteoporosis diagnosis were consistent with a previous study of postmenopausal women in the United States (Asche et al., 2010).

To our knowledge, no other studies have examined the association of use of GI agents with the choice of treatment for osteoporosis. In this regard, our study provides new insights into the role of gastroprotective agents in the treatment of osteoporosis in Germany. It is somewhat counterintuitive that use of these agents would increase the likelihood of osteoporosis treatment (Table 3), unless the explanation is that patients already taking prescription medications are comfortable with taking additional medications. However, the fact that gastroprotective agent use is predictive of choosing non-bisphosphonates (Table 3) suggests that German physicians anticipate GI problems with bisphosphonates and adjust their prescribing practices accordingly.

Regarding compliance, post-treatment GI events in cohort 2 decreased the odds of attaining ≥60% MPR, but not ≥80% MPR, with an oral bisphosphonate. Evidence on the predictors of compliance with oral bisphosphonates is mixed. In Dutch women taking alendronate or risedronate, initiation of intestinal agents, but not of gastroprotective agents, in the first year of bisphosphonate administration was associated with increased odds of non-compliance (defined as an MPR ≤50%) (Penning-van Beest et al., 2008). Other studies of the association of GI events with compliance have included men in the study population (Gallagher et al., 2008) or analyzed a combined set of treatments (e.g., oral and intramuscular bisphosphonates, calcium/vitamin D, and raloxifene) (Rossini et al., 2006), precluding a direct comparison.
with our results. Both studies, however, reported a statistically significant association of GI events or GI medication use with lower compliance.

The primary limitation of this study is the use of medical claims as the data source. Claims data are subject to errors of omission and commission, and the assumption is that patients filling a prescription are actually taking the medication. Coding omissions may explain why the prevalence of vitamin D deficiency (0.3%) in our study was low in comparison to other studies that report vitamin D deficiency in over 50% of the German population (Hintzpeter et al., 2008; Rabenberg et al., 2015; Ringe and Kjølbye, 2012). Another caveat is that our study included almost two decades of data from a period during which many new pharmacologic treatments for osteoporosis were approved for use in Europe. While etidronate, alendronate, and raloxifene were available during the 1990s, the rest of the therapies included in this study were only made available in or after the year 2000 (Hernlund et al., 2013). The availability of suitable treatments, as well as the lag in uptake of new treatments, reimbursement considerations, and evolving guidelines for treatment, are all factors that would have affected the use of pharmacotherapies for osteoporosis during this time period. The advent of injectable therapies in the latter half of the 2000s has almost certainly altered patterns of treatment initiation and types of treatment used. Our results should therefore be interpreted within the limitations of the time period and the data set from which they were derived. However, we note that the combination of data from all time periods provides insight into the overall effects of GI events on treatment with a wide array of therapies, which reflects the current situation in Europe. The implications of this for the current study are that the first few years of the cohort 1 analysis may be biased toward a larger percentage of untreated patients, because the first oral bisphosphonate did not appear in the Medipus database until 1996. Also, while cohort 1 included patients taking both injectable and oral forms of bisphosphonates, cohort 2 was restricted to oral bisphosphonate users, so the results of the latter analyses are not applicable to patients taking injectable forms of bisphosphonates; the results should be interpreted with this in mind. We also note that the covariates included in the logistic regression analyses of GI events do not comprise an exhaustive list of potential factors that physicians may consider when prescribing anti-osteoporosis medication. Finally, our analysis captured only GI events severe enough to warrant a physician visit, so minor symptoms treated with over-the-counter medications would not have been taken into account. This seems particularly appropriate for cohort 2 in that patients with minor symptoms would probably be less likely to discontinue medication because of them, compared to patients with more severe GI symptoms.

5. Conclusions

In conclusion, this study showed that GI events occurring in German women newly diagnosed with osteoporosis decreased the likelihood of treatment and altered the choice of treatment. Among the women initiating oral bisphosphonates, post-treatment GI events decreased the likelihood of patients attaining an MPR of ≥60%. Future studies could shed more light on these issues by adjusting for the type and severity of GI events in the regression analyses, by comparing the findings in oral therapies versus injectable therapies, and by combining medical claims data with patient self-reports to obtain a fuller picture of the experience of osteoporosis patients. Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.bonr.2016.06.001.

Disclosures

AM and JPW are employees of Merck & Co., Inc. AM owns stock in the company. SS was an employee of Merck & Co., Inc. and owned stock in the company at the time of the study. C-PSF and JT are employees of Asclepius Analytics LLC, which has received financial remuneration from Merck & Co., Inc. to participate in the study. The study was funded by Merck & Co., Inc. Other than through the employer relationship disclosed, Merck & Co., Inc. did not have a role in the study design, data collection, interpretation of the data, in writing of the manuscript, and in the decision to submit the manuscript for publication.

Author contributions

Conception and design of the study: AM, JPW, and SS. Analysis and/or interpretation of the data: C-PSF and JT. Drafting and revision of the manuscript: AM, C-PSF, JT, JPW, and SS. Approval of the final version of the manuscript: AM, C-PSF, JT, JPW, and SS.

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