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ORIGINAL ARTICLE

Fracture risk in women with osteoporosis initiated on gastro-resistant risedronate versus immediate release risedronate or alendronate: a claims data analysis in the USA

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Abstract

Summary The study results indicate that women with osteoporosis initiated on gastro-resistant risedronate have a lower risk of fracture than those initiated on immediate release risedronate or alendronate. A large proportion of women discontinued all oral bisphosphonate therapies within 1 year of treatment start.

Purpose Using a US claims database (2009–2019), we compared risk of fractures between women with osteoporosis initiated on gastro-resistant (GR) risedronate and those initiated on (a) immediate release (IR) risedronate or (b) immediate release alendronate.

Methods Women aged ≥ 60 years with osteoporosis who had ≥ 2 oral bisphosphonate prescription fills were followed for ≥ 1 year after the first observed bisphosphonates dispensing (index date). Fracture risk was compared between the GR risedronate and IR risedronate/alendronate cohorts using adjusted incidence rate ratios (aIRRs), both overall and in subgroups with high fracture risk due to older age or comorbidity/medications. Site-specific fractures were identified based on diagnosis codes recorded on medical claims using a claims-based algorithm. Persistence on bisphosphonate therapy was evaluated for all groups.

Results aIRRs generally indicated lower fracture risk for GR risedronate than IR risedronate and alendronate. When comparing GR risedronate to IR risedronate, statistically significant aIRRs ($p < 0.05$) were observed for pelvic fractures in the full cohorts (aIRRs = 0.37), for any fracture and pelvic fractures among women aged ≥ 65 years (aIRRs = 0.63 and 0.41), for any fracture and pelvic fractures among women aged ≥ 70 years (aIRRs = 0.69 and 0.24), and for pelvic fracture among high-risk women due to comorbidity/medications (aIRR = 0.34). When comparing GR risedronate to alendronate, statistically significant aIRRs were observed for pelvic fractures in the full cohorts (aIRR = 0.54), for any fracture and wrist/arm fractures among women aged ≥ 65 years (aIRRs = 0.73 and 0.63), and for any fracture, pelvic, and wrist/arm fractures among women aged ≥ 70 years (aIRRs = 0.72, 0.36, and 0.58). In all cohorts, ~ 40% completely discontinued oral bisphosphonates within 1 year.

Conclusions Discontinuation rates of oral bisphosphonate therapy were high. However, women initiated on GR risedronate had a significantly lower risk of fracture for several skeletal sites than women initiated on IR risedronate/alendronate, particularly those aged ≥ 70 years.

Keywords Osteoporosis · Gastric-resistant risedronate · Immediate release risedronate · Alendronate · Fracture rate · Persistence

Introduction

Osteoporosis, a widespread bone disease associated with high risk of fractures and impaired quality of life [1], affects approximately one in four women and one in ten men worldwide across all ages, with higher prevalence in older patients and variations across countries [1, 2]. Osteoporosis

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is a clinical condition that is asymptomatic until it is complicated by low-trauma fractures, commonly of the wrist/arm, spine, hip, and/or pelvis [3, 4]. Osteoporotic fractures often require inpatient care and are associated with financial burdens for patients and their families, function loss, chronic pain, disability, and mortality [5, 6]. Among women aged ≥ 50 years in the USA, the age-adjusted prevalence of osteoporosis defined by dual-energy X-ray absorptiometry at either the femoral neck and/or lumbar spine has increased over time, from 14.0% in 2007–2008 to 19.6% in 2017–2018; the prevalence was also higher in women aged ≥ 65 years than those aged 50 to 64 years (27.1% vs. 13.1%, respectively, in 2017–2018 [1]).

For patients with osteoporosis, pharmacological therapy aims to reduce the risk of fractures [3, 7]. Oral bisphosphonates, the mainstay therapy for the prevention of osteoporotic fracture in the majority of postmenopausal women and men reduce the risk of fractures through multiple mechanisms of action including bone loss slowing and bone density improvement [8–10]. However, oral bisphosphonates have low (< 1–2%) oral bioavailability due to their poor lipophilicity, which leads to poor absorption in the gastrointestinal tract; furthermore, bioavailability may be reduced if the treatment dosing/administration instructions are not strictly followed [8]. Given patients must take oral bisphosphonates on an empty stomach followed by fasting and maintaining an upright position for 30 to 60 min, the administration of treatment is often perceived as inconvenient, which may explain why many patients do not comply with the dosing instructions [11] and/or discontinue treatment early [6, 12–14]. Indeed, a 2019 systematic review showed that approximately one-third to one-half of the post-menopausal women with osteoporosis were non-adherent to bisphosphonate therapy, and between 28 and 74% discontinued treatment within 1 year of treatment start [12]. Low adherence, including low compliance and low persistence, has been a concern for treating physicians as the reduction of osteoporosis fracture risk and fracture-related hospitalization rates depends on it [4, 8, 15].

Gastric-resistant (GR) risedronate was developed with the goal of providing a more convenient administration without impacting the overall bioavailability and efficacy of the treatment [8, 9]. GR risedronate combines the convenient once weekly with a "no fasting" dosing regimen, an enteric-coating that allows it to bypass the stomach to be absorbed in the small intestine, and an ethylenediaminetetraacetic acid (EDTA)-rich formulation that supports absorption by reducing divalent cation chelation that may interfere with its absorption [8]. However, while GR risedronate has been in clinical use for > 10 years, there are very few head-to-head comparisons of GR risedronate versus other oral bisphosphonates. Notable studies include a 2012–2013 non-inferiority randomized trial that compared the GR and IR formulations of risedronate [9, 11] and a 2021 real-world study that compared fracture risk between women initiated on risedronate GR and women initiated on other oral bisphosphonates [6], but both studies had limitations. The former was only powered to examine non-inferiority for the bone mineral density primary end point and did not have sufficient power to detect differences in fracture rates [9, 11]. The latter found that women initiated on risedronate GR had a lower incidence of any osteoporotic fractures and spine fractures than those initiated on other oral bisphosphonates (incidence rate ratio [IRR], 95% confidence interval [CI]: 0.83, 0.70–0.97 and 0.71, 0.54–0.95, respectively) and those initiated on alendronate (0.81, 0.66–0.98 and 0.69, 0.49–0.97) [6], but it remained unclear whether the observed differences between risedronate GR and other oral bisphosphonates/alendronate were due to the use of a different agent, the use of GR formulation, or both.

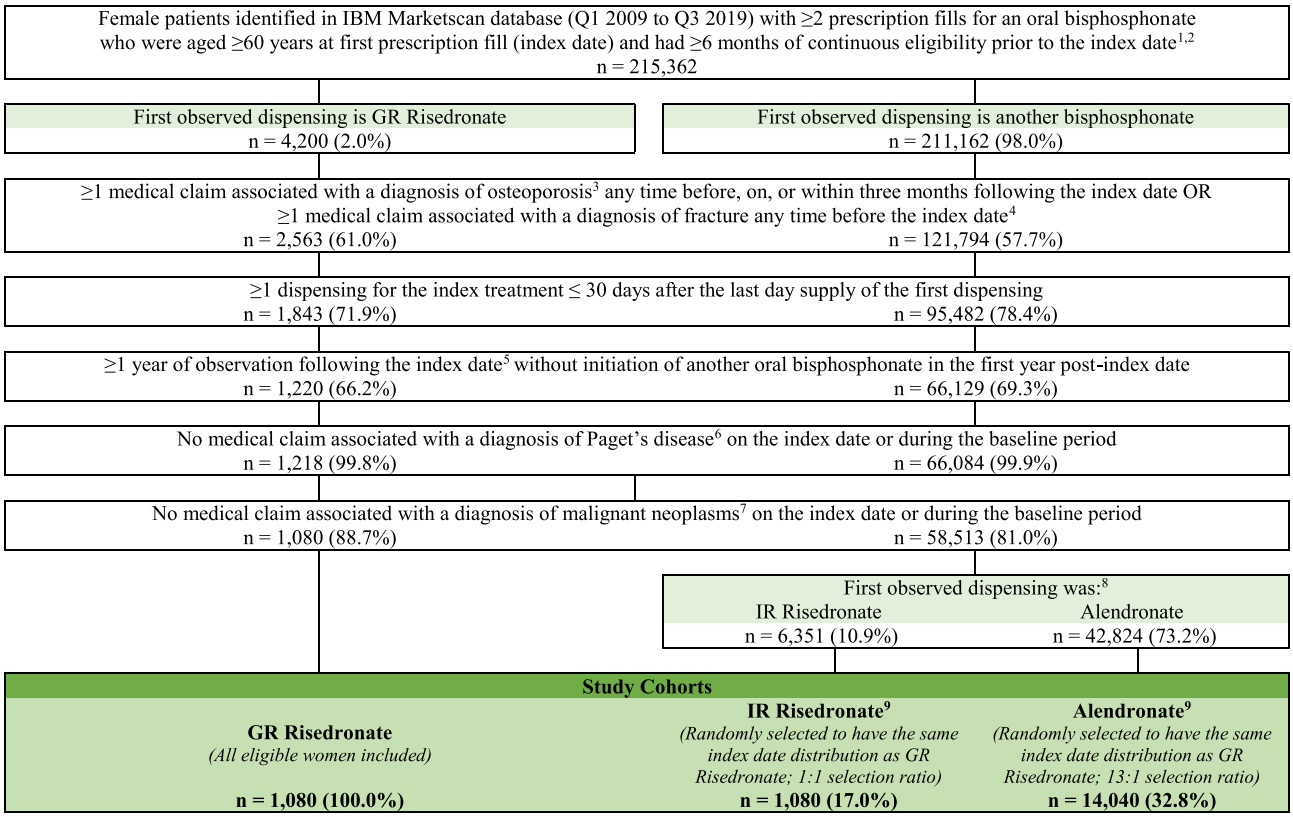
For the current study, we hypothesized that the increased bioavailability of GR risedronate would translate into lower risk of osteoporotic fracture (i.e., fracture of wrist/arm, spine, hip, and/or pelvis) for women initiated on this treatment compared to women initiated on oral bisphosphonates with IR formulations. Accordingly, our primary objective was to compare in a real-world setting the risk of fractures between women with osteoporosis initiated on GR risedronate and those initiated on (a) IR risedronate (a comparison in which the difference between cohorts is exclusively driven by the GR vs. IR formulation) and (b) alendronate (a comparison in which the difference between cohorts may be driven by either/both the GR vs IR formulation or/and the use of a different agent. Alendronate was selected as comparator because prior studies [6] suggested alendronate is the most commonly used oral bisphosphonate in the USA). In addition, we also hypothesized that the more convenient dosing schedule of GR risedronate, which does not require fasting, would translate into lower discontinuation rates. Accordingly, a secondary objective of the current study was to compare persistence on bisphosphonate therapy between GR risedronate and IR risedronate /alendronate.

Methods

Data source

This population-based retrospective study used claims data from the IBM® MarketScan® Commercial and Medicare Supplemental Databases[1] (Q1 2009 to Q3 2019). This large database includes de-identified patient-level claims from

[1] MarketScan is a registered trademark of IBM Corporation in the USA, other countries, or both.



GR, gastro-resistant; IR, immediate release.

[1] Oral bisphosphonates include alendronate (immediate release formulation), ibandronate (immediate release formulation), risedronate (both (immediate release and gastro-resistant formulations). The first dispensing for an oral bisphosphonate is defined as the index date, and the bisphosphonate initiated on the index date is defined as the index treatment. Only women initiated on alendronate or risedronate were included in the study cohorts and analyses.
[2] The 6-month period prior to the index date is defined as the baseline period.
[3] Osteoporosis was identified based on ICD-9 diagnosis code 733.0x and ICD-10 diagnosis codes: M80.xx, M81.xx, M82.xx.
[4] Less than 7% of women were included based on a diagnosis of fracture without a diagnosis of osteoporosis, and that fracture occurred within one year of the index date for 75% of these women.
[5] The observation period spans from the index date to the earliest of data cut-off date, end of insurance eligibility, or initiation of an oral bisphosphonate other than the index treatment (treatment switch)
[6] Paget's disease was identified based on ICD-9 diagnosis code 731.0x and ICD-10 diagnosis code M88.xx.
[7] Malignant neoplasms were identified based on ICD-9 diagnosis codes 140.xx to 209.xx and ICD-10 diagnosis codes C00 to C80, C7A, C7B, C81-C96.
[8] 9,338 (15.9%) women initiated on ibandronate on the index date were excluded in this step as analyses focused on the comparison between gastro-resistant risedronate and (a) immediate release risedronate (i.e. same agent with a different formulation, so differences in effect are due to the formulation) and (b) alendronate (another oral bisphosphonate with immediate release formulation, selected because it was the most commonly used oral bisphosphonate observed in the data).
[9] The IR risedronate and alendronate cohorts were selected such that the distribution of the index year of the women in these cohorts matched exactly that of the women in the GR risedronate cohort. In order to maximize the sample size, the selection ratio was 1:1 for GR risedronate: IR risedronate 1:13 for GR risedronate: alendronate (the selection ratio was driven by the year with the lowest overlap in year of index date between the cohorts).

Fig. 1 Sample selection flowchart

pharmacy and medical health services of approximately 130 million employees, dependents, and retirees in the USA who have healthcare coverage through employer-based commercial and Medicare supplemental health insurance plans. The data are compliant with the Health Insurance Portability and Accountability Act (HIPAA).

Study design

This is a retrospective cohort observational study. For each woman who satisfied the study inclusion criteria (see next paragraph; Fig. 1), the index date corresponded to the first dispensing for GR risedronate, IR risedronate, or alendronate (index treatment/study cohorts). By design, women who had a prescription fill for any other oral bisphosphonate before the index date were excluded from the sample. Unless otherwise specified, patient baseline characteristics were measured in the 6 months preceding the index date (baseline period, inclusive of index date), while fracture rate outcomes were assessed from the index date to the earliest of data cut-off date, end of insurance eligibility, or initiation of an oral bisphosphonate other than the index treatment (observation period). By design, the observation period was ≥ 1 year for all women. Persistence to therapy with any oral bisphosphonates was assessed from index date until the earliest of data cut-off date or end of insurance eligibility. A study design schematic is presented in Online Resource 1.

Selection of study sample and cohorts

Women eligible for inclusion in the study sample were aged ≥ 60 years at the index date, had ≥ 6 months of continuous healthcare plan enrollment prior to the index date, had ≥ 1 indicator of osteoporosis prior to or around the index date (i.e., ICD-9/10 diagnosis code for either osteoporosis or for osteoporotic fracture), had ≥ 1 year of continuous healthcare plan enrollment after the index date without initiation of a new oral bisphosphonate in the first year post-index, had no other bisphosphonate therapy indications (i.e., Paget's disease, malignant neoplasms) during the baseline period or on the index date, and were initiated on one of the index treatments on the index date.

In addition, a criterion of ≥ 2 prescription fills for the index treatment with a maximum of 30-day gap between the last day supply of the prescription fill on the index date and the date of the next prescription fill was used as a surrogate for adherence to therapy (the 30-day-gap duration corresponded to the most commonly observed value in the data for the days' supply associated with the treatments of interest). Figure 1 presents the study sample flowchart and additional details on the sample inclusion criteria. Online Resource 2 presents the diagnosis codes used in the sample selection.

All women initiated on GR risedronate on the index date were included in the GR risedronate cohort, while the IR risedronate and alendronate comparator cohorts were randomly selected from eligible women so that the index year distribution in these cohorts matched the index year distribution in the GR risedronate cohort. To maximize the number of women included in the comparator cohorts, a 1:1 selection ratio was used for IR risedronate, and a 1:13 selection ratio was used for alendronate (Fig. 1).

Definition of outcomes and statistical analyses

Osteoporotic fracture rates and bisphosphonate persistence outcomes were compared between the GR risedronate and the IR risedronate/alendronate cohorts both overall and in the following three subgroups of women considered to have high risk of fracture at the index date: (a) women aged ≥ 65 years [16], (b) women aged ≥ 70 years [16], and (c) women with other fracture risk factors (i.e., heart failure, chronic pulmonary disease, dementia, depression, diabetes, Parkinson's disease comorbidities; prior osteoporotic fracture; or treatment with proton-pump inhibitors, sedatives, systemic corticosteroids, or loop diuretics [3, 17, 18], identified based on ≥ 1 relevant diagnosis code or treatment dispensing in the baseline period).

Fracture rates

Fracture events were identified from medical claims with osteoporotic fracture diagnosis code in the observation period (listed in Online Resource 2). Fracture incidence rates were measured overall and at major skeletal sites (hip, pelvis, spine, wrist/arm). A sensitivity analysis that excluded diagnosis codes of cervical fractures from the spine fracture site was used to assess the possible misclassification of cervical fractures as osteoporosis-related.

A definitional algorithm was applied to distinguish in the claims data between new fracture events and follow-up care associated with a prior fracture [19]. Specifically, if a woman had multiple claims for fracture, all fracture claims occurring at the same skeletal site (hip, pelvis, spine, or wrist/arm) within 90 days of the first claim and those occurring at a distinct skeletal site within 30 days of the first claim were considered follow-up care/fracture aftercare. The first claim at the same skeletal site ≥ 90 days after the first claim or at a distinct skeletal site ≥ 30 days after the first claim indicated a new fracture event. Thus, when calculating incidence rates for any fractures, it is possible that two consecutive fractures at the same major skeletal site were counted as one fracture event if they occurred within 90 days of each other, while two consecutive fractures at different skeletal site were counted as one fracture event if they occurred within 30 days of each other. Of note, because the latter scenario is considered as one fracture involving multiple major skeletal sites, in analyses reporting incidence rates by skeletal site, one fracture involving multiple skeletal sites will be counted as a fracture event for each of the skeletal sites involved.

For each cohort, the incidence rate of fractures was calculated as the number of fracture events divided by the total women-years of observation to account for different lengths of observation across women. The fracture incidence rates were compared between women initiated on GR risedronate and the comparator cohorts using generalized linear models with log link and Poisson/negative binomial distribution, which yielded unadjusted IRRs (models without covariates) and aIRRs (models adjusted for potential confounders) and 95% CIs. The potential confounders available in the data and adjusted for in the regression models included age category, census region, insurance plan type, Medicare coverage, year of the index date, comorbidities during the baseline period, Charlson comorbidity index, the presence of ≥ 1 fracture at any site prior to the index date (anytime), the presence of ≥ 1 dispensing for a drug decreasing the risk of fracture during the baseline period (listed in Table 1), the presence of ≥ 1 dispensing for a drug increasing the risk of fracture during the baseline period (listed in Table 1), and the number of days of supply of the first index prescription (≤ 30 days, > 30 days).

Persistence on the bisphosphonate treatment

Treatment persistence was defined as the time from index date to the discontinuation of all oral bisphosphonate

Table 1 Demographic and clinical characteristics

	GR risedronate cohort $n=1080$	IR risedronate cohort $n=1080$ *(*Statistically significant vs. GR risedronate[a])*	Alendronate (IR) cohort $n=14,040$ *(*Statistically significant vs. GR risedronate[a])*
Demographics			
Age at index date, mean ± SD [median]	69.1 ± 8.9 [66.0]	68.8 ± 8.5 [66.0]	70.2 ± 9.2 [67.0]*
Age category, *n* (%)			
60–64 years	505 (46.8%)	494 (45.7%)	5,603 (39.9%)*
65–69 years	155 (14.4%)	186 (17.2%)	2,243 (16.0%)
70–74 years	130 (12.0%)	124 (11.5%)	1,752 (12.5%)
75–79 years	116 (10.7%)	113 (10.5%)	1,636 (11.7%)
80 + years	174 (16.1%)	163 (15.1%)	2,806 (20.0%)*
Census region, *n* (%)			
Northeast	348 (32.2%)	392 (36.3%)*	2,669 (19.0%)*
North Central	114 (10.6%)	161 (14.9%)*	3,675 (26.2%)*
South	463 (42.9%)	349 (32.3%)*	4,367 (31.1%)*
West	142 (13.1%)	165 (15.3%)	3,228 (23.0%)*
Unknown	13 (1.2%)	13 (1.2%)	101 (0.7%)
Commercial insurance plan type, *n* (%)			
Basic	0 (0.0%)	0 (0.0%)	0 (0.0%)
Comprehensive	183 (16.9%)	156 (14.4%)	3,132 (22.3%)*
EPO/POS	89 (8.2%)	80 (7.4%)	765 (5.4%)*
HMO/POS with capitation	112 (10.4%)	144 (13.3%)*	2,793 (19.9%)*
PPO	622 (57.6%)	624 (57.8%)	6,459 (46.0%)*
CDHP/HDHP	33 (3.1%)	45 (4.2%)	572 (4.1%)
Unknown	41 (3.8%)	31 (2.9%)	319 (2.3%)*
Medicare coverage, *n* (%)	742 (68.7%)	751 (69.5%)	10,208 (72.7%)*
Baseline[b] comorbidities, *n* (%)			
Cardiovascular disease	266 (24.6%)	240 (22.2%)	3,425 (24.4%)
Celiac disease	3 (0.3%)	10 (0.9%)	49 (0.3%)
Chronic pulmonary disease	131 (12.1%)	146 (13.5%)	1,797 (12.8%)
Dementia	24 (2.2%)	20 (1.9%)	396 (2.8%)
Depression	145 (13.4%)	176 (16.3%)	2,181 (15.5%)
Diabetes	158 (14.6%)	126 (11.7%)*	1,987 (14.2%)
Fatigue	112 (10.4%)	125 (11.6%)	1,360 (9.7%)
Gastrointestinal mucositis	0 (0.0%)	0 (0.0%)	0 (0.0%)
Primary or secondary hyperparathyroidism	14 (1.3%)	31 (2.9%)*	196 (1.4%)
Hyperthyroidism	13 (1.2%)	15 (1.4%)	163 (1.2%)
Hypertension	432 (40.0%)	430 (39.8%)	6,147 (43.8%)*
Hypertensive chronic kidney disease	28 (2.6%)	24 (2.2%)	481 (3.4%)
Inflammatory bowel disease	12 (1.1%)	4 (0.4%)*	102 (0.7%)
Joint inflammatory disease	20 (1.9%)	19 (1.8%)	277 (2.0%)
Liver disease	19 (1.8%)	20 (1.9%)	229 (1.6%)
Oseogenesis imperfecta	0 (0.0%)	0 (0.0%)	3 (0.0%)
Parkinson's disease	10 (0.9%)	4 (0.4%)	107 (0.8%)
Peripheral neuropathy	53 (4.9%)	42 (3.9%)	599 (4.3%)
Rheumatoid arthritis	58 (5.4%)	69 (6.4%)	562 (4.0%)*
Underweight	11 (1.0%)	14 (1.3%)	209 (1.5%)
Urination problem	150 (13.9%)	162 (15.0%)	1,896 (13.5%)
Vitamin D deficiency	137 (12.7%)	122 (11.3%)	1,270 (9.0%)*
Baseline[b] CCI			
CCI, mean ± SD [median]	0.2 ± 1.1 [0.0]	0.3 ± 1.2 [0.0]	0.3 ± 1.3 [0.0]*
CCI ≤ 2, *n* (%)	1031 (95.5%)	1027 (95.1%)	13,119 (93.4%)*
Pre-index[c] fractures, *n* (%)			
Fractures during baseline period[b]			
Any site	100 (9.3%)	99 (9.2%)	1,765 (12.6%)*

Table 1 (continued)

	GR risedronate cohort $n = 1080$	IR risedronate cohort $n = 1080$ *(*Statistically significant vs. GR risedronate[a])*	Alendronate (IR) cohort $n = 14{,}040$ *(*Statistically significant vs. GR risedronate[a])*
Hip	25 (2.3%)	29 (2.7%)	518 (3.7%)*
Pelvis	12 (1.1%)	15 (1.4%)	197 (1.4%)
Spine	36 (3.3%)	37 (3.4%)	649 (4.6%)*
Wrist/arm	34 (3.1%)	34 (3.1%)	580 (4.1%)
Fractures anytime before index date			
Any site	159 (14.7%)	154 (14.3%)	2,914 (20.8%)*
Baseline[b] dispensing of drugs affecting the risk of fracture, *n* (%)			
≥ 1 drug *decreasing* the risk of fracture	368 (34.1%)	319 (29.5%)*	4,279 (30.5%)*
Beta blockers	246 (22.8%)	204 (18.9%)*	3,199 (22.8%)
Denosumab	4 (0.4%)	5 (0.5%)	8 (0.1%)*
Estrogens	160 (14.8%)	133 (12.3%)	1,336 (9.5%)*
≥ 1 drug *increasing* the risk of fracture	691 (64.0%)	660 (61.1%)	8,697 (61.9%)
Antidepressants	248 (23.0%)	248 (23.0%)	3,427 (24.4%)
Antiepileptics	123 (11.4%)	138 (12.8%)	1,610 (11.5%)
Antipsychotics	16 (1.5%)	14 (1.3%)	322 (2.3%)
Loop diuretics	67 (6.2%)	47 (4.4%)	1,130 (8.0%)*
Opioids	273 (25.3%)	275 (25.5%)	4,283 (30.5%)*
Proton-pump inhibitors	274 (25.4%)	230 (21.3%)*	2,492 (17.7%)*
Sedatives	210 (19.4%)	183 (16.9%)	2,517 (17.9%)
Systemic corticosteroids	294 (27.2%)	267 (24.7%)	3,194 (22.7%)*
High risk of fracture based on baseline comorbidity and/or medication[d], *n* (%)	799 (74.0%)	758 (70.2%)*	10,057 (71.6%)
Days supply of the first prescription of the index treatment, *n* (%)			
≤ 30 days	727 (67.3%)	605 (56.0%)*	8,699 (62.0%)*
> 30 days	353 (32.7%)	475 (44.0%)*	5,341 (38.0%)*
Year of the index date, *n* (%) *(by design same distribution)*			
2009	0 (0.0%)	0 (0.0%)	0 (0.0%)
2010	1 (0.1%)	1 (0.1%)	13 (0.1%)
2011	434 (40.2%)	434 (40.2%)	5,642 (40.2%)
2012	254 (23.5%)	254 (23.5%)	3,302 (23.5%)
2013	175 (16.2%)	175 (16.2%)	2,275 (16.2%)
2014	70 (6.5%)	70 (6.5%)	910 (6.5%)
2015	65 (6.0%)	65 (6.0%)	845 (6.0%)
2016	40 (3.7%)	40 (3.7%)	520 (3.7%)
2017	27 (2.5%)	27 (2.5%)	351 (2.5%)
2018	14 (1.3%)	14 (1.3%)	182 (1.3%)
2019	0 (0.0%)	0 (0.0%)	0 (0.0%)

CCI Charlson comorbidity index, *CDHP* consumer directed health plan, *EPO* exclusive provider organization, *GR* gastro-resistant, *HDHP* high-deductible health plan, *HMO* health maintenance organization, *IR* immediate release, *POS* point of service, *SD* standard deviation.

[a]*P*-value < 0.05; *p*-values were based on *t*-tests for continuous variables, and chi-square tests for categorical variables.

[b]The 6-month period prior to the index date is defined as the baseline period. All women had health insurance coverage and were observed for at least 6 months before the index date.

[c]Entire time period for a given woman in the data before the index date during the 2009–2019 study period.

[d]Women with a high baseline risk of fracture due to comorbidities and/or medications were identified based on the presence of ≥ 1 baseline diagnosis for heart failure, chronic pulmonary disease, dementia, depression, diabetes, Parkinson's disease, or osteoporotic fracture; and/or ≥ 1 baseline dispensing of a treatment increasing the risk of fracture (e.g., systemic corticosteroids, sedatives, proton pump inhibitors), or loop diuretics.

therapies, where bisphosphonate treatment discontinuation was considered to occur at the last day supply of an oral bisphosphonate before a gap of > 90 days without any oral bisphosphonate treatment. Women who did not discontinue oral bisphosphonates were censored on the data cut-off date, or the end of insurance eligibility, whichever occurred first. Treatment persistence was compared between the GR risedronate versus IR risedronate/alendronate cohorts using time-to-event analyses, which included Kaplan–Meier plots (for discontinuation rates at one and two years post-index date) and Cox proportional hazards regression models (for unadjusted and adjusted hazard ratios (HR). The adjusted models controlled for the same potential confounders as the Poisson/negative binomial regression models for the risk of fracture outcomes, as listed above, and account for censoring.

Results

Patient characteristics

Among the 59,593 women with osteoporosis initiated on oral bisphosphonates who satisfied the study inclusion criteria, the first oral bisphosphonate fill was GR risedronate in 1.8% ($n = 1{,}080$), IR risedronate in 10.7% ($n = 6351$), and alendronate in 71.9% ($n = 42{,}824$). All 1080 women with the prescription fill for GR risedronate on index date were included in the GR risedronate cohort. The 1:1 selection ratio for GR risedronate and IR risedronate resulted in 1080 women included in the IR risedronate cohort (17.0% of all selected women eligible women initiated on IR risedronate), while the 1:13 selection ratio for GR risedronate and alendronate resulted in 14,040 women in the alendronate cohort (32.8% of all selected women initiated on alendronate).

Patient characteristics are described in Table 1. The median ages were 66, 66, and 67 years for women in the GR risedronate, IR risedronate, and alendronate cohorts, respectively ($p < 0.05$ for GR risedronate vs. alendronate). Clinical characteristics that were statistically different between the GR risedronate cohort and IR risedronate and/or alendronate cohorts included history of fracture at any skeletal site any time before the index date (14.7% vs. 14.3% and 20.8%*) as well as hypertension (40.0% vs 39.8% and 43.8%*), diabetes (14.6% vs. 11.7%* and 14.2%), vitamin D deficiency (12.7% vs 11.3% and 9.0%*), rheumatoid arthritis (5.4% vs 6.4% and 4.0%*), primary or secondary hyperparathyroidism (1.3% vs 2.9%* and 1.4%), baseline use of drugs that decrease the risk of fracture (beta blockers, denosumab, and estrogens; pooled: 34.1% vs 29.5%* and 30.5%*), baseline use of drugs that increase the risk of fracture (proton pump inhibitors: 25.4% vs 21.3%* and 17.7%*; opioids: 25.3% vs 25.5% and 30.5%*; systemic corticosteroids: 27.2% vs 24.7% and 22.7%*; loop diuretics: 6.2% vs 4.4% and 8.0%*), and overall burden of disease (Charlson Comorbidity Index ≤ 2: 95.5% vs 95.1% and 93.4%*; *indicates $p < 0.05$ vs GR risedronate).

Fracture rates

Fracture rates were measured over a median observation time of 29, 32, and 32 months for the GR risedronate, IR risedronate, and alendronate cohorts, respectively. In all three cohorts, the unadjusted fracture rates per 1000 women-years were numerically higher for the subgroups aged ≥ 70 years than the subgroups aged ≥ 65 years, the subgroups with high fracture risk due to comorbidity/medications, and the full study cohorts (Table 2). For example, the unadjusted rates of any fracture were 67.4 per 1000 women-years for those aged ≥ 70 years treated with GR risedronate versus 58.3, 59.8, and 50.6 for those aged ≥ 65 years, those at high fracture risk due to comorbidity/medications, and the full cohort treated with GR risedronate, respectively (IR risedronate: 97.3 vs. 88.2, 79.6, 64.8, respectively; alendronate: 101.5 vs. 87.2, 80.3, 66.8, respectively; Table 2). Across the three cohorts, the unadjusted rates of fracture were numerically lowest for GR risedronate cohort, regardless of the skeletal site or subgroup (Table 2).

In analyses adjusted for potential confounders (Fig. 2; Online Resource 3), there was a numerically lower risk of fracture among women initiated on GR risedronate compared to IR risedronate/alendronate, and statistical significance ($p < 0.05$) was reached for several comparisons overall, by skeletal site and/or within high-risk subgroups. Compared with IR risedronate, GR risedronate was associated with significantly lower risk of any fracture among women aged ≥ 65 years (aIRR = 0.63, 95% CI 0.46–0.86) and ≥ 70 years (0.69, 0.50–0.96) and with significantly lower risk of pelvic fracture both overall (0.37, 0.17–0.81) and in all high-risk subgroups (age ≥ 65 years: 0.41, 0.18–0.93; age ≥ 70 years: 0.24, 0.08–0.68; high risk based on comorbidity/medication: 0.34, 0.15–0.78). Compared with alendronate, GR risedronate was associated with significantly lower risk of any fracture among women aged ≥ 65 years (0.73, 0.58–0.91) and ≥ 70 years (0.72, 0.56–0.92), with significantly lower risk of pelvic fracture both overall (0.54, 0.29–0.99) and in women aged ≥ 70 years (0.36, 0.15–0.84), and with significantly lower risk of wrist/arm fractures among women aged ≥ 65 years (0.63, 0.41–0.95) and ≥ 70 years (0.58, 0.36–0.94) (Fig. 2; Online Resource 3).

Most aIRR estimates remained significant after applying a Bonferroni adjustment. Specifically, for the GR risedronate versus IR risedronate comparison, the aIRR

Table 2 Unadjusted fracture rates overall and in high-risk women due to older age or comorbidity/medication

	Full study cohorts	Subgroups with high-risk of fracture at baseline		
		Aged ≥ 65 years	Aged ≥ 70 years	High-risk due to comorbidity/medication[a]
Women, *N* (women-years of observation[b])				
GR risedronate	1080 (3204)	575 (1871)	420 (1394)	799 (2392)
IR risedronate	1080 (3506)	586 (2086)	400 (1428)	758 (2437)
Alendronate	14,040 (44,566)	8437 (28,635)	6194 (21,097)	10,057 (31,988)
Fractures, *N* (unadjusted rate per 1000 women-years)				
Any fracture				
GR risedronate	162 (50.6)	109 (58.3)	94 (67.4)	143 (59.8)
IR risedronate	227 (64.8)	184 (88.2)	139 (97.3)	194 (79.6)
Alendronate	2977 (66.8)	2498 (87.2)	2142 (101.5	2568 (80.3)
Hip				
GR risedronate	45 (14.0)	35 (18.7)	31 (22.2)	40 (16.7)
IR risedronate	53 (15.1)	43 (20.6)	42 (29.4)	50 (20.5)
Alendronate	835 (18.7)	746 (26.1)	658 (31.2)	744 (23.3)
Pelvis				
GR risedronate	11 (3.4)	11 (5.9)	6 (4.3)	10 (4.2)
IR risedronate	24 (6.9)	21 (10.1)	18 (12.6)	23 (9.4)
Alendronate	309 (6.9)	281 (9.8)	248 (11.8)	274 (8.6)
Spine				
GR risedronate	60 (18.7)	46 (24.6)	43 (30.9)	55 (23.0)
IR risedronate	96 (27.4)	80 (38.4)	59 (41.3)	81 (33.2)
Alendronate	1,087 (24.4)	949 (33.1)	840 (39.8)	968 (30.3)
Wrist/arm				
GR risedronate	58 (18.1)	27 (14.4)	20 (14.4)	49 (20.5)
IR risedronate	66 (18.8)	51 (24.5)	31 (21.7)	52 (21.3)
Alendronate	924 (20.7)	684 (23.9)	527 (25.9)	740 (23.1)

GR gastro-resistant, *IR* immediate release.

[a]Women with a high baseline risk of fracture due to comorbidities and/or medications were identified based on the presence of ≥ 1 baseline diagnosis for heart failure, chronic pulmonary disease, dementia, depression, diabetes, Parkinson's disease, or osteoporotic fracture, and/or ≥ 1 baseline dispensing of a treatment increasing the risk of fracture (e.g., systemic corticosteroids, sedatives, proton pump inhibitors), or loop diuretics.

[b]Fractures were measured over an observation period measured from the index date to the earliest of data cut-off date, end of insurance eligibility, or initiation of an oral bisphosphonate other than the index treatment

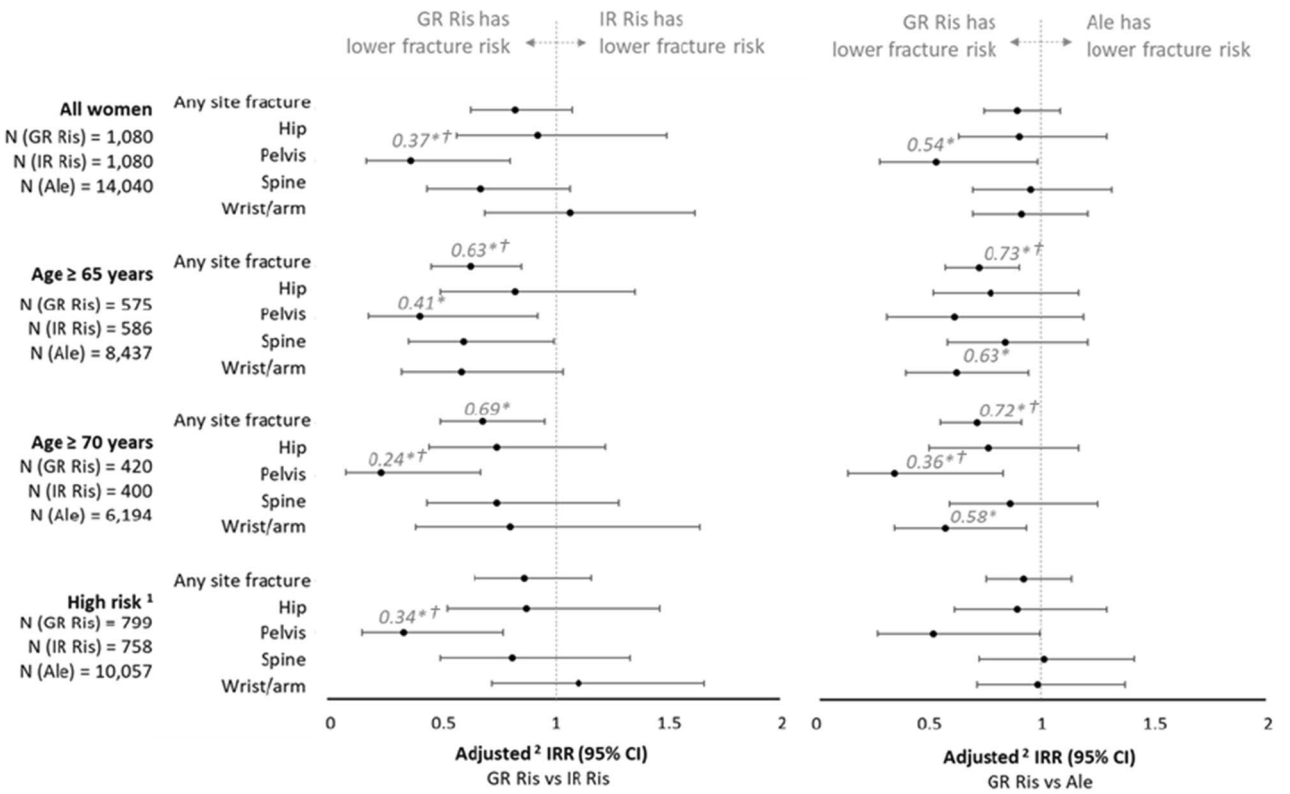
estimates that remained significant included any fracture for the subgroup aged ≥ 65 years and pelvic fracture for all women, the subgroups aged ≥ 70 years and at high risk based on comorbidity/medication; for the GR risedronate versus alendronate comparisons, the aIRR estimates that remained significant included any fracture for subgroups aged ≥ 65 and ≥ 70 years, and pelvic fracture for women aged ≥ 70 years (Fig. 2).

Fracture rates and aIRRs did not change in a sensitivity analysis excluding diagnosis codes for cervical fractures (< 2% of all fracture events), which may not have been osteoporotic.

Persistence on bisphosphonate therapy after the index treatment initiation

Prescriptions with dosages per label accounted for 86% of all prescription fills for alendronate (per label daily dosages: 10 mg/day [81%] and 5 mg/day [5%]), 95% prescription fills for IR risedronate (5 mg/day), and 94% of all prescription fills for GR risedronate (5 mg/day).

Across all cohorts within 1 and 2 years of treatment initiation, ~ 40% and ~ 60% completely discontinued oral bisphosphonate therapy, respectively (Fig. 3). Given women who failed to receive a second prescription fill



Ale, alendronate; CI, confidence interval; GR, gastro-resistant; IR, immediate release; IRR, incidence rate ratio (estimated from negative binomial or Poisson regression models); Ris, risedronate.

** IRRs with p <0.05.*

† IRRs with p <0.0025, i.e., statistically significant if Bonferroni adjustment is applied to account for 20 models for each comparison.

[1] High risk of fracture due to comorbidities/medications were identified based on the presence of ≥1 baseline diagnosis for heart failure, chronic pulmonary disease, dementia, depression, diabetes, or Parkinson's disease, or osteoporotic fracture; and/or ≥1 baseline dispensing of a treatment increasing the risk of fracture (e.g., systemic corticosteroids, sedatives, proton pump inhibitors), or loop diuretics.

[2] Regression models were adjusted for age, census region, healthcare insurance type, baseline comorbidities, pre-index fractures, baseline dispensing of drugs decreasing / increasing the risk of fracture, duration days supply for first index therapy prescription fill, and year of index date.

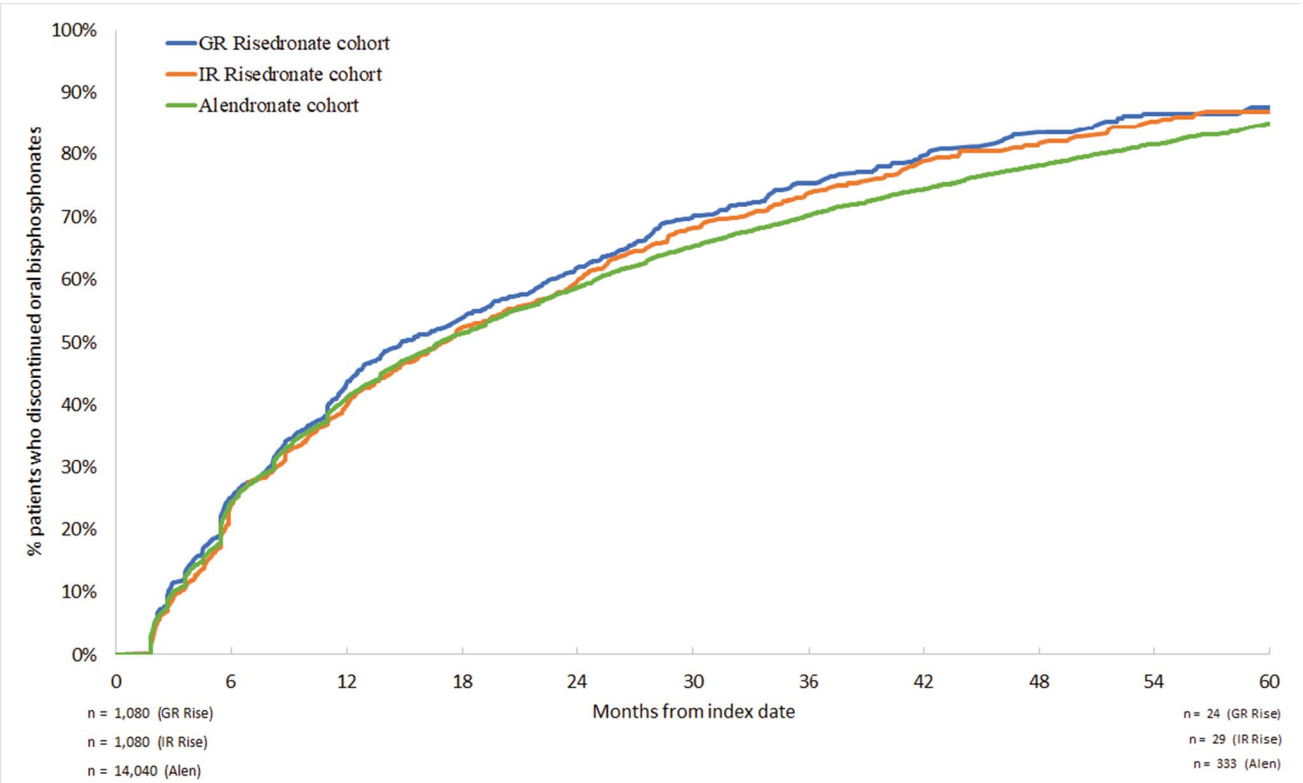
Fig. 2 Adjusted incidence rate ratios for fracture rates overall and in high-risk women due to older age or comorbidity/medication

of the index treatment within 30 days of the first prescription's last day supply were excluded from the current study, these are underestimates of the oral bisphosphonate true discontinuation rates (38.7%, 33.3%, and 29.0% of eligible women initiated on GR risedronate, IR risedronate, and alendronate, respectively, failed to receive a second prescription fill for the index treatment and were thus excluded; Fig. 1).

Persistence was not significantly different between the GR risedronate and the IR risedronate and alendronate cohorts in either unadjusted analyses (discontinuation rates at 1 year: 44% vs. 40% and 41%; discontinuation rates at 2 years 62% vs. 60% and 59%, respectively; log-rank $p \geq 0.05$ for all comparisons; Fig. 3) or adjusted analyses (aHR, 95% CI: 1.03, 0.93–1.14 for GR risedronate vs IR risedronate; and 1.06, 0.99–1.15 for GR risedronate vs alendronate).

Discussion

Results from this real-world study are supportive of the hypothesis that the increased bioavailability expected from the GR formulation of risedronate translates into lower risk of fracture for women initiated on this treatment compared to women initiated on oral bisphosphonates with IR formulations, including both IR risedronate and alendronate. The protective effect of GR risedronate appeared to be most manifest for the women with osteoporosis aged ≥ 70 years where significant effects ($p < 0.05$) were observed for both any fracture (aIRRs = 0.69 and 0.72 vs. IR risedronate and alendronate, respectively), pelvic fractures (aIRRs = 0.24 and 0.36), and wrist/arm fractures (aIRR = 0.58 vs. alendronate). Statistically significant protective effects of GR risedronate ($p < 0.05$) were also observed for women aged ≥ 65 years for any fracture (aIRRs = 0.63 and 0.73 vs. IR risedronate



Time from Index date	Rates of Complete Discontinuation of Oral Bisphosphonates[1] (CI)		
	GR Risedronate cohort	IR Risedronate cohort	Alendronate cohort
6 months	25% (23-28)	23% (21-26)	24% (23-25)
1 year	44% (41-47)	40% (37-43)	41% (40-42)
2 years	62% (59-65)	60% (56-63)	59% (58-60)
3 years	75% (72-78)	74% (70-77)	70% (69-71)
4 years	83% (80-87)	82% (78-85)	78% (77-79)
5 years	88% (84-91)	87% (83-90)	85% (84-86)

	Hazard Ratios[2] (95% CI)	P-value
GR Risedronate vs. IR Risedronate		
Unadjusted	1.07 (0.96 - 1.18)	0.206
Adjusted[3]	1.03 (0.93 - 1.14)	0.601
GR Risedronate vs. Alendronate		
Unadjusted	1.09 (1.02 - 1.18)	0.016*
Adjusted[3]	1.06 (0.99 - 1.15)	0.107

GR, gastro-resistant; IR, immediate release.

[1] Treatment discontinuation is defined as a treatment gap for any oral bisphosphonate of ≥90 consecutive days. Women who did not discontinue the treatment were censored on the data cut-off date, the end of insurance eligibility or lost to follow-up, whichever occurs first.
[2] Hazard ratios were estimated using Cox proportional hazard regression models.
[3] The Cox proportional hazards regression models were adjusted for age category, census region, insurance plan type, Medicare coverage, year of the index date, comorbidities during the baseline period, Charlson comorbidity index, the presence of ≥ 1 fracture (any site) anytime before the index date, the presence of ≥ 1 dispensing for a drug decreasing the risk of fracture during the baseline period (beta blockers, denosumab, or estrogens), the presence of ≥ 1 dispensing for a drug increasing the risk of fracture during the baseline period (antidepressants, antiepileptics, antipsychotics, systemic corticosteroids, opioids, proton-pump inhibitors, or sedatives), and the category of days supply of the first index prescription.

Fig. 3 Persistence on bisphosphonate therapy after the index treatment initiation

and alendronate), pelvic fractures (aIRR = 0.41 vs. IR risedronate), and wrist/arm factures (aIRR = 0.63 vs. alendronate). A protective effect of GR risedronate for pelvic fractures was also observed in the overall cohorts (aIRRs = 0.37 and 0.54 vs. IR risedronate and alendronate, respectively) and among women at high-osteoporotic risk due to comorbidities and/or medications (aIRR = 0.34 vs. IR risedronate). The study results are relevant to clinicians because the incidence and prevalence of osteoporotic fractures increases with age [16], and osteoporotic fractures, including pelvic fractures, are associated with significant morbidity and mortality [20].

A secondary hypothesis of the current study was that the more convenient dosing schedule of GR risedronate, which did not require fasting, would translate into higher persistence (i.e., lower discontinuation rates) for patients initiated on this treatment. However, this hypothesis was not supported by the current study. In fact, in all three cohorts, large proportions completely discontinued oral bisphosphonates within 1 and 2 years of treatment initiation (approximately 40% within 1 year and approximately 60% within 2 years). Importantly, this discontinuation pattern was observed among women who had at least one refill after the initial prescription fill, which presumably included women who

had a stronger intent to receive osteoporosis preventive therapy. While compliance with the dosing and administration instructions could not be assessed using claims data, it is possible the more convenient dosing schedule of GR risedronate impacts treatment adherence through improved compliance without any persistence benefit. Given GR risedronate is absorbed whether taken before or after the morning meal, improved absorption may result in better outcomes even when patients are equally adherent. Finally, bisphosphonates accumulate in bone matrix and can persist in the matrix for many years [21], which may also contribute to the observed effect. Further studies are needed to assess whether compliance with treatment is a possible mediator for the reduced risk of fracture observed in the current study for GR risedronate.

Given GR risedronate and IR risedronate therapies are only different in the type of formulation used, the GR formulation is likely the main driver for the protective effect of GR risedronate when compared to IR risedronate. In contrast, when comparing GR risedronate with alendronate, the GR formulation, the use of a different agent, and the use of a different dosage could have impacted the results, complicating the interpretation. Based on prior studies that had mixed results when comparing IR risedronate and alendronate [22, 23], a differential impact of the risedronate versus alendronate agents cannot be ruled out. However, in the current study, we observed similar trends when comparing GR risedronate with IR risedronate and alendronate and did not find significant differences in the fracture risk between IR risedronate and alendronate (sensitivity analyses; data not shown). Thus, it is plausible that the increased bioavailability of GR risedronate and possibly simplified dosing instructions explain the observed protective effect of GR risedronate when compared with alendronate [8, 9]. The fact that the protective effect of GR risedronate was observed over a relatively short period of time (median observation time of 29–32 months across the three cohorts) and among patients with high rates of early treatment discontinuation further suggests the impact of GR risedronate on fracture risk manifests soon after treatment initiation.

Interestingly, in the current study, the protective effect of GR risedronate appeared to be stronger for pelvis than other skeletal sites. While the reasons for a differential effect for pelvic factures remain unknown and the number of incident pelvic fractures was low (3.4–6.9 per 1000 women-years; Table 2), this study finding is nevertheless relevant for clinical practice due to the heavy disease burden associated with pelvic fractures. Specifically, osteoporotic pelvic fractures are often seen in very elderly patients with combined bone demineralization etiologies including osteoporosis and vitamin D deficiency/insufficiency [24], a frail and vulnerable subgroup of patients. Patients with a pelvic fracture have significant risk for morbidity and mortality [20]. Given a rise in the incidence of pelvic fractures has been observed recently [25], it is important that clinicians have confidence in treatment options to prevent pelvic fractures, particularly among elderly.

In the current study, the more convenient dosing schedule of GR risedronate did not translate into lower discontinuation rates. One possible explanation for this unexpected finding is the higher out-of-pocket cost of GR risedronate compared to other oral bisphosphonate therapies in the USA [6], similar to other chronic conditions where higher out-of-pocket costs correlate with lower compliance and persistence [26–29]. Furthermore, given persistence barriers are multifactorial, it is possible other factors have a stronger impact on persistence. Indeed, results from a systematic review that assessed 60 persistence studies using real-world data from over 4 million patients treated with oral bisphosphonates showed persistence rates similar to those reported in the current study (range: 17.7 to 74.8% 1 year after treatment initiation and 12.9 to 72.0% 2 years after treatment initiation [13]). This and other studies showing either high discontinuation rates and/or a decline over time in the number of patients who are initiated on osteoporosis therapy raised concerns about the suboptimal levels of fracture prevention among patients with osteoporosis and the unmet treatment needs in these patients [30–33]. Factors, identified by these authors as contributors to both the low use of osteoporosis therapy and the low persistence with therapy among the users, include patients' concerns with rare adverse events of oral bisphosphonates (e.g., atypical femoral fractures or osteonecrosis of the jaw), physicians treating osteoporosis as a low-priority condition, and limited access to and reimbursement of osteoporosis diagnostic investigations such as DXA [30, 31]. Hence, as pointed out in prior studies, efforts need to be made to educate physicians and patients, and to clarify the favorable risk–benefit ratio of oral bisphosphonates for patients, physicians, and third-party payers alike [31].

To our knowledge, this is the first head-to-head study that compared risk of fracture between women initiated on GR risedronate and specific oral bisphosphonates with IR formulation in a real-world setting. Data on this topic are also sparse in clinical trial settings. Indeed, the only report of fracture rates in GR risedronate versus other oral bisphosphonates comes from a randomized control trial that had bone mineral density as primary outcome [9]. In this study, the proportion of patients experiencing clinical vertebral and non-vertebral fractures (listed as adverse events) up to 2 years post-randomization was comparable between patients randomized to IR risedronate (0.3% and 4.9%, respectively; $N = 307$ women) and patients randomized to GR risedronate taken immediately after breakfast (0.0% and 4.2%; $N = 307$ women) [9]. However, given this was a non-inferiority trial powered for a different primary outcome [9], the study did not have sufficient power to detect significant differences in fracture rates. While head-to-head comparisons of GR risedronate versus IR risedronate or alendronate

are lacking, our estimates are roughly aligned with estimates from studies that reported fracture rates for oral bisphosphonates (the unadjusted risks for any fracture were 50.6–66.8 fracture events per 1000 women-years in the current sample vs. 15–81 fracture events per 1000 women-years in other studies [6, 34–38]; unadjusted risks for site-specific fractures: 3.4–27.4 vs. 3–14 fracture events per 1000 women-years, respectively [34, 38]).

In the current study, patient characteristics were adjusted for in analyses to eliminate confounding when comparing the risk of fracture and persistence between the cohorts. However, it is interesting to note some differences between the study cohorts at baseline. When comparing patients initiated on GR risedronate with those initiated on IR formulations, patients initiated on GR risedronate were significantly more likely to have higher risk of fracture at baseline based on comorbidity and medications, higher baseline use of proton pump inhibitors, and slightly higher baseline use of drugs decreasing the risk of fracture than both patients initiated on IR risedronate and those initiated on alendronate. When focusing on the GR risedronate versus alendronate comparison specifically, patients initiated on GR risedronate were significantly more likely to have vitamin D deficiency and rheumatoid arthritis and to use systemic corticosteroids in the baseline period and were significantly less likely to have hypertension, to have pre-index fractures at any site, or to use opioids in the baseline period than those initiated on alendronate. These differences in baseline characteristics suggest physicians may channel certain patients for specific oral bisphosphonates based on their perceived baseline risk or other characteristics that go beyond the general instructions in the osteoporosis treatment guidelines [3, 7, 10]. Given physicians' rationale for the treatment choice is not available in claims data, our focus was on identifying factors that may impact outcomes to control for confounding rather than identifying factors that influence treatment choice. Further studies are needed to investigate this topic and to determine whether any baseline covariates modify the effect of oral bisphosphonate therapy on the risk of fractures. Of particular interest, for the latter would be the role vitamin D when combined with specific types of oral bisphosphonates, as prior studies have shown low vitamin D levels reduce the efficacy of oral bisphosphonates in general [39].

An unexpected finding in the current sample was that between a quarter and a third of the patients treated with risedronate and alendronate used systemic corticosteroids in the baseline period. Nevertheless, given the systemic corticosteroid labels recommend frequent monitoring for osteoporosis, it is plausible that women treated with systemic corticosteroids will be screened more often, resulting in an overrepresentation of women treated with systemic corticosteroids in our sample. Furthermore, we used the same measurement across the three cohorts to minimize the impact of any measurement error when comparing the study cohorts. Finally, the average duration of oral corticosteroid use in the baseline period was relatively moderate (50.4 days; data not shown), and adjustment for corticosteroids did not have a major impact on the results.

The study findings should be interpreted in the light of its limitations:

First, given the retrospective nature of the data used, these association-level results could not establish causal inference.

Second, the current data only included patients with commercial health plans and Medicare Supplemental health plan resulting in a sample that may not be representative of the general osteoporosis population. This can be perceived by the relatively young age of the women in our sample.

Third, the total number of fractures may have been underestimated or overestimated in the current study as they were based on a claims-based algorithm that did not count multiple fractures that occurred contemporaneously at the same skeletal site (hip, spine, pelvis, and arm/wrist) and relied on the timing between diagnoses to distinguish between a visit for the initial fracture event and subsequent visits for follow-up care. This claims-based algorithm, described in the "Methods" section, was applied because diagnosis codes recorded on administrative claims are for billing purposes and thus include limited clinical information. Of note, results remained consistent in sensitivity analyses in which the 90-day window to define a fracture episode was replaced by shorter (30-day) and longer (180- and 365-day) windows (Online Resource 4).

Fourth, claims data do not provide any information on how medications are consumed. To ensure patients had exposure to the oral bisphosphonates of interest, we required that all patients had at least two consecutive prescription fills for their index treatment. Overall, 38.7%, 33.3%, and 29.0% of women in the GR risedronate, IR risedronate, and alendronate cohorts, respectively, did not meet this criterion. As a result, the discontinuation rates reported in the current study are likely underestimating the true discontinuation rates among patients initiated on oral bisphosphonates.

Fifth, in our outcome analyses, a large number of potential confounders were adjusted for, but residual confounding may have remained from factors that are not available in claims data or are inadequately measured. For example, we may not have captured all factors considered by physicians when assessing the patient baseline risk of fracture and making treatment decisions, such as body mass index or family history of osteoporotic fractures. Similarly, many patients use over the counter multivitamins or over the counter vitamin D supplements [40] that are not captured in the claims data, which may contribute to unobserved confounding.

Sixth, relatively few fracture events were observed, particularly for pelvic fracture, which may have limited our

ability to adequately control for confounding for this comparison. However, consistent with the results presented in Table 1 showing baseline characteristics were generally similar between the treatment groups, we also found that the unadjusted IRR estimates were similar to the adjusted IRR estimates across all comparisons (Online Resource 3), suggesting confounding was limited in the current study.

Finally, treatments that negatively or positively impact bone density (e.g., estrogens) may have been continued past index date or newly initiated after the index date. However, this would only impact the results if the decision to continue or initiate these treatments past index date was influenced by the type of oral bisphosphonate used, which seems unlikely.

The current study also showed that discontinuation rates of oral bisphosphonates remain high in the USA even among women who refilled their initial prescription fill, suggesting unmet patient needs in preventing fractures among women with osteoporosis [30–33] have yet to be addressed.

Notwithstanding its limitations, the current study has generated evidence suggesting that the lower fracture rates associated with GR risedronate observed in prior studies [6] are at least partially explained by advantages of GR formulations of oral bisphosphonates relative to IR formulations. This finding is consistent with data that the GR formulation of risedronate has better absorption properties because it bypasses the stomach [8, 41]. The protective effect of GR risedronate appeared to be stronger among women aged ≥ 70 years and among other subgroups with higher baseline risk of fracture based on comorbidity/medications.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00198-022-06627-0.

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Author contribution All the authors contributed to the conception, design, and interpretation of the data. JH, RII, and FV performed the analyses. All the authors provided constructive feedback during manuscript development and have read and approved the final manuscript.

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Data Availability The data that support the findings of this study are available from Truven Health Analytics, but restrictions apply to the availability of these data, which were used under a license agreement for the current study and, accordingly, are not publicly available. Access to the IBM® MarketScan® Commercial Database and the Medicare Supplemental Database can be requested by contacting Truven Health Analytics.

Code availability Codes can be provided upon request.

Declarations

Ethics approval Not applicable. Data are de-identified and comply with the Health Insurance Portability and Accountability Act (HIPAA) of 1996. Accordingly, this study did not require approval from an institutional review board or collection of inform consent.

Consent to participate Not applicable.

Consent for publication Not applicable.

Competing interests JAE had received research support and/or consultation fees from Amgen, MSD, Lilly, Theramex. BC has conducted occasional work (consultancies, advice, conferences, clinical studies, courses) for Alexion, Amgen, Aptissen, Expanscience, Ferring, Lilly, Kyowa-Kirin, MSD, Novartis, Theramex, UCB, and Viatris. MB is an employee of Theramex. RII and FV are employees of STATLOG, Inc., which have received research funding from Theramex for this study. JH is an employee of Héroux Consulting, Inc., which has received research funding from STATLOG for this study. FT has received fees for lectures and consultancy or investigator fees from Amgen, Gedeon Richter, Lilly, Hexal, Kyowa Kirin, Hologic, Novartis, Stada, Synexus, Theramex, and UCB.

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