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ORIGINAL ARTICLE

Longitudinal change in hip fracture incidence after starting risedronate or raloxifene: an observational study

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Abstract This study examined patients' risk profiles and adherence to treatment in relation to the effect of risedronate and raloxifene on hip fracture incidence. Administrative billing data were used to follow two cohorts of women aged 65 and older after starting therapy with either risedronate ($n = 86{,}735$) or raloxifene ($n = 37{,}726$). The fracture risk profile was described using a 6-month history period before starting therapy. Effectiveness of each therapy was evaluated by comparing the incidence of hip fractures during the first 3 months with the subsequent 12 months among women adherent (medication possession ratio >80%) compared with those non-adherent to treatment. At the start of therapy, the raloxifene cohort was younger than the risedronate cohort (median age 73 vs. 76 years) and had fewer prior fractures ($p < 0.01$ for both). In the first 3 months of therapy, hip fracture incidence was lower in the raloxifene group (0.51 per 100 person-years) compared with the risedronate group (0.94 per 100 person-years). In the subsequent 12 months, the incidence of hip fractures decreased among patients adherent to the risedronate regimen [relative risk (RR) 0.70, 95% CI 0.59–0.84, $p < 0.01$] and did not change significantly among patients adherent to the raloxifene regimen (RR 1.02, 95% CI 0.73–1.44). In poorly adherent patients, neither drug decreased hip fracture risk. Risedronate treatment in adherent patients rapidly decreased the risk of hip fractures, whereas raloxifene treatment did not.

Keywords Bisphosphonate · Hip fracture · Osteoporosis · Raloxifene · Risedronate

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Introduction

Randomized controlled clinical trials are the gold standard for measuring the efficacy of a therapy. All osteoporosis drugs approved to treat postmenopausal osteoporosis have demonstrated reduction of vertebral fractures in placebo-controlled clinical trials. Observations from non-comparative trials suggest that some drugs may reduce the incidence of vertebral fractures more efficiently than others [1–3]. Moreover, evidence for a reduction of hip fractures exists for certain drugs, including risedronate, alendronate, and zoledronate, but not with ibandronate and raloxifene [1, 4]. These apparent differences may pertain to the mode of action and

distribution of the various drugs, and/or to the clinical characteristics of patients included in the trials. Indeed, recent data suggest that anti-fracture efficacy of osteoporosis drugs may be greater in patients with a higher 10-year fracture probability [5, 6]. Adherence to therapy is another major contributor to drug efficacy. Subjects who maintain a medication possession ratio (MPR) of ≥80% during all the observation time are usually considered adherent to treatment, and in these circumstances a higher level of efficacy is achieved [7–15]. How drug efficacy, baseline fracture risk, and adherence to therapy combine to determine fracture risk reduction in clinical practice however remains to be investigated [16].

Because health data on millions of patients on osteoporosis therapies in real-world clinical practice have been collected through administrative billing, medical records, and registries, many recent observational studies have examined the effectiveness of osteoporosis therapies for reducing clinical fractures [7–15, 17–30]. Some of these studies support that the effectiveness in reducing clinical fractures, particularly hip fractures, in actual patients varies among drugs, in keeping with the respective clinical trials [20, 26, 27, 30]. In the current observational study using administrative billing data, we first sought to describe and compare the fracture risk profile of patients initiating a bisphosphonate (risedronate) and an estrogen agonist/antagonist (raloxifene) therapy. The fracture risk profile included factors known to affect the probability of fracture such as demographic characteristics, co-morbidities, concomitant medication use, and history of prior fractures. We next sought to observe the hip fracture incidence in these patients according to their level of adherence to therapy. For this analysis, we followed two cohorts of women aged 65 and older after starting either risedronate or raloxifene therapy. Within each cohort, the baseline hip fracture incidence was defined by the 3-month period after starting therapy. To assess if therapy resulted in a change in fracture incidence over time, the fracture incidence during the subsequent 12 months on treatment was compared to the baseline incidence (first 3 months on treatment) within each cohort among women adherent to therapy as well as those who were non-adherent. Given the observed differences in the fracture risk profile of patients initiating a bisphosphonate or a selective estrogen receptor modulator, we further explored the hip fracture incidence in a subgroup of risedronate patients whose risk profile was matched more closely to those receiving a selective estrogen receptor modulator and conversely how effective a selective estrogen receptor modulator would be for reducing hip fractures among patients with a risk profile closer to those receiving a bisphosphonate.

Materials and methods

Data source

Computerized records of administrative billing provide a convenient data source for studying filled prescription use and outcomes in large populations. Records include patient-level data concerning: (1) inpatient and outpatient services specified by diagnosis codes of the International Classification of Diseases, 9th revision, clinical modification (ICD-9-CM); (2) retail and mail-order pharmacy dispensations specified by national drug codes; and (3) demographic information including sex, age, and eligibility dates of health plan coverage. The data for this study, from January 2000 through December 2008, originated from two mutually exclusive sources: Ingenix® Lab/Rx (Eden Prairie, MN) and Thomson Reuters' MarketScan® (Ann Arbor, MI). During the study period, the average number of eligible enrollees was 13 million in MarketScan, representing multiple health plans, and 12 million in Ingenix, representing a single health plan. Geographically, one half of this population was located in the states of Michigan, California, Florida, Ohio, Georgia, and Texas, and one half in the other 44 states.

Study population

The study population was comprised of two cohorts—one starting risedronate (5 or 35 mg) and one starting raloxifene (60 mg) therapy. Study patients were entered on the date of their initial filled prescription between July 2000 and December 2007. Inclusion criteria were: (1) being women ages 65 and over to provide a study population similar in age to that of the randomized controlled trials and for which clinical fractures are likely to be related to osteoporosis [31]; (2) having at least 3 months of coverage in the data source after cohort entry to provide a minimum observation period; and (3) having no diagnosis of a malignant neoplasm (ICD-9-CM codes 140–208) or Paget's disease (731.0) within 6 months prior to and 3 months after cohort entry to maximize the probability that patients were being treated for either post-menopausal osteoporosis or glucocorticoid-induced osteoporosis. Further description of subject identification is provided in Table 1.

Outcome

After patients were identified, each was followed to identify the first new hip fracture. "Hip fracture" was defined by an inpatient diagnosis of a fracture at the hip (ICD-9-CM code 820, 733.14). "New" was defined as no evidence of hip fracture in the 6 months before cohort entry.

Table 1 Identification of the study population

Risedronate	
Number of women in data source with first use of risedronate 5 mg (daily) (NDC = 001490471) or risedronate 35 mg (weekly) (NDC = 001490472) between July 2000 and December 2007; aged 65 years and over	202,028
Exclude women with less than 6 months of enrollment data before first use of bisphosphonate	−69,475
Exclude women with less than 3 months of enrollment data after first use of bisphosphonate	−7,445
Exclude women with diagnosis of Paget's disease (ICD-9 731.0) during period 6 months before and 3 months after first use of bisphosphonate	−193
Exclude women with malignancy diagnoses (ICD-9 140–208) during period 6 months before and 3 months after first use of bisphosphonate	−14,762
Exclude women with any other use of another **bisphosphonate** form in 6 months before first use of bisphosphonate	−17,025
Exclude women with any use of any *raloxifene* form during period 6 months before and 3 months after first use of bisphosphonate	−6,393
Number of women in bisphosphonate cohort	86,735
Raloxifene	
Number of women in data source with first use of raloxifene 60 mg (daily) (NDC = 000024165) between July 2000 and December 2007; aged 65 years and over	125,139
Exclude women with less than 6 months of enrollment data before first use of raloxifene	−68,314
Exclude women with less than 3 months of enrollment data after first use of raloxifene	−2,616
Exclude women with diagnosis of Paget's disease (ICD-9 731.0) during period 6 months before and 3 months after first use of raloxifene	−30
Exclude women with malignancy diagnoses (ICD-9 140–208) during period 6 months before and 3 months after first use of raloxifene	−5,897
Exclude women with any other use of another **raloxifene** form in 6 months before first use of raloxifene	−4
Exclude women with any use of any *bisphosphonate* form during period 6 months before and 3 months after first use of raloxifene	−10,552
Number of women in raloxifene cohort	37,726

NDC National Drug Code

To increase the probability of only including osteoporotic-related fractures, we excluded likely traumatic fractures by eliminating diagnoses of an open fracture or of a documented cause of injury from a transportation accident (E codes E800–E848).

Risk factors

Risk factors for fracture, which may be confounding variables, include age, fracture history, glucocorticoid use, and diagnosis of rheumatoid arthritis. Age was at the year of cohort entry. Fracture history was any fracture diagnosis at the hip, wrist, humerus, clavicle, pelvis, leg, or vertebrae in the 6 months prior to cohort entry. Glucocorticoid use was receiving 450 mg prednisone-equivalent pills within ±90 days of cohort entry—an approximation of a daily dose of 5 mg prednisone for at least 90 days [32]. A diagnosis of rheumatoid arthritis was any inpatient or outpatient diagnosis (ICD-9-CM code 714.0) within 6 months before and 3 months after cohort entry. Risk factors not available in the data source included bone mineral density, body mass index, smoking, alcohol consumption, and family history of fracture.

Statistical analysis

To calculate change in hip fracture incidence within each therapy cohort, we used a method described previously [30]. Briefly, within each cohort, fracture incidence during the first 3 months of therapy (baseline period) was compared with the fracture incidence during the subsequent 12 months among patients adherent to treatment. Fracture incidence during the baseline period after starting an osteoporosis therapy likely reflects the fracture risk of the cohort independent of any drug effect (i.e., fracture reduction does not begin immediately after the start of therapy). For the calculation of hip fracture incidence during the baseline period, the denominator was the sum of observation time within a cohort during the 3 months, and the numerator was the number of patients within a cohort with a new hip fracture during the 3 months.

For the calculation of hip fracture incidence during the subsequent 12 months, the denominator included all observation time where patients maintained a MPR of at least 80% to filled prescriptions of risedronate (5 or 35 mg) or raloxifene (60 mg). The 80% level utilized for the MPR has been suggested to provide a high level of therapy

effectiveness for bisphosphonates [7–15, 21–25]. The MPR was calculated at 3-month intervals after cohort entry. Therefore, patients with an MPR of at least 80% at the end of 3 months were followed into the subsequent 3-month period. The same process was applied at the end of 6, 9, and 12 months. The numerator was the number of patients with a new hip fracture preceded by a MPR of at least 80%. A simple ratio was used to compare the incidence of fractures between the baseline and subsequent periods. Poisson regression was used to compute the 95% confidence intervals around the ratio.

Two additional analyses were completed to further evaluate the primary analysis. One analysis assessed if there was any change in the hip fracture incidence between the first 3 months of therapy and the subsequent period of 12 months of all observation time where patients had a MPR <80% (i.e., not adherent to treatment). A second analysis attempted to equate the fracture risk profile of the two cohorts by matching. A 1:1 match on year of age (ages 65–100), fracture history (yes or no), and estrogen therapy use (yes or no) was completed so the risedronate cohort matched the raloxifene cohort. Hence, the number of strata matched on was 144 ($36 \times 2 \times 2$). If the raloxifene cohort had more patients in a stratum than the risedronate cohort, there was a reduction in the number of risedronate matches (i.e., of the 37,726 raloxifene patients; 37,501 had a match in the risedronate cohort). If the risedronate cohort had more patients in a stratum than the raloxifene cohort, then a random sample of risedronate patients was selected. The results presented in the matched cohort reflect the average of three random samples.

Results

Characteristics of patients starting risedronate or raloxifene

The study population included women 65 years of age and older who entered into a cohort on the date of their initial prescription filling for risedronate 5 mg daily or 35 mg weekly ($n = 86{,}735$) or raloxifene 60 mg daily ($n = 37{,}726$) between July 2000 and December 2007. The data source provided a record of health care utilization for the entire 15-month study period after cohort entry for approximately 75% of each cohort. At cohort entry, the patients receiving risedronate were older, had more prior fractures, had greater use of glucocorticoids, and overall appeared to be at greater risk for hip fracture than patients receiving raloxifene (Table 2).

Table 2 Characteristics of patients starting therapy

Characteristics	Risedronate	Raloxifene
Number of women in cohort	86,735	37,726
Year of cohort entry (% cohort)		
2000–2002	14	43
2003–2005	69	44
2006–2007	17	13
Age at entry (cohort median)	76	73
Age 75 and over (% cohort)	53	38
Any clinical fracture in 6 months before entry (% cohort)	9	4
Glucocorticoid use within 3 months of entry (% cohort)	6	3
Rheumatoid arthritis diagnosis within 3 months of entry (% cohort)	3	2
Estrogen use within 3 months of entry (% cohort)	14	26
Documented osteoporosis diagnosis in 6 months before entry (% cohort)	40	28
Medical specialty seen closest to entry (% cohort)		
Internal medicine/family practice	55	49
Obstetrics/gynecology	4	9
Other/undetermined	41	42
Estimated 10-year probability of hip fracture at cohort entry, cohort median[a]	6.0	4.0

For every characteristic, there is a statistical difference ($p < 0.01$) between raloxifene and risedronate cohorts based upon chi-square test for dichotomous variables and Wilcoxon rank sum test for continuous variables

[a] To summarize the impact of the available risk factors, a partial FRAX™ analysis was used to obtain an estimate of the 10-year probability of hip fracture based on age, fracture history, glucocorticoid use, and rheumatoid arthritis diagnosis, and assuming a body mass index of 25 for all (160 cm and 64 kg) in Caucasian women from the United States [6]. Among all patients in the cohort, the median FRAX value was reported

Incidence of hip fractures during the baseline period

During the 3 months after starting therapy in both cohorts, the incidence of hip fractures was higher among those of older age, prior fracture history, and glucocorticoid use, and lower among those using estrogen therapy (Table 3). During these 3 months, patients receiving risedronate, for whom a higher proportion had these risk factors, had an incidence of hip fractures of 0.94 per 100 person-years, nearly twice as high ($p < 0.01$) as the incidence among

Table 3 Hip fracture incidence in the 3 months after cohort entry by baseline characteristics

Characteristics	Risedronate			Raloxifene		
	Women	Women with fracture	Annualized incidence per 100 women	Women	Women with fracture	Annualized incidence per 100 women
Complete cohort	86,735	204	0.9	37,726	48	0.5
Year of entry						
2000–2002	12,591	32	1.0	16,090	17	0.4
2003–2005	59,778	134	0.9	16,594	24	0.6
2006–2007	14,366	38	1.1	5,042	7	0.6
Age 65–74 years	40,830	37	0.4	23,287	13	0.2
Age 75 and over	45,905	167	1.5	14,439	35	1.0
Clinical fracture prior to entry	8,006	44	2.2	1,466	4	1.1
No clinical fracture	78,729	160	0.8	36,260	44	0.5
Glucocorticoid use	5,261	18	1.4	1,054	2	0.8
No use	81,474	186	0.9	36,672	46	0.5
Hormone therapy use	12,292	10	0.3	9,938	3	0.1
No use	74,443	194	1.0	27,788	45	0.6
Documented osteoporosis	34,764	93	1.1	10,637	21	0.8
No documentation	51,971	111	0.9	27,089	27	0.4
Medical specialty						
Internal medicine	47,508	130	1.1	18,495	28	0.6
Gynecology	3,977	1	0.1	3,349	3	0.4
Other	35,250	73	0.8	15,882	17	0.4
Ten-year hip fracture probability						
1.2–6.0%	45,067	29	0.3	25,698	15	0.2
6.1–34.0%	41,668	175	1.7	12,028	33	1.1

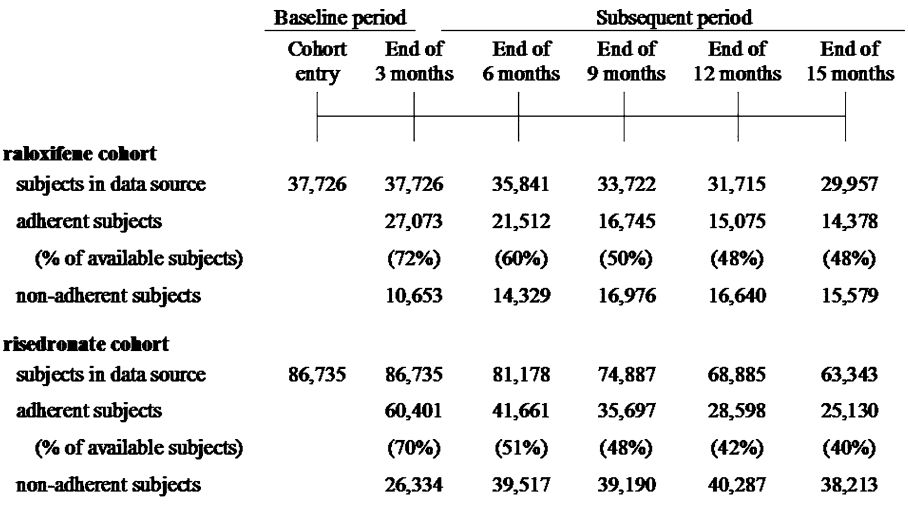

Fig. 1 Follow-up for measure of fracture incidence

those receiving raloxifene, which was 0.51 per 100 person-years.

Adherence to treatment

Patients with a MPR of at least 80% were considered to be treatment adherent and those with less than 80% MPR were considered to be non-adherent. At the end of the first 3 months, 72% of patients in the raloxifene cohort were adherent, while 70% of the patients were adherent in the risedronate cohort. These numbers continued to decrease during the subsequent 12-month period. At the end of the 15-month observation period, the percentage of patients adherent to treatment was 48% for raloxifene and 40% for risedronate (Fig. 1).

Incidence of hip fractures during the subsequent 12 months

In the subsequent 12 months compared to the baseline period, the incidence of hip fractures decreased among patients adherent to risedronate therapy (RR 0.70, 95% CI 0.59–0.84, $p < 0.01$), whereas no change was seen among patients adherent to raloxifene (RR 0.99, 95% CI 0.72–1.37). In contrast, among those patients not adhering to therapy, hip fracture incidence remained unchanged across the baseline period through the subsequent 12 months for both the risedronate and raloxifene cohorts (Table 4).

Matched analysis

To investigate the contribution of differences in baseline fracture risk between patients treated with risedronate or raloxifene (Table 1) in relation to the effectiveness of these drugs in reducing hip fractures, we attempted to match the risedronate cohort to the lower risk raloxifene cohort based on age, fracture history, and use of estrogen therapy. In this case, the resulting matching was incomplete as differences ($p < 0.01$) in the incidence of hip fractures remained during the baseline period (Table 5). Nevertheless, in the raloxifene-matched risedronate cohort, the initial hip fracture incidence decreased to 0.70 per 100 patient-years (from 0.94 per 100 patient-years in the overall risedronate cohort) (Table 4). In this relatively lower risk group, the incidence of hip fracture in the subsequent 12 months was still significantly reduced with risedronate therapy (Table 5).

Discussion

In this large, observational study of women aged 65 years and older initiating either risedronate or raloxifene therapy,

Table 4 Comparison of hip fracture incidence between baseline period and subsequent period

Cohort (number of patients)	Baseline period			Subsequent period				Ratio (95% CI) of fracture incidence for follow-up/baseline
	Initial 3 months after starting therapy			Subsequent 12 months after baseline period				
	Number patients with fracture	Person-years of observation	Fracture incidence per 100 person-years		Number patients with fracture	Person-years of observation	Fracture incidence per 100 person-years	
Raloxifene ($n = 37,726$)	48	9,432	0.51	Adherent	102	19,594	0.52	1.02 (0.73–1.44)
				Non-adherent	69	14,192	0.49	0.96 (0.66–1.38)
Risedronate ($n = 86,735$)	204	21,684	0.94	Adherent	266	40,214	0.66	0.70 (0.59–0.84)
				Non-adherent	316	34,787	0.91	0.97 (0.81–1.15)

Adherent defined as medication possession ratio of at least 80%
Non-adherent defined as medication possession ratio less than 80%

Table 5 Matched analysis (year of age, fracture history, estrogen use)

Cohort (number of patients)	Baseline period			Subsequent period			Ratio (95% CI) of fracture incidence for follow-up/ baseline
	Three-month period after starting therapy			Subsequent 1-year period adherent to therapy			
	Number subjects with fracture	Person-years of observation	Fracture incidence per 100 person-years	Number subjects with fracture	Person-years of observation	Fracture incidence per 100 person-years	
Raloxifene							
Complete cohort ($n = 37{,}726$)	48	9,432	0.51	102	19,594	0.52	1.02 (0.73–1.44)
Risedronate							
Matched cohort[a] ($n = 37{,}501$)	66	9,375	0.70	81	17,933	0.45	0.64 (0.46–0.89)
Risedronate							
Complete cohort ($n = 86{,}735$)	204	21,684	0.94	266	40,214	0.66	0.70 (0.59–0.84)
Raloxifene							
Matched cohort[b] ($n = 17{,}074$)	25	4,268	0.59	59	8,730	0.68	1.15 (0.72–1.84)

[a] A 1:1 match on year of age, fracture history (yes or no), and hormone replacement therapy use (yes or no) was completed so the risedronate cohort matched the raloxifene cohort. If the raloxifene cohort had more patients in a stratum than the risedronate cohort, there was a reduction in the number of risedronate matches (i.e., of the 37,726 raloxifene patients, 37,501 had a match in the risedronate cohort). If the risedronate cohort had more patients in a stratum than the raloxifene cohort, then a random sample of risedronate patients was selected. The numbers presented in the matched cohort reflect the average of three random samples

[b] A 1:5 match on year of age, fracture history (yes or no), and hormone replacement therapy use (yes or no) was completed so the raloxifene cohort matched the risedronate cohort. If the risedronate cohort had more than 5× patients in a stratum than the raloxifene cohort, there was a reduction in the number of raloxifene matches (i.e., of the 17,347 needed patients in the raloxifene group, 17,074 had a match in the risedronate cohort). If the raloxifene cohort had more patients in a stratum than 1/5 of the risedronate cohort, then a random sample of raloxifene patients was selected. The numbers presented in the matched cohort reflect the average of three random samples

we made three inquiries: (1) Were there any differences in the fracture risk profile at the time of initial prescription among these women? (2) How effective was each osteoporosis therapy in reducing hip fractures over time considering the adherence level? (3) What is the contribution of the baseline fracture risk to the effectiveness of these drugs in reducing hip fractures?

Consistent with prior observations [27, 33], we observed that patients receiving risedronate had more risk factors for fracture at the time of initial prescription than the population of patients receiving a selective estrogen receptor modulator. These observations suggest that physicians are selectively prescribing osteoporosis therapies based on their appreciation of the patients' risk profile and/or specialty. While these prescription patterns are likely clinically appropriate, selective prescribing creates a meaningful bias for any epidemiological study of drug effects. This bias, confounded by indication, results because the allocation of treatment is not randomized and the indication for treatment is related to the risk of future outcomes [34]. As a result, this bias may lead to a false interpretation of any comparison between treatment groups. While there is no one best way to manage this bias, we utilized a method in this study that makes a comparison within a population rather than between populations. A limitation of our method, which is a comparison in the fracture incidence during the first 3 months of therapy to the fracture incidence during the subsequent 12 months among patients adherent to treatment, is the presumption that fracture reduction does not begin immediately after therapy; consequently, the short baseline period after starting an osteoporosis therapy likely reflects the fracture risk of a cohort independent of any drug effect. One observation supporting this presumption includes changes in bone mineral density, a surrogate marker of therapeutic effect, whose least significant change may not be reached until at least 1 year on therapy [35]. Another supporting observation is that fracture reductions have not been noted earlier than 6 months after start of therapy within post hoc, pooled analysis of clinical trials [36, 37].

Based on our method of measuring effectiveness in this study, we observed that the patients receiving and adherent to risedronate had a reduction over time in the incidence of hip fractures, whereas the patients receiving and adherent to raloxifene had no reduction in hip fracture incidence. The strength of this observation is the consistency between these results and the results of clinical trials [1, 4] and another observational study [38]. Limitations of this observation include the limited availability of information to describe patients (e.g., no bone mineral density results), the inclusion of fracture outcomes not verified by medical charts, and the potential that differences in fracture risk profile at baseline between the risedronate and raloxifene populations may be linked to interpretation of results. In a recent study, McCloskey et al. [5] showed that the bisphosphonate clodronate was effective in women identified by the FRAX® tool (World Health Organization, Centre for Metabolic Bone Diseases, University of Sheffield, UK) to be at high risk even in the absence of bone mineral density information. Kanis et al. [6] showed that bazedoxifene, an estrogen angonist/antagonist, was effective at reducing vertebral and clinical fractures in postmenopausal women at high risk as assessed by FRAX. Thus, the observed differences in the present study may be partly due to the fracture risk profile at baseline.

To control for differences in fracture risk profile at baseline, we attempted to equate the risedronate and raloxifene populations on fracture risk at the time of initial prescription by matching on several major risk factors, including age, prior fracture, and use of estrogen therapy. However, even after matching on these risk factors, there remained significant differences in baseline fracture risk during the initial 3 months of therapy (i.e., matching did not fully control for differences between populations). It remains possible, therefore, that even modest differences in baseline fracture risk have an impact on the effectiveness of these therapies [6]. On the other hand, these results suggest that treating women at lower risk with risedronate might be more beneficial than treating them with raloxifene.

In conclusion, for this observational study of more than 100,000 patients receiving either risedronate or raloxifene, differences existed in the fracture risk profile of patients at the time of initial prescription between those starting different osteoporosis therapies. Among these patients, we found that adherence to risedronate therapy rapidly decreased the risk of hip fractures, whereas raloxifene prescribed to women at lesser fracture risk did not. Hence, cost-effective strategies to reduce the burden of clinical fractures should take into account both drug efficacy and baseline fracture risk.

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