

Longitudinal change in clinical fracture incidence after initiation of bisphosphonates

A. Abelson · J. D. Ringe · D. T. Gold · J. L. Lange · T. Thomas

Received: 28 June 2009 / Accepted: 9 July 2009 / Published online: 1 September 2009
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Abstract

Summary There are differences in the risk profile of patients prescribed alendronate, risedronate, or ibandronate. Observed reductions in fracture incidence over time suggest that the effectiveness of each bisphosphonate in clinical practice has been consistent with their efficacies demonstrated in randomized controlled trials.

Introduction Observational studies of bisphosphonate effectiveness for fracture prevention are subject to bias from unknown characteristics of baseline fracture risk at the start of therapy. The fracture incidence during the short period after starting a bisphosphonate and before any expected clinical benefit likely reflects baseline fracture risk. Bisphosphonate effectiveness may then be

estimated by measuring the change in fracture incidence over time on therapy.

Methods Administrative billing data were used to follow three cohorts of women aged 65 and older (total $n=210,144$) after starting therapy either on alendronate, risedronate, or ibandronate in the USA between market introduction and 2006. Within each cohort, the baseline incidence of clinical fractures at the hip, vertebral, and nonvertebral sites was defined by the initial 3-month period after starting therapy. Relative to these baselines, we then compared the fracture incidence during the subsequent 12 months on therapy.

Results At the start of therapy, the ibandronate cohort was younger and had fewer prior fractures than either the risedronate or alendronate cohorts. Accordingly, the baseline incidence of hip fractures was higher in the risedronate cohort (0.90 per 100 person-years) and in the alendronate cohort (0.77) than in the ibandronate cohort (0.64). Relative to the baseline incidence, fracture incidence was significantly lower in the subsequent 12 months in both cohorts of alendronate (18% lower at hip, 28% at nonvertebral sites, and 57% at vertebral sites) and risedronate (27% lower at hip, 21% at nonvertebral sites, and 54% at vertebral sites). In the ibandronate cohort, the fracture incidence was lower (31%) only at vertebral sites.

Conclusions Differences in the baseline fracture incidence among the cohorts may reflect differences in the risk profile of patients prescribed each bisphosphonate. The reductions observed in fracture incidence over time within each cohort suggest that the effectiveness of each bisphosphonate in clinical practice has been consistent with their efficacies demonstrated in randomized controlled trials.

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Keywords Bisphosphonates · Clinical fractures · Effectiveness · Epidemiology · Osteoporosis

Introduction

The demonstrated efficacy of a therapy in a randomized clinical trial may not predict its actual effectiveness in clinical practice because of differences in characteristics of patients and level of medical care [1]. As a therapy for osteoporosis, the oral bisphosphonates have been widely utilized in recent years. These bisphosphonates include once-a-week alendronate (marketed in the USA since 2000), once-a-week risedronate (since 2002), and once-a-month ibandronate (since 2005). Since health data on large numbers of bisphosphonate patients in clinical practice have now been collected (through administrative billing data, medical records, and registries), many recent observational studies have examined the effectiveness of oral bisphosphonates for reducing clinical fractures. The designs of these observational studies have included comparisons between patient populations with or without a fracture [2, 3], with or without bisphosphonate use [4, 5], compliant or not compliant with bisphosphonate use [6–19], or between patient populations on different bisphosphonate molecules [20–23]. A key limitation in interpreting any of these comparisons is uncertainty if known or unknown differences in baseline fracture risk between patient populations could account for some or all of the reported results.

An approach to directly measure the baseline risk of an outcome within patient populations that has been used in effectiveness studies of other therapies may be applicable to the study of bisphosphonates. In a comparison of patients receiving a bare or drug-eluting stent, the mortality 2 days after procedure was used to assess risk of the mortality outcome independent of possible drug effect [24]. In a comparison of patients receiving influenza vaccine or not, the mortality after vaccination but before flu season was used to assess risk of mortality outcome independent of possible vaccination effect [25]. Likewise, following initiation of bisphosphonate therapy, the realization of fracture reduction is likely not immediate. Bone mineral density, a surrogate marker of therapeutic effect, begins to change after start of therapy though does not reach its maximum level of change until at least 1 year on therapy [26]. As changes in bone density and quality take time, correspondingly, fracture reductions have not been noted earlier than 6 months after start of therapy within post hoc, pooled analysis of clinical trials [27, 28].

Hence, for an observational study of bisphosphonates, the fracture incidence during the short period after starting a therapy and before any expected clinical benefit likely reflects baseline fracture risk. We propose that bisphosphonate effectiveness may then be estimated by measuring the change in fracture incidence over time on therapy. For this study, administrative billing data were used to follow three

cohorts of women aged 65 and older after starting therapy either on alendronate, risedronate, or ibandronate. Within each cohort, the baseline incidence of clinical fractures at the hip, vertebral, and nonvertebral sites was defined by the initial 3-month period after starting therapy. Relative to these baselines, we then compared the fracture incidence during the subsequent 12 months on therapy.

Materials and methods

Data source

Computerized records of administrative billing provide a convenient data source for studying drug use and outcomes in large populations. Records include patient-level data of: (1) inpatient and outpatient services specified by diagnoses 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, inclusive of January 2000–December 2007, originated from two mutually exclusive sources: Ingenix Lab/Rx (Eden Prairie, MN, USA) and Medstat MarketScan (Ann Arbor, MI, USA). During that period, the average number of eligible enrollees was 14 million in Medstat, representing multiple health plans, and 10 million in Ingenix, representing a single health plan. Geographically, one half of this population was located in Michigan, California, Florida, Ohio, Georgia, or Texas and one half in the other 44 states.

Study population

The study population consisted of three cohorts—one prescribed alendronate, one prescribed risedronate, and one prescribed ibandronate. Subjects entered a cohort on the date of their initial filled prescription for alendronate 70 mg/week, risedronate 35 mg/week, or ibandronate 150 mg/month during the time period of market introduction through December 2006. Market introduction was November 2000 for alendronate cohort, May 2002 for risedronate cohort, and April 2005 for ibandronate cohort. The initial bisphosphonate prescription was defined by a subject having at least 6 months of prior coverage in the data source without any other bisphosphonate use (e.g., another bisphosphonate type or dose). After 6 months without any bisphosphonate use, a subject was allowed to enter a new cohort (i.e., a subject could be in more than one cohort—1% of alendronate cohort, 4% of risedronate cohort, and 20% of ibandronate cohort was preceded by inclusion in another cohort).

In addition, subjects were required to: (1) be women aged 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 [29]; (2) have at least 3 months of coverage in data source after cohort entry to provide for minimum follow-up; and (3) have no diagnosis of malignant neoplasm (ICD-9-CM codes 140–208) or Paget’s disease (731.0) within 6 months prior- and 3 months post-cohort entry to maximize the probability that subjects were being treated for either post-menopausal osteoporosis or glucocorticoid-induced osteoporosis.

Risk factors for fracture

Available risk factors in the data source included age, history of prior fracture, glucocorticoid use, and diagnosis of rheumatoid arthritis. Age was calculated at the year of cohort entry. History of prior fracture was defined by any clinical fracture diagnosis at the hip, wrist, humerus, clavicle, pelvis, leg, or vertebrae in the

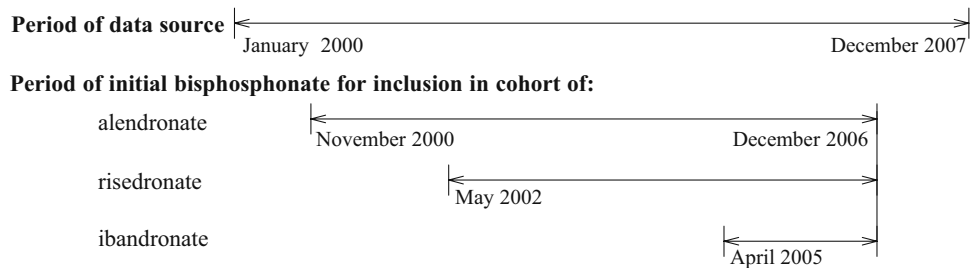
6 months prior to cohort entry. Glucocorticoid use was defined by receiving 450 mg prednisone-equivalent pills within ±90 days of cohort entry—an approximation of the American College of Rheumatology guideline of 5 mg prednisone for at least 90 days [30]. A diagnosis of rheumatoid arthritis was based on any inpatient or outpatient diagnosis (ICD-9-CM code 714.0) within 6 months prior- and 3 months post-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.

Fracture outcomes

After subjects entered a cohort, each was followed to identify three outcomes: a new hip fracture, a new nonvertebral fracture, or a new clinical vertebral fracture. During the follow-up, subjects were allowed to have each outcome once. Hip fractures were defined by an inpatient diagnosis at the hip (ICD-9-CM code 820, 733.14). Nonvertebral fractures were inclusive of inpatient diag-

Fig. 1 Time period for cohort identification and follow-up for measure of fracture incidence

A) Identification



B) Follow-up

	Initial period of therapy		Subsequent period of therapy			
	Cohort entry	End of 3 months	End of 6 months	End of 9 months	End of 12 months	End of 15 months
alendronate						
subjects in data source	116,996	116,996	110,333	104,098	98,583 (84%) ^A	
and high compliance		84,534	61,594	54,681	45,802 (46%) ^B	
risedronate						
subjects in data source	78,860	78,860	73,629	68,694	64,448 (82%)	
and high compliance		55,842	39,228	34,232	28,132 (44%)	
ibandronate						
subjects in data source	14,288	14,288	13,444	12,975	12,553 (88%)	
and high compliance		10,426	7,756	6,595	5,447 (43%)	

^A of subjects entering cohort, percentage remaining in data source after 12 months

^B of subjects remaining in data source, percentage maintaining high compliance to therapy (medical possession ratio ≥ 80%)

nosis at the hip, and inpatient or outpatient diagnosis at the wrist (813, 733.12), humerus (812, 733.11), clavicle (810), pelvis (808), and leg (821, 823, 733.15, 733.16). Clinical vertebral fractures were defined by either inpatient or outpatient diagnosis at vertebral sites (805.2, 805.4, 805.8, 733.13). New fractures were defined as a fracture at each body site for which there was no fracture at that same site in the 6 months before cohort entry. 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 other than an accidental fall (ecode of E880–E888). These exclusions removed less than 10% of fracture outcomes.

Follow-up

All subjects contributed 3 months of follow-up after cohort entry, during which the baseline fracture incidence was calculated. The denominator was the sum of observation time for all subjects within a cohort during the 3 months. For example, within the alendronate cohort, the 116,996 subjects contributed 91 days of follow-up each for

10.6 million days/364 days per year or 29,249 person-years of observation. The numerator was number of subjects with a new fracture during the 3 months.

After 3 months of follow-up, subsequent observation was available for subjects through December 2007 unless their individual coverage ceased in the data source (Fig. 1a). The fracture incidence was calculated for the subsequent 1 year on therapy. We limited our observation to the subsequent 1 year of therapy because of concerns that a subject's fracture risk may change over a period of multiple years independent of any therapeutic effect. Two examples of changing fracture risk over time include: the risk of hip fracture increasing with each year of age [31] and the risk of fractures increasing substantially within the year after a fracture but then decreasing thereafter [32]. All subjects who had received a sufficient quantity of pills (of the same bisphosphonate type initiated at cohort entry) to provide for a medical possession ratio $\geq 80\%$ at the end of 3 months were followed into the subsequent 3-month period (Fig. 1b). The level utilized for the medical possession ratio has been frequently suggested to provide a high level of therapy effectiveness for bisphosphonates [6–19]. Subjects

Table 1 Baseline characteristics of study population

	Alendronate 70 mg	Risedronate 35 mg	Ibandronate 150 mg
Number of women in cohort	116,996	78,860	14,288
Year of cohort entry, % cohort			
2000–2004	78%	73%	0%
2005–2006	22%	27%	100%
Age at cohort entry, mean	75	76	75
Age 75 and over, % cohort	51%	53%	47%
Clinical fracture in 6 months before cohort entry ^a	9%	9%	7%
Clinical fracture in 4 years before cohort entry ^b	19%	18%	17%
Glucocorticoid use at cohort entry	5%	6%	6%
Rheumatoid arthritis diagnosis at cohort entry	2%	3%	3%
Hormone replacement therapy at cohort entry	14%	12%	9%
Prior bisphosphonate use, % cohort ^c			
6 months before cohort entry	0%	0%	0%
1 year	4%	5%	18%
2 years	6%	10%	30%
3 years	7%	12%	36%
4 years	7%	13%	40%

^a Fracture diagnosis at the hip, clavicle, wrist, humerus, leg, pelvis, or vertebral sites

^b Fracture diagnosis at any time in the 4 years before cohort entry among those with 4 years of available administrative billing data before cohort entry (17,128 subjects in alendronate cohort had 4 years of such data, 15,054 in risedronate cohort, 7,884 in ibandronate cohort)

^c Use of any bisphosphonate (e.g., daily formulations or other bisphosphonate) before cohort entry regardless of duration of administrative billing data before entry. Note: among those with 4 years of available data before entry, the percent of cohort in the preceding 4 years with bisphosphonate use was 9%, 19%, and 47% for alendronate, risedronate, and ibandronate cohorts, respectively

were followed until the end of this 3-month period or the end of their coverage in data source. The same process was applied at the end of 6, 9, and 12 months after cohort entry. For the calculation of incidence, the denominator was the sum of observation during follow-up preceded by a medical possession ratio of at least 80%. For example, within the alendronate cohort:

84,534 subjects had an average of 89 days of follow-up between 3 and 6 months of therapy, 61,594 subjects had an average of 89 days of follow-up between 6 and 9 months of therapy, 54,681 subjects had an average of 89 days of follow-up between 9 and 12 months of therapy, and 45,802 subjects had an average of 89 days of follow-up between 12 and 15 months of therapy—for a sum of 60,108 person-years of observation. The numerator included number of subjects with a new fracture, preceded by medical possession ratio of 80%, akin to previous study [7].

Statistical analysis

A simple ratio was used to compare the incidence of fractures between the period of 3 months after starting therapy and the subsequent 1-year period on therapy. Poisson regression was used to compute the 95% confidence intervals around the ratio. An independent review and replication of statistical analyses was completed by

Esteban Walker, Ph.D., of the Department of Quantitative Health Sciences at the Cleveland Clinic.

Results

Cohort characteristics

The study population included women who entered into a cohort on the date of their initial filled prescription for alendronate 70 mg ($n=116,996$) or risedronate 35 mg ($n=78,860$) or ibandronate 150 mg ($n=14,288$) (Fig. 1a). The data source provided a record of health care utilization for at least 1 year after initial bisphosphonate prescription for more than 80% of each cohort (Fig. 1b). Of those subjects in the data source for at least 1 year, between 43% and 46% of the cohorts were highly compliant to therapy (i.e., maintained a medical possession ratio to initiated therapy of at least 80%).

At cohort entry, the ibandronate cohort was the youngest and had the smallest percentage with a recent fracture history among the three cohorts (Table 1). Since a subject was allowed to enter a cohort after 6 months without any bisphosphonate use, some subjects had some previous use of bisphosphonates. Prior use of bisphosphonates in the 4 years prior to cohort entry ranged from 7% of alendronate cohort to 40% of ibandronate cohort.

Table 2 Incidence of hip fractures in the 3 months after starting therapy by baseline characteristic

	Alendronate ($n=116,996$) (person-years=29,249)			Risedronate ($n=78,860$) (person-years=19,715)			Ibandronate ($n=14,288$) (person-years=3,572)		
	% cohort	Number of fractures	Rate/100 p-y	% cohort	Number of fractures	Rate/100 p-y	% cohort	Number fracture	Rate/100 p-y
Complete cohort	100	225	0.77	100	177	0.90	100	23	0.64
Cohort entry 2000–2004	78	166	0.78	73	113	0.86	0		
Cohort entry 2005–2006	22	59	0.74	27	64	0.97	100	23	0.64
Age 65–74 years	49	38	0.26	47	33	0.35	53	5	0.26
Age 75 and over	51	187	1.26	53	144	1.38	47	18	1.07
Glucocorticoid use	5	20	1.26	6	18	1.55	6	1	–
No glucocorticoid use	95	205	0.74	94	159	0.86	94	22	0.65
Hormone therapy use	14	23	0.55	12	9	0.37	9	1	–
No hormone use	86	202	0.81	88	168	0.97	91	22	0.68
Prior clinical fracture ^a	9	49	1.86	9	32	1.85	7	1	–
No fracture	91	176	0.66	91	145	0.81	93	22	0.66
Prior bisphosphonate use ^b	7	19	0.90	13	28	1.09	40	10	0.71
No prior use	93	206	0.76	87	149	0.87	60	13	0.60

p-y person-years. The calculation of rate is based on the number of fractures divided person-years of observation during first 3 months after starting therapy. No rates reported for three or less fractures

^a In the 6 months before cohort entry, any clinical fracture diagnosis at the hip, clavicle, wrist, humerus, leg, pelvis, or vertebral sites

^b In the 4 years before cohort entry, use of any bisphosphonate regardless of duration of administrative billing data before cohort entry.

Baseline incidence of hip fractures

During the 3 months after starting therapy in all three cohorts, the incidence of hip fractures was higher among those of greater age, prior fracture history, and glucocorticoid use, and lower among those with use of hormone replacement therapy (Table 2). During these 3 months, patients receiving risedronate had an incidence of hip fractures that was 141% of the incidence among those receiving ibandronate and 117% of the incidence among those receiving alendronate. After statistically adjusting (by direct standardization to risedronate cohort) for age, fracture history, and prior bisphosphonate use, patients receiving risedronate had an incidence of hip fractures that was 132% of the incidence among those receiving ibandronate and 114% of the incidence among those receiving alendronate.

Change in fracture incidence over time

After the initial 3-month period, the incidence of fractures was observed in the subsequent 1 year while on therapy. Relative to the baseline incidence of the initial 3-month period, the incidence of clinical fractures at the hip, vertebral, and nonvertebral sites was significantly lower in the subsequent 12 months in both cohorts of alendronate and risedronate (Table 3). The incidence of vertebral fractures in the subsequent 1 year was lower in the ibandronate cohort.

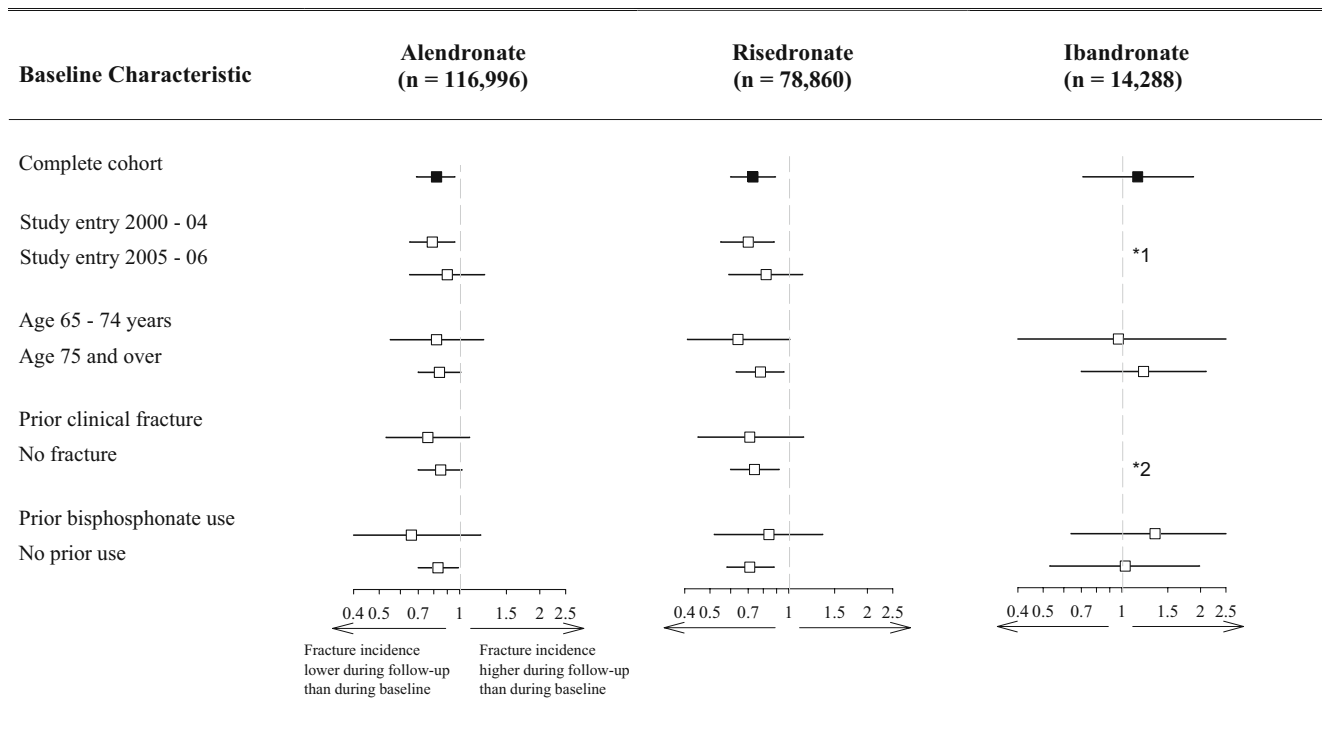
We examined whether different levels of fracture risk at the start of therapy modified the longitudinal change in fracture incidence—by using stratification to limit the analyses to subgroups of similar baseline characteristics of fracture risk. The strata were based upon prior clinical fracture (yes or no), prior bisphosphonate use (yes or no), age (one quantile above or below population median of 75 years), and date of study entry (period before or after all three therapies were on the market). For every subgroup, its 95% confidence interval included the point estimate of overall analyses (Fig. 2).

Discussion

In this observational study of cohorts containing patients starting alendronate, risedronate, or ibandronate, there were apparent differences among the cohorts in age and prior fracture history, in prior use of bisphosphonates, and in the fracture incidence during the short period after starting therapy and before any expected clinical benefit. These differences in the risk profile of patients prescribed each bisphosphonate are significant for the consideration of bias in interpretation of results of any observational study of bisphosphonates.

Table 3 Incidence of clinical fractures in the 3 months after starting therapy and subsequent 1 year on therapy

Cohort (cohort size)	Fracture site	Baseline		Follow-up			Ratio (95% CI) of fracture incidence for follow-up/baseline	
		Three-month period after starting therapy			Subsequent 1-year period on therapy			
		Number of subjects with fracture	Person-years of observation	Fracture incidence per 100 person-years	Number of subjects with fracture	Person-years of observation		Fracture incidence per 100 person-years
Alendronate (<i>n</i> =116,996)	Nonvertebral	1,026	29,249	3.51	1,524	60,108	2.52	0.72 (0.67–0.78)
	Hip	225	29,249	0.77	378	60,108	0.63	0.82 (0.69–0.96)
	Vertebral	736	29,249	2.52	647	60,108	1.08	0.43 (0.38–0.48)
Risedronate (<i>n</i> =78,860)	Nonvertebral	669	19,715	3.39	1,021	38,140	2.68	0.79 (0.72–0.87)
	Hip	177	19,715	0.90	250	38,140	0.66	0.73 (0.60–0.89)
	Vertebral	499	19,715	2.53	442	38,140	1.16	0.46 (0.40–0.52)
Ibandronate (<i>n</i> =14,288)	Nonvertebral	113	3,572	3.16	212	7,274	2.91	0.92 (0.73–1.16)
	Hip	23	3,572	0.64	54	7,274	0.74	1.15 (0.71–1.88)
	Vertebral	87	3,572	2.43	122	7,274	1.68	0.69 (0.52–0.91)



*1 Not applicable

*2 Rate ratios not reported when ≤ 3 hip fractures in either baseline or follow-up period

Fig. 2 Ratio and 95% confidence interval of hip fracture incidence for subsequent 1 year on therapy (follow-up) versus 3-month period after starting therapy (baseline)—subgroup analyses

In this study and prior studies [7, 20, 22, 23], the inclusion criterion for new use of bisphosphonate was defined by a subject having at least 6 months of no other bisphosphonate use. In order to further evaluate this criterion, we were able to examine up to four prior years for a subset of the population. As evident by the large number of ibandronate patients in this study with prior bisphosphonate use, the six month criterion was not always adequate to truly define new users of bisphosphonates. Indeed, the median gap between stopping and restarting bisphosphonate therapy has been reported to be 16 months [33]. Since bisphosphonates have residual treatment effects, for example, alendronate has effects for up to 5 years after stopping treatment [34], it may not be readily possible to disentangle the fracture outcome with the current bisphosphonate exposure from past bisphosphonate exposure [35].

The study approach to account for differences in patient profiles is often techniques of regression modeling, propensity score modeling, or instrument variable analysis [36]. However, statistical techniques cannot exclude the possibility of bias arising from the nonrandom allocation of subjects [37]. In the current study, given the differences between cohorts in patient profiles including prior use of

bisphosphonates, we proposed a study design that estimated bisphosphonate effectiveness by measuring the change in fracture incidence over time within a cohort. In such an approach, the cohort population receiving the same therapy is its own control, thus limiting the potential bias associated with a comparison of outcomes between cohorts.

In this study, two observations suggested that change in fracture incidence over time within a cohort may indeed be utilized to measure bisphosphonate effectiveness. The first observation supporting the study design was that the baseline fracture incidence during the initial 3 months after starting therapy accurately reflected the underlying risk of cohort. During this baseline period, the incidence of hip fractures corresponded with well-accepted risk factors for fracture, including age, prior fracture history, and glucocorticoid use [38]. These relationships between risk factors and fracture incidence were consistently observed across all three cohorts (Table 2). The second observation supporting the study design was the consistency in results between this observational study and the prospectively planned analyses of respective phase III randomized controlled trials [39–45]. As summarized in a government-funded systematic review of bisphosphonates [46], alendronate, risedronate, and ibandronate have all been shown to reduce vertebral

fractures, while only alendronate and risedronate have been shown to reduce nonvertebral fractures, including hip fractures. Of note, the results of subgroup [45] or post hoc [47] analyses of randomized controlled trial data have suggested a reduction of nonvertebral fractures among subjects using ibandronate. To date, no data from randomized controlled trials appear available in the literature concerning hip fractures and ibandronate.

There are several limitations in interpretation of change in fracture incidence as a measure of bisphosphonate effectiveness. One limitation arises from the differences in risk profile of patients between cohorts. It is conceivable that the lack of an observable effectiveness on nonvertebral fractures for ibandronate could relate to the lower risk profile of those patients. In a study of another bisphosphonate, clodronate, the magnitude of fracture reduction was greatest among those at highest probability of fracture [48]. Another limitation in interpretation of results comes from the relatively small sample size of ibandronate cohort relative to the other cohorts. Hence, the 95% confidence interval (0.71–1.88) around the estimate of longitudinal change in hip fracture incidence was the widest in the ibandronate cohort. A third limitation in interpretation of results is the data source does not indicate the reason starting therapy (e.g., post-menopausal osteoporosis or glucocorticoid-induced osteoporosis), hence these results may not generalize to defined populations. An additional limitation in interpretation may arise from misclassification of outcomes. In a prior study, the proportion of fracture claims confirmed by chart review to be a fracture was highest for the hip relative to other fracture sites [49]. Since the effect of misclassification of outcomes is likely no different between cohorts (i.e., misclassification does not depend on cohort), the study results for the measure of nonvertebral sites and for vertebral sites are likely more attenuated by misclassification than results at the hip.

In conclusion, for this large observational study of more than 200,000 bisphosphonate patients, the apparent differences in the baseline incidence of hip fractures among the alendronate, risedronate, and ibandronate cohorts likely reflect differences in the risk profile of patients prescribed each bisphosphonate. Statistical adjustments could not account for these differences and therefore the design of epidemiological studies should be given careful consideration to account for these differences. Relative to the baseline fracture incidence, the longitudinal analyses indicated that alendronate and risedronate decreased nonvertebral and hip fractures over time, whereas ibandronate did not. All three bisphosphonates decreased vertebral fractures. The reductions observed in fracture incidence over time within each cohort suggest that the effectiveness of each bisphosphonate in clinical practice has been

consistent with their efficacies demonstrated in randomized controlled trials.

Acknowledgement Funding by The Alliance for Better Bone Health (Procter & Gamble Pharmaceuticals and sanofi-aventis).

Conflicts of interest Dr. Abelson reports receiving consulting fees from sanofi-aventis, Procter & Gamble, Novartis; serving on speaker's bureaus for Amgen, Procter & Gamble, Roche, Novartis, and sanofi-aventis. Dr. Gold reports receiving consulting or advisory committee fees from Amgen, Eli Lilly, GlaxoSmithKline, Merck, Procter & Gamble, Roche, sanofi-aventis; serving on speaker's bureaus for Amgen, Eli Lilly, GlaxoSmithKline, Procter & Gamble, Roche, and sanofi-aventis. Dr. Thomas reports receiving consulting or advisory committee fees from Amgen, Daichi-Sankyo, Ipsen, Lilly, MSD, Novartis, Procter & Gamble, Roche/GlaxoSmithKline, sanofi-aventis, and Servier; grant support from Lilly, MSD, Nicomed, Novartis, Procter & Gamble, sanofi-aventis, and Servier. Dr. Lange is an employee of Procter & Gamble.

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