Fractures and mortality in relation to different osteoporosis treatments

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Abstract

Objective

Few studies have assessed the effectiveness of different drugs for osteoporosis (OP). We aimed to determine if fracture and mortality rates vary among patients initiating different OP medications.

Methods

We used the Medicare 5% sample to identify new users of intravenous (IV) zoledronic acid (n=1.674), oral bisphosphonates (n=32.626), IV ibandronate (n=492), calcitonin (n=2.606), raloxifene (n=1.950), or parathyroid hormone (n=549). We included beneficiaries who were ≥65 years of age, were continuously enrolled in fee-for-service Medicare and initiated therapy during 2007–2009. Outcomes were hip fracture, clinical vertebral fracture, and all-cause mortality, identified using inpatient and physician diagnosis codes for fracture, procedure codes for fracture repair, and vital status information. Cox regression models compared users of each medication to users of IV zoledronic acid, adjusting for multiple confounders.

Results

During follow-up (median, 0.8–1.5 years depending on the drug), 787 subjects had hip fractures, 986 had clinical vertebral fractures, and 2.999 died. Positive associations included IV ibandronate with hip fracture (adjusted hazard ratio (HR), 2.37; 95% confidence interval (CI) 1.25–4.51), calcitonin with vertebral fracture (HR=1.59, 95%CI 1.04–2.43), and calcitonin with mortality (HR=1.31; 95%CI 1.02–1.68). Adjusted HRs for other drug-outcome comparisons were not statistically significant.

Conclusion

IV ibandronate and calcitonin were associated with higher rates of some types of fracture when compared to IV zolendronic acid. The relatively high mortality associated with use of calcitonin may reflect the poorer health of users of this agent.

Key words

comparative effectiveness, osteoporosis medications, fracture, all-cause mortality

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Introduction

Osteoporosis is a condition defined by low bone mass and micro architectural deterioration of bone tissue, which may lead to an increased risk of fracture in patients and a substantial economic burden at hospital (1-3). Drugs approved by the Food and Drug Administration for the prevention and/or treatment of postmenopausal osteoporosis include bisphosphonates (alendronate, oral and infusion [IV] ibandronate, risedronate and IV zoledronic acid), calcitonin, raloxifene, parathyroid hormone, and denosumab. Among these, bisphosphonates have become established as first-line treatments (4-6). Few randomised clinical trials (RCTs) compared the agents to one another, and most were not powered to detect effects on fracture outcomes (7-10). In one observational study comparing the effectiveness of raloxifene to bisphosphonates or calcitonin in reducing non-vertebral fracture risk, differences among the three agents were minimal (11). Curtis *et al*. reported similar absolute rates of clinical fractures among users of alendronate and risedronate (12). Neither study evaluated parenteral bisphosphonates. The population in the latter study was relatively young and healthy, and results may not apply to older patients with osteoporosis. Thus, the comparative effectiveness of parenteral bisphosphonates remains unclear.

The efficacy of osteoporosis medications may be comparable if the medications are taken under ideal conditions. However, adherence and other factors are relevant in considering if efficacy results observed in RCTs translate into effectiveness in the real world. Infusion and injection drugs including IV ibandronate (infusion every three months), IV zoledronic acid (infusion annually) and denosumab (subcutaneous injection every six months) may improve adherence by avoiding the more complex dosing instructions and more frequent dosing frequency necessary for oral bisphosphonates and may reduce the risk of adverse upper gastrointestinal events that can lead to discontinuation (13). Better adherence may, in turn, enhance treatment effectiveness of treatment in reducing fractures (14, 15) and mortality.

In this study, we compared the effectiveness of IV zoledronic acid to that of other types of osteoporosis medications among Medicare beneficiaries. We hypothesised that IV zoledronic acid users would have lower rates of incident clinical fractures (hip, vertebral) and lower mortality compared to users of other osteoporosis medications. Several reports have noted that users of oral bisphosphonates, compared to non-users, may have a lower incidence of all-cause mortality (16-20). Users of alendronate have been observed to have a lower incidence of acute myocardial infarction (AMI) than raloxifene users (20). Thus, to further understand the mediating factors that could underlie a potential mortality benefit for bisphosphonates, we also evaluated the relation between osteoporosis medications and AMI.

Methods

Study design and data sources

This cohort study used claims from 2006 through 2009 (the time period for which the necessary data were available) for a 5% random sample of Medicare beneficiaries, obtained from the Centres for Medicare and Medicaid Services (CMS) Chronic Condition Data Warehouse (21). The data included Medicare enrolment files, hospital (Part A) and outpatient medical care (Part B) claims, and claims for prescription drugs (Part D). The institutional review board of the University of Alabama at Birmingham approved the study.

Eligibility

Eligible subjects were 65 years of age or older; lived in the United States; were continuously enrolled in traditional Medicare Parts A, B and D; and were newly treated with IV zoledronic acid, IV ibandronate, oral bisphosphonates (oral ibandronate, alendronate, risedronate), calcitonin, raloxifene, or parathyroid hormone during the period 2007 to 2009. New treatment was therapy initiated after a baseline period of 12 months during which no osteoporosis medication prescription was filled or infusion given. The earliest baseline start date was January 1, 2006, and the earliest date of initiating one of the drugs of interest was, therefore, January 1, 2007.

We excluded individuals taking bisphosphonates at doses approved for Paget's disease.

Osteoporosis medication exposures

We identified users of osteoporosis medications using pharmacy and infusion claims. For drugs filled at outpatient pharmacies, we computed days of medication exposure using days of supply for each prescription. For infusion drugs, we assigned days of exposure based upon the suggested dosing intervals (90 days for IV ibandronate, 365 days for zoledronic acid). For analytical purposes, we determined if the patient became non-adherent by computing time-varying medication possession ratios (MPRs) on each day of observation after treatment initiation as the number of days exposed since initiation divided by the total time since initiation (22, 23). A subject was considered non-adherent when the MPR was <80%.

Outcomes

Outcomes of interest were hip fracture, clinical vertebral fracture, death from any cause and AMI. We identified fractures using inpatient, outpatient and physician claims and adaptations of validated algorithms that compared claims data to the gold standard of medical record review. These algorithms have positive predictive values of 98% for hip fracture, (24) and 61% for clinical vertebral fracture (25). We identified mortality using vital status information included in Medicare enrolment files. We defined AMI as a hospitalisation lasting at least three days and no more than 180 days with a primary discharge diagnosis code indicating AMI. This algorithm has positive predictive value of 94% (26, 27).

Covariates

The demographic characteristics considered as potential confounders included gender, self-reported race, age, geographic region of residence, and area-level income as of the first treatment date. We developed data on all other potential confounders listed in Table I using inpatient, outpatient hospital, physician and drug claims during the 12-month baseline period preceding osteoporosis treatment initiation.

Analysis

We computed person-years of follow-up for each subject, starting on the earliest treatment initiation date during the period January 1, 2007–December 31, 2009, and ending on the earliest date corresponding to loss of coverage, occurrence of the outcome of interest, death or end of the study period. In the primary, intention-to-treat analysis we classified all follow-up time of a subject according to the first osteoporosis medication initiated and ignored adherence or switching.

We determined the distribution of subjects in each medication cohort by age, gender, geographic region, median income in zip code of residence, comorbidities, history of fractures, costs, service utilisation, and other medication use. Using Cox regression with days since entering a medication cohort as the time scale, we estimated the hazard ratio (HR) for hip fracture, clinical vertebral fracture, AMI and all-cause mortality for each medication compared to IV zoledronic acid, adjusting for all potential confounders described above. We chose IV zoledronic acid users as the referent category because IV zoledronic acid was newly approved and had the least amount of published comparative data available, and we hypothesised that users of this medication would have lower rates of incident fractures and mortality compared to other osteoporosis therapies. We assessed the proportional hazards assumption using cumulative sum of martingale residuals over follow-up time or covariate values and did not identify any violation of this assumption (28).

We conducted an as-treated analysis among adherent patients with adjustment for the same factors in the intention-to-treat analysis. Because previous research has suggested that the risk of fractures is increased for MPRs below 80% (29, 30), we censored subjects in each medication cohort when they became non-adherent, *i.e.* their MPR declined below 80%, or when they switched to other osteoporosis drugs.

We also conducted several sensitivity analyses. We used propensity score methods to control for multiple confounders (31). For these analyses, we used logistic regression to estimate the predicted probability of exposure to a particular osteoporosis drug referent to IV zoledronic acid and used greedy matching to select 1:1 propensity score-matched exposure cohorts. We also conducted analyses of subgroups defined on the basis of history of fractures and analyses that excluded the first six months of follow-up, as fracture risk reduction within 6 months after starting an osteoporosis drug is uncertain (32).

Results

A total of 1.674 subjects were new users of IV zoledronic acid, 492 new users of IV ibandronate were identified, along with 32.626, 1.956, 2.606 and 549 new users of oral bisphosphonates, raloxifene, calcitonin and parathyroid hormone, respectively (Table I). The average length of follow-up ranged from 0.8 to 1.5 years among the six medication cohorts. IV zoledronic acid, IV ibandronate, and oral bisphosphonate cohorts had a median age of 78 years; calcitonin users had the oldest median age of 82; and raloxifene users had the youngest median age of 76. Compared to IV zoledronic acid users, oral bisphosphonate users were less likely to be female and white, and raloxifene users were less likely to be white. Among the six cohorts, the proportion of new users with a prior fracture was 26–28% among calcitonin and parathyroid hormone users but only 6–14% among new users of other osteoporosis medications. The proportion of new users with a DXA test during baseline varied from 28% for calcitonin users to 68% for parathyroid hormone users. The proportion of each cohort with long-term care during baseline was highest in calcitonin (25%) and parathyroid hormone users (18%) and lowest in raloxifene group (5%). Calcitonin and parathyroid hormone users were also more likely than other cohorts to have been hospitalised in the 12-month baseline period. Compared to other groups, the calcitonin users were more likely to have used several medications that negatively affect bone, and they had higher Charlson comorbidity scores.

Across all cohorts, 787 subjects had hip fractures, 986 had vertebral fractures,

Table I. Baseline characteristics[a] of new users of six osteoporosis drugs among Medicare beneficiaries during the period 2006–2009.

	IV Zoledronic acid n=1674(%)	IV Ibandronate n=492 (%)	Oral bisphos-phonates n=32626 (%)	Raloxifene n=1950 (%)	Calcitonin n=2606 (%)	Parathyroid hormone n=549 (%)
Follow-up years, median (IQR)	0.8 (1.0)	1.5 (1.5)	1.4 (1.3)	1.5 (1.4)	1.4 (1.3)	1.3 (1.5)
Fracture during baseline	165 (9.9)	67 (13.6)	3326 (10.2)	107 (5.5)	691 (26.5)	151 (27.5)
Osteoporosis during baseline	811 (48.4)	197 (40.0)	7860 (24.2)	463 (23.7)	720 (27.6)	307 (55.9)
History of DXA	960 (57.3)	318 (64.6)	18538 (56.8)	983 (50.4)	716 (27.5)	371 (67.6)
Female	1581 (94.4)	451 (91.7)	29.129 (89.3)	1937 (99.3)	2327 (89.3)	491 (89.4)
White	1587 (94.0)	457 (92.9)	27017 (82.8)	1608 (82.5)	2344 (89.9)	453 (82.5)
Age, years, mean (SD)	78 (6.4)	78 (6.7)	78 (7.0)	76 (6.8)	81 (7.7)	79 (7.2)
Income of residence, $, mean (SD)	45153 (20452)	47797 (25508)	45136 (22693)	43283 (21606)	43529 (21476)	43883 (23802)
Hospitalisation at baseline	374 (22.3)	124 (25.2)	8138 (24.9)	342 (17.5)	1176 (45.1)	215 (39.2)
Long-term care at baseline	96 (5.7)	37 (7.5)	2758 (8.5)	96 (4.9)	646 (24.8)	101 (18.4)
Geographic region						
Midwest	496 (29.62)	115 (23.4)	7784 (23.9)	385 (19.7)	680 (26.1)	97 (17.7)
Northeast	209 (12.48)	87 (17.7)	5705 (17.5)	346 (17.7)	436 (16.7)	77 (14.0)
South	762 (45.51)	200 (40.7)	12881 (39.5)	892 (45.7)	1082 (41.5)	311 (56.6)
West	207 (12.36)	90 (18.3)	6256 (19.2)	327 (16.8)	408 (15.7)	64 (11.7)
Comorbidities during baseline						
Glucocorticoid-related (summary indicator)	485 (29.0)	173 (35.2)	7580 (23.2)	362 (18.6)	773 (29.7)	192 (35.0)
Bone disease-related	38 (2.3)	11 (2.2)	583 (1.8)	24 (1.2)	45 (1.7)	<11 (1.8)
Diabetes mellitus	251 (15.0)	62 (12.6)	6574 (20.1)	319 (16.4)	554 (21.3)	106 (19.3)
Renal disease	90 (5.4)	20 (4.1)	1628 (5.0)	90 (4.6)	285 (10.9)	40 (7.3)
Other bone mass-related	448 (26.8)	111 (22.6)	9745 (29.9)	530 (27.2)	895 (34.3)	165 (30.1)
Fall-related conditions	416 (24.9)	107 (21.7)	7406 (22.7)	380 (19.5)	934 (35.8)	186 (33.9)
Depressive illness	104 (6.2)	36 (7.3)	2472 (7.6)	113 (5.8)	339 (13.0)	68 (12.4)
Stroke	70 (4.2)	21 (4.3)	1597 (4.9)	77 (3.9)	191 (7.3)	47 (8.6)
Chronic obstructive pulmonary disease	297 (17.7)	95 (19.3)	5456 (16.7)	277 (14.2)	605 (23.2)	141 (25.7)
Medications during baseline						
Anti-epileptics	238 (14.2)	72 (14.6)	3839 (11.8)	194 (9.9)	417 (16.0)	91 (16.6)
Anti-depression	510 (30.5)	171 (34.8)	8997 (27.6)	477 (24.5)	993 (38.1)	201 (36.6)
Anti-psychotics	42 (2.5)	12 (2.4)	1288 (3.9)	44 (2.3)	220 (8.4)	42 (7.7)
Beta-blocker	647 (38.6)	177 (36.0)	12088 (37.1)	642 (32.9)	1150 (44.1)	196 (35.7)
Anti-dementia	103 (6.2)	17 (3.5)	2325 (7.1)	93 (4.8)	319 (12.2)	66 (12.0)
Alpha-blocker	21 (1.3)	<11 (1.2)	587 (1.8)	19 (1.0)	56 (2.1)	<11 (1.5)
Angiotensin converting enzyme inhibitor	446 (26.6)	121 (24.6)	9567 (29.3)	453 (23.2)	776 (29.8)	150 (27.3)
Angiotensin receptor blocker	273 (16.3)	95 (19.3)	5331 (16.3)	328 (16.8)	416 (16.0)	87 (15.8)
Calcium channel blocker	392 (23.4)	134 (27.2)	8460 (25.9)	474 (24.3)	744 (28.5)	157 (28.6)
Non-steroidal anti-inflammatory drugs	330 (19.7)	77 (15.7)	6268 (19.2)	362 (18.6)	430 (16.5)	117 (21.3)
Statin	681 (40.7)	202 (41.1)	15658 (48.0)	858 (44.0)	1026 (39.4)	231 (42.1)
Other lipid lowering drugs	152 (9.1)	47 (9.6)	3234 (9.9)	148 (7.6)	314 (12.0)	71 (12.9)
Steroid	472 (28.2)	155 (31.5)	7127 (21.8)	406 (20.8)	1200 (46.0)	154 (28.0)
Hormone therapy	124 (7.4)	47 (9.6)	1918 (5.9)	147 (7.5)	142 (5.4)	32 (5.8)
Charlson score at baseline						
0	654 (39.1)	187 (38.0)	13277 (40.7)	896 (45.9)	773 (29.7)	176 (32.1)
1–2	705 (42.1)	196 (39.8)	12975 (39.8)	762 (39.1)	941 (36.1)	214 (39.0)
>=3	315 (18.8)	109 (22.2)	6374 (19.5)	292 (15.0)	892 (34.2)	159 (29.0)

[a]Number of subjects (%) unless otherwise indicated.

426 experienced AMIs, and 2.999 died during follow-up (Table II). Multivariable Cox regression analyses of hip fracture indicated that HRs for oral bisphosphonate, calcitonin, raloxifene and parathyroid hormone users were numerically greater than those of IV zoledronic acid users, but these results were not statistically significant. In contrast, IV ibandronate users had a statistically significantly increased HR for hip fracture of 2.37 (95%CI 1.25–4.51) when compared to IV zoledronic acid users. For clinical vertebral fracture, adjusted HRs were 1.03 (95%CI 0.69–1.53), 1.07 (95%CI 0.65–1.76), and 1.04 (95%CI 0.57–1.89), respectively, for oral bisphosphonates, raloxifene, and parathyroid hormone compared to IV zoledronic acid. HRs were 1.59 (95%CI 1.04–2.43) for calcitonin and 1.41 (95%CI 0.77–2.57) for IV ibandronate. For all-cause mortality, adjusted HRs were 0.92 (95%CI 0.72–1.16), 0.91 (95%CI 0.60–1.38), and 0.84 (95%CI 0.62–1.13), respectively, for oral bisphosphonate, IV ibandronate and raloxifene, compared to IV zoledronic acid. Adjusted HRs were 1.32 (95%CI 1.02–1.68) for calcitonin and 1.32 (95%CI

Table II. Events, crude rate, crude and adjusted hazard ratio (HR) and 95% confidence interval (CI) for hip fracture, vertebral fracture, mortality and acute myocardial infarction among new users of osteoporosis medications.

Medications	Events	Crude rate per 100 PY[a]	Crude HR (CI)	Adjusted HR[b] (CI)
		Hip Fracture		
IV zoledronic acid	19	1.25	1.0 (Ref)	1.0 (Ref)
IV ibandronate	19	2.68	2.19 (1.15–4.14)	2.37 (1.25-4.51)
Oral bisphosphonate	599	1.28	1.05 (0.66–1.66)	1.22 (0.77–1.95)
Calcitonin	100	2.64	2.16 (1.32–3.53)	1.39 (0.83–2.30)
Raloxifene	36	1.19	0.97 (0.56–1.70)	1.32 (0.75–2.33)
Parathyroid hormone	14	1.79	1.46 (0.73–2.93)	1.12 (0.55–2.26)
		Vertebral Fracture		
IV zoledronic acid	27	1.80	1.0 (Ref)	1.0 (Ref)
IV ibandronate	18	2.52	1.50 (0.82–2.72)	1.41 (0.77–2.57)
Oral bisphosphonate	694	1.49	0.89 (0.60–1.30)	1.03 (0.69–1.53)
Calcitonin	149	4.00	2.38 (1.58–3.59)	1.59 (1.04–2.43)
Raloxifene	40	1.32	0.79 (0.48–1.30)	1.07 (0.65–1.76)
Parathyroid hormone	19	2.49	1.48 (0.82–2.66)	1.04 (0.57–1.89)
		Mortality		
IV zoledronic acid	76	5.00	1.0 (Ref)	1.0 (Ref)
IV ibandronate	33	4.54	0.84 (0.55–1.26)	0.91 (0.60–1.38)
Oral bisphosphonate	2199	4.68	0.87 (0.69–1.09)	0.92 (0.72–1.16)
Calcitonin	517	13.35	2.47 (1.94–3.15)	1.31 (1.02–1.68)
Raloxifene	101	3.31	0.61 (0.45–0.82)	0.84 (0.62–1.13)
Parathyroid hormone	73	9.27	1.72 (1.24–2.37)	1.32 (0.95–1.84)
		Acute Myocardial Infarction		
IV zoledronic acid	<11	0.39	1.0 (Ref)	1.0 (Ref)
IV ibandronate	<11	0.41	1.06 (0.26–4.24)	1.00 (0.25–4.04)
Oral bisphosphonate	337	0.72	1.84 (0.82–4.12)	1.74 (0.77–3.93)
Calcitonin	57	1.48	3.80 (1.63–8.82)	2.51 (1.06–5.91)
Raloxifene	14	0.46	1.17 (0.45–3.06)	1.30 (0.49–3.43)
Parathyroid hormone	<11	1.14	2.93 (1.04–8.24)	2.41 (0.85–6.86)

[a] Person-years.

[b]Adjusted for age, gender, race, geographic region, income, osteoporosis related conditions, glucocorticoid-related disease, bone disease related, diabetics, renal disease, fall related conditions, cancer, acute myocardial infarction, depressive illness, other heart problems and medications including hormone therapy at baseline.

0.95–1.84) for parathyroid hormone.

The HRs for AMI were numerically higher for all medication exposures compared to zoledronic acid. Calcitonin users had a significantly higher adjusted rate of AMI (HR 2.51; 95%CI 1.06–5.91). Of note, there were few AMI events (<11) in the IV zoledronic acid group.

Results of the as-treated secondary analysis that censored patients at the time they became non-adherent and of additional sensitivity analyses (*e.g.* propensity score-matched) were similar qualitatively to those of the main, intention-to-treat analyses (Fig. 1–3), with few exceptions. The positive association between IV ibandronate and hip fracture persisted in the as-treated analysis (adjusted HR 2.85; 95%CI 1.52–5.32) and was present but not statistically significant in the propensity-score matched (adjusted HR 2.71; 95%CI 0.72–7.22) and subgroup analyses (adjusted HR 1.63; 95%CI 0.78–3.42). Sensitivity analysis results for calcitonin and vertebral fracture differed little from those of the main analysis. For calcitonin and mortality, propensity score-matched and as-treated analysis results and results for the subgroup without a history of fracture at baseline were similar to those of the main analysis. However, calcitonin was not associated with mortality in the analysis that excluded the first six months of follow-up (adjusted HR 1.08; 95%CI 0.80–1.47).

Discussion

In this observational study of Medicare patients initiating various osteoporosis therapies in 2007–2009, we found that oral bisphosphonate, raloxifene and parathyroid hormone users had adjusted HRs of hip fracture, clinical vertebral fracture and mortality that were not statistically significantly different from those of IV zoledronic acid users. Although IV ibandronate users did not differ significantly from IV zoledronic acid users with respect to vertebral fracture or mortality, they had a significantly higher rate of hip fracture. Calcitonin users had a higher rate of clinical vertebral fracture and of mortality. We also observed a higher rate of AMI among calcitonin users compared to IV zoledronic acid users.

RCTs and meta-analyses (33, 34) have shown that compared to no treatment, use of alendronate, risedronate and IV zoledronic acid reduces the risk of hip fracture in postmenopausal osteoporosis patients, and all osteoporosis drugs are efficacious in preventing vertebral fractures (35). The established evidence of efficacy and safety of osteoporosis medications in RCTs may not predict their actual effectiveness in clinical practice because of differences in patient characteristics and suboptimal persistence and adherence. Several retrospective cohort studies showed similar fracture rates for users of oral alendronate, risedronate, ibandronate or raloxifene (11, 12, 36). And our observation of similar hip and vertebral fracture rates among oral bisphosphonate and raloxifene users is consistent with these observations.

Previous efficacy analyses have suggested that although all osteoporosis medications reduced fracture risk when compared to placebo, the beneficial effect on hip fracture was weakest for IV ibandronate (37). The latter finding is consistent with our observation that compared to IV zoledronic acid users, IV ibandronate users had a significantly higher rate of hip fracture, while new users of oral bisphosphonate, parathyroid hormone, calcitonin, or raloxifene had similar rates. Our results for calcitonin and hip fracture are not consistent with a study by Cadarette *et al.* that found a higher rate of hip fracture among calcitonin compared to alendronate users in elderly residents of New Jersey and Pennsylvania (11) but is

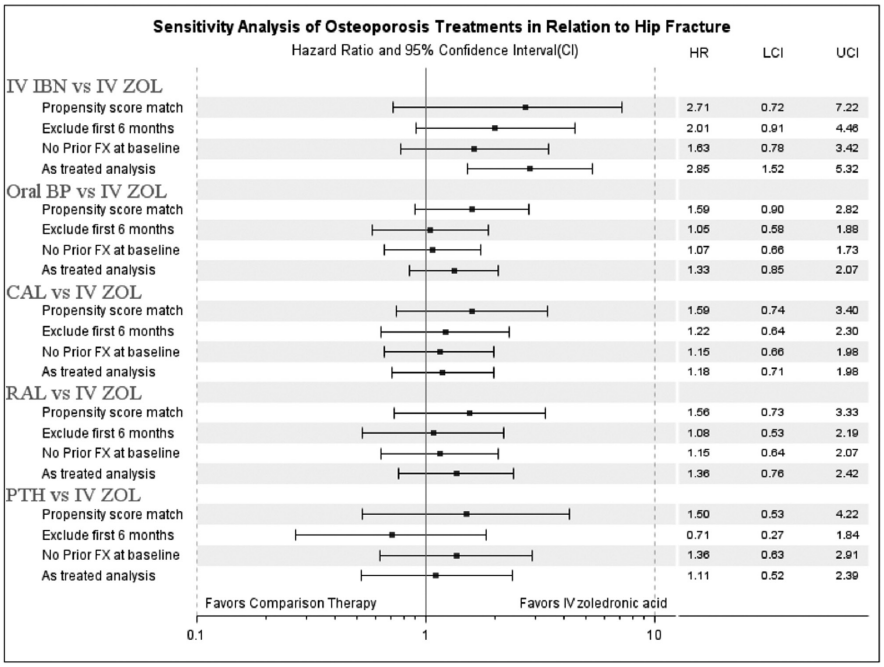

Fig. 1. Sensitivity analysis of osteoporosis treatments in relation to hip fracture.
IV ZOL: intravenous zoledronic acid; IV IBN: intravenous ibandronate; BP: bisphosphonate; CAL: calcitonin; RAL: raloxifene; PTH: parathyroid hormone.
HR: hazard ratio; LCI: lower confidence interval, UCI: upper confidence interval.

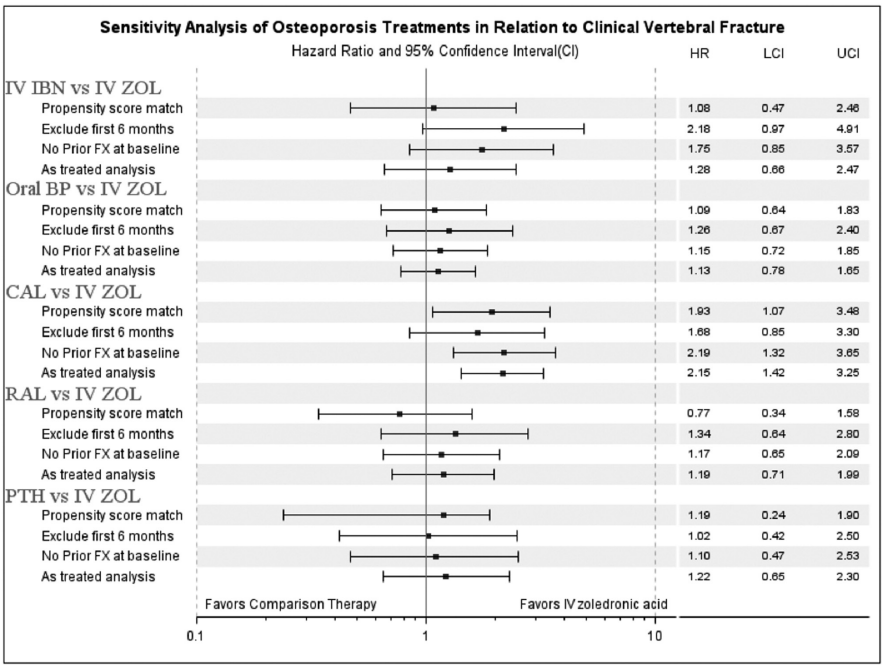

Fig. 2. Sensitivity analysis of osteoporosis treatments in relation to clinical vertebral fracture.
IV ZOL: intravenous zoledronic acid; IV IBN: intravenous ibandronate; BP: bisphosphonate; CAL: calcitonin; RAL: raloxifene; PTH: parathyroid hormone.
HR: hazard ratio; LCI: lower confidence interval, UCI: upper confidence interval.

consistent with a previous observational study suggesting no large difference between calcitonin and alendronate recipients (38).

Hopkins *et al*. reviewed the literature on the efficacy of nine anti-osteoporosis medications and showed that vertebral fracture risk reduction was likely to be greatest for parathyroid hormone, IV zoledronic acid, and denosumab (39). MacLean *et al*., in a systematic review, reported that the vertebral fracture reduction was not as convincing for calcitonin as for zoledronic acid users (35). Our findings suggest that IV zoledronic acid, as well as parathyroid hormone, might have greater effectiveness than calcitonin in reducing clinical vertebral fractures, but these results should be interpreted with caution because of study limitations discussed below.

Several studies have reported that compared to no treatment, IV zoledronic acid and oral bisphosphonates were associated with reductions in all-cause mortality after fractures (16-20). Although the apparent protective effect may be due in part to the suppression of bone turnover and the prevention of new fractures, other mechanisms are possible and perhaps even more likely given that most patients who died did not experience a new fracture (40). Specifically, bisphosphonates appear to have a favourable impact on several components of the atherogenic process including monocyte adhesion to the endothelial surface, platelet aggregation, vascular smooth muscle cell proliferation, and vasoconstriction (41, 42). We found that compared to IV zoledronic acid users, calcitonin users had a higher rate of mortality, while IV ibandronate, oral bisphosphonate, and raloxifene users had comparable mortality rates. We also found that calcitonin users had higher rate of AMI compared to IV zoledronic acid users, suggesting that the lower rate of mortality among IV zoledronic acid users could be partially mediated through a lower rate of AMI. AMI rates also were numerically but not significantly elevated for users of oral bisphosphonates and raloxifene when compared to IV zoledronic acid, and there were few events in the zoledronic acid group.

Our study contributes to the limited literature comparing effectiveness of all available bisphosphonates, including the more recently introduced IV zoledronic acid and IV ibandronate, and it has several additional strengths. Our study provides results that are generalisable to the entire fee-for-service Medicare population. Our new user design minimises bias compared to observational designs that include prevalent users (43). Instead of using self-reported

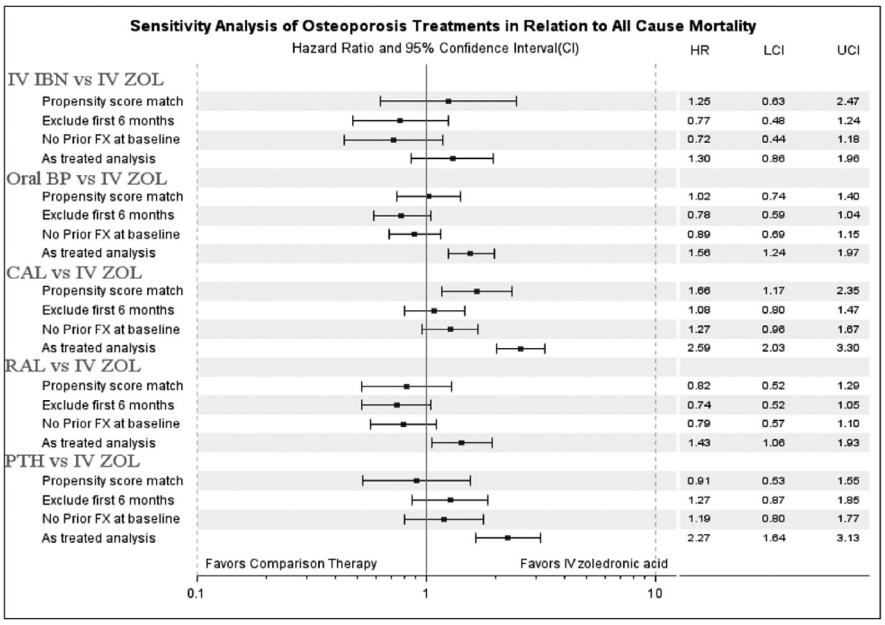

Fig. 3. Sensitivity analysis of osteoporosis treatments in telation to all-cause mortality.
IV ZOL: intravenous zoledronic acid; IV IBN: intravenous ibandronate; BP: bisphosphonate; CAL: calcitonin; RAL: raloxifene; PTH: parathyroid hormone.
HR: hazard ratio; LCI: lower confidence interval, UCI: upper confidence interval.

medications and outcomes, we used claims data to identify the drug exposure and endpoints of interest, avoiding the possibility of differential misclassification. We conducted a series of sensitivity analyses that yielded results generally similar to those of the main analysis, indicating robust relationships. Despite these strengths, our research also has several potential limitations. Some cohorts were small, yielding results that were subject to considerable statistical variability, and follow-up time was generally short. The study was observational rather than experimental, and relied on claims data that lacked detailed information on clinical and other factors that could influence the prescription of a given anti-osteoporosis medication. Thus, misclassification and residual confounding are possible. Because anti-osteoporosis medications are dispensed only with a prescription, and pharmacy dispensing information is usually seen as the gold standard compared with self-reported information (44), we believe misclassification of exposure was minimal and random in our study. We used procedures to identify the hip fracture and AMI outcomes that were based upon published algorithms for administrative data having high positive predictive values reported in validation studies (24-26). The algorithm used to detect incident vertebral fracture required a fracture diagnosis to have an accompanying imaging test, a requirement that is conservative (25). Thus, misclassification is a greater potential problem for clinical vertebral fracture than for the other outcomes. However, because of the objective nature of claims data, misclassification should be random for all of the outcomes, and the effect of such misclassification would be to minimise differences in hazard rates between zoledronic acid users and users of the other medications studied. Comparison of baseline characteristics among the various medication cohorts showed that calcitonin users were older and sicker, and raloxifene users were younger and had fewer comorbidities, than zoledronic acid or other bisphosphonate users. Also, we observed marked differences between crude and adjusted HRs for some of the exposures and outcomes, underscoring the importance of controlling for confounding. For example, adjusted HRs were substantially lower than the corresponding crude HRs for associations between calcitonin and hip fracture, vertebral fracture and mortality. Such a pattern suggests that residual confounding is a possible explanation of the positive associations seen for calcitonin, although our results were consistent in several sensitivity analyses. Factors associated with frailty, which may have been poorly measured using claims data, may be especially important in comparing these outcomes in calcitonin and IV zoledronic acid users.

Conclusion

In conclusion, the effectiveness of IV zoledronic acid appears comparable to that of osteoporosis medications other than IV ibandronate in lowering hip fracture risk. Results indicating that IV ibandronate users had higher rate of hip fracture than IV zoledronic acid users requires confirmation in larger studies with longer follow-up time. Positive associations seen for calcitonin with vertebral fracture and all-cause mortality may reflect the relatively poorer health of users of this agent.

Competing interests

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R. Mathews, L. Guo, N. Wright and W. Smith have received research support from Amgen;
C. Colón-Emeric is a consultant for Amgen and Novartis, has received a research grant from Pfizer and Novartis, and is co-founder of Cardiobis, Llc: Patent Application Co-Inventor "Bisphosphonate Compositions and Methods for Treating Heart Failure" US Patent 20100447417;
C.M. O'Connor is co-founder of Cardiobis, Llc: Patent Application Co-Inventor "Bisphosphonate Compositions and Methods for Treating Heart Failure" US Patent 20100447417;
K.W. Lyles has received: grant support in part by NIH 2P30AG028716-06 for Patent Application Co-Inventor "Bisphosphonate Compositions and Methods for Treating Heart Failure" US Research Support: Novartis, Alliance for Better Bone Health, Amgen. He is a consultant for Novartis, Procter & Gamble, Merck, Amgen, Kirin

Pharmaceutical, GTx, Eli Lilly, GSK, Bone Medical Ltd., Wyeth, Osteologix, and is co-founder of Cardiobis, Llc: Patent Application Co-Inventor "Bisphosphonate Compositions and Methods for Treating Heart Failure" US Patent 20100447417; J.R. Curtis has received grant support from the NIH (AR053351) and AHRQ (R01HS018517), research grants from Amgen, Eli Lilly, Merck, Novartis, Proctor & Gamble, and Roche, and consulting fees from Merck, Amgen, Eli Lilly, Roche, Novartis.

References

1. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of a WHO Study Group. WHO technical report series 1994; 843: 1-129.
2. NIH consensus development panel on osteoporosis prevention, diagnosis, and therapy. osteoporosis prevention, diagnosis, and therapy. *JAMA* 2001; 285: 785-95.
3. MARAVIC M, JOUANETON B, VAINCHTOCK A, TOCHON V: Economic burden of osteoporosis in women: data from the 2008 French hospital database (PMSI). *Clin Exp Rheumatol* 2012; 30: 222-7.
4. RABENDA V, HILIGSMANN M, REGINSTER J: Poor adherence to oral bisphosphonate treatment and its consequences: a review of the evidence. *Expert Opin Pharmacother* 2009; 10: 2303-15.
5. MELTON LJ, 3RD, THAMER M, RAY NF *et al*.: Fractures attributable to osteoporosis: report from the National Osteoporosis Foundation. *J Bone Miner Res* 1997; 12: 16-23.
6. PETRELLA RJ, JONES TJ: Do patients receive recommended treatment of osteoporosis following hop fracture in primary care? *BMC Family Parctice* 2006; 7.
7. HOSKING D, CHILVERS CED, CHRISTIANSEN C *et al*.: Prevention of bone loss with alendronate in postmenopausal women under 60 years of age. Early Postmenopausal Intervention Cohort Study Group. *N Engl J Med* 1998; 338: 485-92.
8. ROSEN CJ, HOCHBERG MC, BONNICK SL *et al*.: Treatment with once-weekly alendronate 70 mg compared with once-weekly risedronate 35 mg in women with postmenopausal osteoporosis: a randomized double-blind study. *J Bone Miner Res* 2005; 20: 141-51.
9. BODY JJ, GAICH GA, SCHEELE WH *et al*.: A randomized double-blind trial to compare the efficacy of teriparatide [recombinant human parathyroid hormone (1-34)] with alendronate in postmenopausal women with osteoporosis. *J Clin Endocrinol Metab* 2002; 87: 4528-35.
10. KUSHIDA K, FUKUNAGA M, KISHIMOTO H: A comparison of incidences of vertebral fracture in Japanese patients with involutional osteoporosis treated with risedronate and etidronate: a randomized, double-masked trial. *J Bone Miner Metab* 2004; 22: 469-78.
11. CADARETTE SM, KATZ JN, BROOKHART MA, STURMER T, STEDMAN MR, SOLOMON DH: Relative effectiveness of osteoporosis drugs for preventing nonvertebral fracture. *Ann Intern Med* 2008; 148: 637-46.
12. CURTIS JR, WESTFALL AO, CHENG H, SAAG KG, DELZELL E: RisedronatE and ALendronate Intervention over Three Years (REALITY): minimal differences in fracture risk reduction. *Osteoporos Int* 2008; 20: 973-8.
13. TOSTESON AN, GROVE MR, HAMMOND CS *et al*.: Early discontinuation of treatment for osteoporosis. *Am J Med* 2003; 115: 209-16.
14. MARTENS MG, SHAW H: Maximizing effectiveness of bisphosphonate therapy for osteoporosis. *South Med J* 2008; 101: 824-30.
15. REGINSTER J: Oral and intravenous ibandronate in the management of postmenopausal osteoporosis: a comprehensive review. *Curr Pharm Des* 2005; 11: 3711-28.
16. LYLES KW, COLON-EMERIC CS, MAGAZINER JS *et al*.: Zoledronic acid and clinical fractures and mortality after hip fracture. *N Engl J Med* 2007; 357: 1799-809.
17. BEAUPRE L, MORRISH D, HANLEY D *et al*.: Oral bisphosphonates are associated with reduced mortality after hip fracture. *Osteoporos Int* 2011; 22: 983-91.
18. SAMBROOK PN, CAMERON ID, CHEN JS *et al*.: Oral bisphosphonates are associated with reduced mortality in frail older people: a prospective five-year study. *Osteoporos Int* 2011; 22: 2551-6.
19. CENTER JR, BLIUC D, NGUYEN ND, NGUYEN TV, EISMAN J: Osteoporosis Medication and Reduced Mortality Risk in Elderly Women and Men. *J Clin Endocrin Metab* 2011; 96: 1006-14.
20. LU PY, HSIEH CF, TSAI YW, HUANG WF: Alendronate and Raloxifene Use Related to Cardiovascular Diseases: Differentiation by Different Dosing Regimens of Alendronate. *Clin Ther* 2011; 33: 1173-9.
21. COOPER C, ATKINSON EJ, JACOBSEN SJ, O'FALLON WM, MELTON LJ: III. Population-based survival after osteoporotic fractures. *Am J Epidemiol* 1993; 137: 1001-5.
22. CURTIS JR, XI J, WESTFALL AO *et al*.: Improving the prediction of medication compliance: the example of bisphosphonates for osteoporosis. *Med Care* 2009; 47: 334-41.
23. SIKKA R, XIA F, AUBERT R: Estimating medication persistency using administrative claims data. *Am J Manag Care* 2005; 11: 449-57.
24. RAY WA, GRIFFIN MR, FOUGHT RL, ADAMS ML: Identification of fractures from computerized Medicare files. *J Clin Epidemiol* 1992; 45: 703-14.
25. CURTIS JR, MUDANO AS, SOLOMON DH, XI J, MELTON ME, SAAG KG: Identification and validation of vertebral compression fractures using administrative claims data. *Med Care* 2009; 47: 69-72.
26. KIYOTA Y, SCHNEEWEISS S, GLYNN RJ, CANNUSCIO CC, AVORN J, SOLOMON DH: Accuracy of Medicare claims-based diagnosis of acute myocardial infarction: estimating positive predictive value on the basis of review of hospital records. *Am Heart J* 2004; 148: 99-104.
27. CURTIS JR, CHENG H, DELZELL E *et al*.: Adaptation of Bayesian data mining algorithms to longitudinal claims data: coxib safety as an example. *Med Care* 2008; 46: 969-75.
28. LIN DY, WEI LJ, YING Z: Checking the cox model with cumulative sums of martingale-based residuals. *Biometrika* 1993; 80: 557-72.
29. CURTIS JR, WESTFALL AO, CHENG H, DELZELL E, SAAG KG: Risk of hip fracture after bisphosphonate discontinuation: implications for a drug holiday. *Osteoporos Int* 2008; 19: 1613-20.
30. SHEEHY O, KINDUNDU C, BARBEAU M, LELORIER J. Adherence to weekly oral bisphosphonate therapy: cost of wasted drugs and fractures. *Osteoporos Int* 2009; 20: 1583-94.
31. JOFFE MM, ROSENBAUM PR: Invited commentary: propensity scores. *Am J Epidemiol* 1999; 150: 327-33.
32. PENNING-VAN BEEST F, ERKENS J, OLSON M, HERINGS R: Loss of treatment benefit due to low compliance with bisphosphonate therapy. *Osteoporos Int* 2008; 19: 511-7.
33. CRANNEY A, WELLS G, WILLAN A *et al*.: Meta-analyses of therapies for postmenopausal osteoporosis. II. Meta-analysis of alendronate for the treatment of postmenopausal women. *Endocr Rev* 2002; 23: 508-16.
34. CRANNEY A, TUGWELL P, ADACHI J *et al*.: Meta-analyses of therapies for postmenopausal osteoporosis. III. Meta-analysis of risedronate for the treatment of postmenopausal osteoporosis. *Endocr Rev* 2002; 23: 517-23.
35. MACLEAN C, NEWBERRY S, MAGLIONE M *et al*.: Systematic review: comparative effectiveness of treatments to prevent fractures in men and women with low bone density or osteoporosis. *Ann Intern Med* 2008; 148: 197-213.
36. MARTIN KE, YU J, CAMPBELL HE, WHITE TJ: Analysis of the comparative effectiveness of 3 oral bisphosphonates in a larger managed care organization: adherence, fracture rates and all-cause cost. *J Manag Care Pharm* 2011; 17: 596-609.
37. KANIS JA, REGINSTER JY, KAUFMAN JM *et al*.: A reappraisal of generic bisphosphonates in osteoporosis. *Osteoporos Int* 2012: 23: 213-21.
38. WATTS N, WORLEY K, SOLIS A, DOYLE J, SHEER R: Comparison of risedronate to alendronate and calcitonin for early reduction of nonvertebral fracture risk: results from a managed care administrative claims database. *J Manag Care Pharm* 2004; 10: 142-51.
39. HOPKINS RB, GOEREE R, PULLENAYEGUM E *et al*.: The relative efficacy of nine osteoporosis medications for reducing the rate of fractures in post-menopausal women. *BMC Musculoskelet Disord* 2011; 12: 209.
40. CURTIS JR, ARORA T, MATTHEWS RS *et al*.: Is withholding osteoporosis medication after fracture sometimes rational? A comparison of the risk for second fracture versus death. *J Am Med Dir Assoc* 2010; 11: 584-91.
41. UGUR URAL A, AVCU F, OZTURK K: Bisphosphonates may retrieve endothelial function in vascular diseases similar to statins. *Eur J Haematol* 2008; 81: 77-8.
42. BOLLAND MJ, GREY AB, GAMBLE GD, REID IR: Effect of osteoporosis treatment on mortality: a meta-analysis. *J Clin Endocrinol Metab* 2010; 95: 1174-81.
43. RAY WA: Evaluating medication effects outside of clinical trials: new-user designs. *Am J Epidemiol* 2003; 158: 915-20.
44. SCHNEEWEISS S, AVORN J: A review of uses of health care utilization databases for epidemiologic research on therapeutics. *J Clin Epidemiol* 2005; 58: 323-37.