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Effect of Bisphosphonates on Fracture Outcomes among Frail Older Adults

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Abstract

Background: Bisphosphonates are seldom used in frail, older adults, in part due to lack of direct evidence of efficacy in this population and increasing concerns about safety.

Objective: We estimated the effects of bisphosphonates on hip fractures, non-vertebral fractures, and severe esophagitis among frail, older adults.

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Conflict of Interest Explanations:

D.P.K.

D.P.K. serves as an author for the “Falls” chapters in UpToDate and receives royalties from Wolters Kluwer for this. D.P.K. also served as editor for the book “Osteoporosis in Older Persons” and received an honorarium from Springer for this activity.

V.M.

V.M.’s research is in a related area to that of several different paid activities. V.M. also periodically serves as a paid speaker at national conferences where he discusses trends and research findings in long term and post-acute care. V.M. holds stock of unknown value in PointRight, Inc. an information services company providing advice and consultation to various components of the long term care and post-acute care industry, including suppliers and insurers. PointRight sells information on the measurement of nursing home quality to nursing homes and liability insurers. V.M. was a founder of the company but has subsequently divested much of his equity in the company and relinquished his seat on board. In addition, V.M. Chairs the Independent Quality Committee for HRC Manor Care, Inc., a nursing home chain, for which he receives compensation in the \$20,000-\$40,000 range. V.M. also serves as chair of a Scientific Advisory Committee for NaviHealth, a post-acute care service organization, for which he also receives compensation in the \$20,000-40,000 per year range. V.M. serves as a Technical Expert Panel member on several Centers for Medicare/Medicaid quality measurement panels. V.M. is a member of the board of directors of Tufts Health Plan Foundation; Hospice Care of Rhode Island; and The Jewish Alliance of Rhode Island.

S.D.B.

S.D.B. serves as an author for the “Falls” chapters in UpToDate and receives royalties from Wolters Kluwer for this.

Design: Population-based retrospective cohort using 2008-2013 linked national Minimum Data Set assessments; Online Survey, Certification and Reporting records; and Medicare claims.

Setting: U.S. nursing homes (NH).

Participants: Long-stay NH residents ≥ 65 years without recent osteoporosis medication use (N=24,571). Bisphosphonate initiators were 1:1 propensity score matched to calcitonin initiators (active comparator).

Measurements: Hospitalized hip fracture, non-vertebral fracture, and esophagitis outcomes were measured using Part A claims. Hazard ratios and 95% confidence intervals (CI) were estimated controlling for over 100 baseline characteristics.

Results: The matched cohort included 5,209 new bisphosphonate users and an equal number of calcitonin users (mean age [SD], 85 [8] years; 87% female; 52% moderate-severe cognitive impairment). Over a mean follow-up of 2.5 years (SD 1.7), 568 residents (5.5%) had a hip fracture, 874 (8.4%) a non-vertebral fracture, and 199 (1.9%) a hospitalized esophagitis event. Users of bisphosphonates were less likely than calcitonin users to experience hip fracture (HR, 0.83; 95% CI, 0.71 to 0.98), with an average gain in time without fracture of 28.4 days (95% CI, 6.0 to 50.8). Bisphosphonate and calcitonin users had similar rates of non-vertebral fracture (HR, 0.91; 95% CI, 0.80 to 1.03) and esophagitis events (HR, 1.11; 95% CI, 0.84 to 1.47). The effects of bisphosphonates on fractures and esophagitis were generally homogenous across subgroups, including those defined by age, sex, history of prior fracture, and baseline fracture risk.

Conclusions: Use of bisphosphonates is associated with a meaningful reduction in hip fracture among frail, older adults, but little difference in non-vertebral fracture or severe esophagitis.

Keywords

Bisphosphonates; hip fracture; non-vertebral fracture; nursing homes; Medicare

INTRODUCTION

Osteoporosis is common among older adults and hip fracture is the most devastating consequence. A number of osteoporosis medications, including the first-line bisphosphonate class, reduce hip fracture risk in older, community-dwellers at high risk.[1] However, it is less clear whether these drugs prevent fracture in frail, older adults. Nearly 1.4 million older Americans reside in nursing homes (NHs) and are at particularly high risk for fracture.[2] Hip fractures are the most common site of fracture in NH residents,[3] with an estimated 10% of all hip fractures in the U.S. occurring in NH residents.[2] Hip and other osteoporotic fractures among NH residents lead to high rates of healthcare utilization,[4] functional decline,[5] impaired quality of life,[5] and increased mortality.[6] Further, osteoporotic fractures are associated with a high financial cost[7] and are a frequent source of litigation for NH facilities.

Despite the significance of fractures in this setting, bisphosphonates are infrequently prescribed for many reasons. First, there is no direct evidence that they prevent fractures in NH residents or other frail, older adults because these individuals were excluded from pivotal bisphosphonate fracture trials. Second, increasing concerns about the safety of

bisphosphonates may explain infrequent use of these drugs in the NH. In particular, oral bisphosphonates can cause gastroesophageal reflux or esophagitis,[8] particularly when administered improperly. A large randomized trial of bisphosphonates in NH residents that is powered to detect a difference in fracture and adverse events is unlikely to occur. Therefore, an observational study that can emulate such a trial is necessary to understand whether osteoporosis medications are effective and safe in this setting.[9]

We studied the comparative effectiveness and safety of bisphosphonates for fracture and hospitalized esophagitis outcomes among NH residents using a large observational database. We hypothesized that bisphosphonates would reduce the risk of hip and non-vertebral fracture and confer no differential risk of hospitalized esophagitis.

METHODS

Study Design and Data Source

This was a retrospective new-user[10] cohort study using national Medicare data linked to the Minimum Data Set (MDS)[11] version 2.0 and Online Survey Certification and Reporting System (OSCAR) data. The MDS is a quarterly clinical assessment tool that is required for all NHs certified to receive Medicare or Medicaid funding. The OSCAR data[12] provides facility-level information on NH characteristics, staffing levels, and quality indicators. Medicare claims include information on inpatient care (Part A), outpatient care (Part B), and prescription drug dispensings (Part D[13]). Our observational study was designed to emulate the pragmatic randomized trial that would have ideally been conducted had it been feasible (Supplementary Table S1).[14, 15]

Study Population

Our study population comprised all NH residents aged ≥ 65 years who became a long-stay resident (>100 days in the NH) between January 1, 2008 and December 31, 2009 and were new users of a bisphosphonate or calcitonin after becoming long-stay through December 31, 2011. The index date was the first eligible dispensing of a bisphosphonate or calcitonin. Individuals with a dispensing of a bisphosphonate, calcitonin, or any other osteoporosis treatment (e.g., raloxifene, teriparatide), in the 365-days before the index date were excluded. Study subjects were excluded if they had less than 365 days of continuous enrollment in fee-for-service Medicare Parts A, B, and D or were enrolled in Medicare Advantage at any time. Other exclusions are shown in Supplementary Figure S1.

Exposures and Causal Contrast of Interest

We initially considered comparing the effect of new bisphosphonate use compared to non-use on hip fracture risk; however, after propensity score matching, we estimated a hazard ratio (HR) of 1.15 (confidence interval [CI], 1.04-1.28), suggesting intractable residual confounding given the implausibility that bisphosphonate use would increase the risk of hip fracture. Alternatively, selecting an appropriate active comparator minimizes unmeasured confounding bias. Calcitonin was approved for the treatment of osteoporosis, yet lack of a plausible dose-response relationship and inconsistent evidence suggests that it has no or a very weak effect on non-vertebral fracture outcomes, and no relationship with esophagitis.

[16] The use of calcitonin for the same clinical indication as bisphosphonates during the study period and its lack of efficacy made it a suitable “active” comparator.

Initiation of an oral bisphosphonate or calcitonin was ascertained using Medicare Part D claims, whereas intravenous bisphosphonates were ascertained using Part B claims (individual medications in Supplementary Table S2).

The effect of initiating bisphosphonates versus calcitonin on fracture risk was measured regardless of subsequent treatment discontinuation or switching among treatment groups (i.e., intention-to-treat).[14, 15]

Outcomes

The outcomes were hospitalized 1) hip fracture, 2) non-vertebral fracture, and 3) esophagitis. Each outcome was defined using previously validated *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9) codes in the primary or secondary position on inpatient claims.[17–20] In validation studies, the positive predictive value (PPV) was 98% for the hip fracture definition and 95-96% for non-vertebral fractures (Supplementary Table S2).[18–20]

Follow-up

Follow-up started on the day of bisphosphonate or calcitonin dispensing and continued until Medicare disenrollment, death, occurrence of one of the outcomes of interest, or study end (December 31, 2013).

Baseline Characteristics

Common causes (i.e., potential confounders) or proxies of common causes of treatment and outcomes were pre-specified, measured in the 365-day assessment period up to and including the index date (treatment initiation), and included in propensity score estimation (described below). The variables included demographic characteristics, medical history, medication use, health services utilization, and NH facility characteristics.[21–24] MDS data were used to generate several validated scales for cognition, functioning, and frailty.[25–27] Time between long-stay qualification and treatment initiation (mean=287 days) was included in the propensity score estimation. A complete list of all 111 characteristics included in the propensity score is provided in Supplementary Table S3.

Statistical Analyses

We adjusted for confounding by baseline covariates using methods that rely on estimating the propensity score (i.e., the probability of receiving bisphosphonates versus calcitonin, conditional on covariates). Propensity scores were estimated using a logistic regression model. We limited our main analyses to the complete cases (>91.5% of patients; N=23,101). The unit of analysis was the individual person after matching (N=10,418).

We used the propensity score to match one new user of bisphosphonates to one new user of calcitonin using a greedy 5-to-1 digit matching algorithm without replacement.[28] We examined the propensity score distributions between treatment groups using histograms and

descriptive statistics and evaluated covariate balance using standardized mean differences. [29]

We estimated HRs with 95% CIs using Cox proportional hazards regression models to compare bisphosphonate versus calcitonin initiators for all outcomes. The cluster-robust Huber-White estimator was used to account for the correlation within propensity score-matched pairs. To better understand the magnitude of the difference in outcomes between treatment groups, we calculated the absolute difference in restricted mean survival time (RMST).[30] Cumulative incidence function graphs were used to visualize the occurrence of outcome events in each treatment group over time accounting for the competing risk of death.

Effect modification[31] was examined by estimating treatment effects within strata defined by age (<85 versus ≥85), sex (male versus female), race (white versus non-white), prior fracture, prior fall, cognition (cognitive performance score 0-2 versus 3-5), physical functioning (ADL score 0-13 versus 14-28), cancer, and estimated fracture risk (FRAiL score[22], below median [$<5.3\%$] versus at or above median).

Stability Analyses

We evaluated alternate approaches to determine if our main results were robust to various decisions about effect estimation. Alternative approaches included Fine and Gray competing risk regression models to account for the competing risk of death,[32] multiple imputation to address missing covariate information[33], estimation of the propensity score using generalized boosted regression to address potential model misspecification[34], estimation of the as-treated effect estimand[14, 15], inverse probability of treatment weighting[35], and multivariable Cox regression.

We also used a negative control outcome of hospitalized heart failure measured using a validated claims-based definition.[36, 37] An association between the drugs and heart failure would suggest our primary outcome estimates were biased and that residual confounding may explain the findings.[37]

Finally, as an alternative to the absolute difference in RMST, we estimated 1-year, 3-year, and 6-year risk differences with 95% CIs calculated using the non-parametric bootstrap, and the accompanying numbers needed to treat (NNT) or harm (NNH).

Analyses were conducted using SAS version 9.4 (SAS Institute; Cary, NC), Stata version 14.0 (Stata Corp., College Station, TX), and R version 3.4.3. We considered a two sided P value less than 0.05 to be statistically significant.

Ethics approval

This study was approved by the Hebrew SeniorLife Institutional Review Board.

RESULTS

Study Cohort

Our initial cohort of 24,571 patients (20,956 female [85.3%] and 3,614 men [14.7%]; mean [SD] age, 84 [8] years; 51% moderate to severe cognitive impairment) included 18,869 bisphosphonate users and 5,702 calcitonin users (Supplementary Figure S1). Before matching, bisphosphonate users were more likely to be younger, female, non-white, and have received a dual-energy X-ray absorptiometry scan (Table 1; Supplementary Table S4). Bisphosphonate users also had less cognitive and functional impairment than calcitonin users.

Propensity score matching yielded a cohort of 5,209 new bisphosphonate users and an equal number of new calcitonin users (Table 1). Mean (SD) age was 85 (8) years; 9,071 were women (87.1%); and 1,347 were men (12.9%). Mean (SD) follow-up was 2.4 (1.7) years. All but four covariates had absolute standardized mean differences of 0.04 or less (Supplementary Table S3).

During follow-up, 567 of 10,418 participants (5.4%) experienced a hip fracture; 874 (8.4%) a non-vertebral fracture; and 199 (1.9%) esophagitis. There were 8,189 (78.6%) deaths overall during follow-up, and 4,024 (77.3%) of bisphosphonate users and 4,165 (80.0%) of calcitonin users died.

Treatment Effects

After propensity score matching, the rate of hip fracture was 0.83 (HR, 0.83; 95% CI, 0.71 to 0.98) times lower in residents receiving bisphosphonates (Table 2). The average gain in time without hip fracture due to prescribing bisphosphonates instead of calcitonin was 28.4 days (absolute difference in RMST, 28.4; 95% CI, 6.0 to 50.8) over a 6-year follow-up period (Table 2). The corresponding NNTs were 239 over 3 years of follow-up and 154 over 6 years of follow-up. Separation in the cumulative incidence curves for hip fracture between treatment groups began within 6 months after treatment initiation (Figure 1A).

Users of bisphosphonates were less likely than calcitonin users to have a non-vertebral fracture before propensity score matching (HR, 0.84, 95% CI, 0.76 to 0.94), though this result was highly compatible with chance after matching (HR, 0.91; 95% CI, 0.80 to 1.03) (Table 2; Figure 1B).

Bisphosphonate versus calcitonin use had no significant effect on hospitalized esophagitis events before matching (HR, 1.08; 95% CI 0.86 to 1.35) or after (HR, 1.11; 95% CI, 0.84 to 1.47)(Table 2; Figure 1C).

Stability Analyses

Stability analyses (Supplementary Figure S2; Supplementary Table S5) produced results that were generally consistent with the main finding of a reduction in the risk of hip fracture associated with bisphosphonates and no significant difference in other outcomes. There was no ITT effect of bisphosphonates on the negative control outcome of heart failure after

propensity score matching (HR, 0.97; 95% CI, 0.87 to 1.07)(Supplementary Table S6). Risk difference and NNH/NT estimates are in Supplementary Table S7.

Treatment Effects in Subgroups

Subgroup results suggested that bisphosphonates were generally associated with a reduction in hip (Figure 2) and no significant difference in non-vertebral (Figure 3) fracture. Bisphosphonate use may have been associated with a reduction in non-vertebral fracture among residents with prior fracture or good baseline functioning, but not among those without prior fracture or poor physical functioning, though the p-values for effect modification were non-significant (Figure 3). The effect of bisphosphonates versus calcitonin on fractures did not appear to vary by baseline fracture risk (as defined by the FRAiL score[22]). There were few notable differences across subgroups for severe esophagitis with the exception of race (Supplementary Figure S3)—white residents initiating a bisphosphonate were more likely to have an esophagitis event, whereas non-white residents had a *decreased* risk.

DISCUSSION

In this national study of older NH residents, initiating bisphosphonates instead of calcitonin resulted in a 17% reduced rate of hip fracture, which corresponds to an average gain of 28 days without a hip fracture event. There were similar rates of non-vertebral fracture or severe esophagitis events between treatment groups. These data help fill important evidence gaps about the relative benefits and harms of bisphosphonates in frail, older adults.

Our findings are consistent with small trials that suggest that bisphosphonates may reduce the risk of fracture in NH residents. Greenspan et al. randomized 327 women (mean age 78.5 years) with low bone mineral density residing in a retirement community or NH to alendronate versus placebo.[1] After two years follow-up, there were numerically fewer fractures in women receiving alendronate (13 fractures among 13 women) compared with placebo (28 fractures among 18 women) and no difference in gastrointestinal events.

In a second trial by Greenspan, 181 women (mean age 85.5 years) living in a NH or assisted living facility were randomized to a single intravenous bisphosphonate infusion (zoledronic acid) versus placebo.[38] After two years follow-up, there were numerically fewer vertebral fractures in women receiving zoledronic acid as compared with placebo (6 versus 8), although the total number of fractures was greater in the zoledronic acid group (18 versus 15). Of note, a trial randomizing 514 older NH residents to zoledronic acid or placebo is planned ([ClinicalTrials.gov](https://clinicaltrials.gov) Identifier:), but may not have sufficient statistical power to detect an effect on hip fracture outcomes.

In bisphosphonate fracture trials, subgroup analyses have consistently demonstrated efficacy among the oldest individuals [39–41] and those with neurologic impairment, though these estimates were imprecise and not directly representative of frail adults or NH residents.[42, 43] In the Fracture Intervention Trial comparing alendronate versus placebo among 3,658 community-dwelling postmenopausal women, the NNT was 189 over 2 years of follow-up

in the oldest subgroup (patients aged 75-85), which is similar to our 3-year estimate of 239. [39]

Prior trials suggest that bisphosphonates may start to reduce fracture risk as early as 6 months after treatment initiation.[44] Our study found a similar lag time to benefit for hip fracture. Since NH residents have a median life expectancy of 2.5 years, many residents stand to benefit from treatment with bisphosphonates. Of note, the absolute difference between treatment groups was quite small. Nevertheless, given the mortality and expenses associated with a single hip fracture, it may be reasonable to treat at-risk residents with a one year or greater life expectancy.

With few exceptions, our results suggest bisphosphonate initiation reduces the risk of hip fractures across subgroups. Our finding that drug effectiveness did not differ according to age is consistent with post-hoc analyses of randomized trials of bisphosphonates.[39, 40, 45] We also found no significant difference in drug efficacy according to a history of fracture or the estimated 2-year risk of fracture calculated by the FRAiL model.[22] Conflicting data exist on whether osteoporosis medications differentially affect the risk of fracture based on estimated fracture risk in community dwellers.[46–48] Despite the overall lack of an effect for bisphosphonates on non-vertebral fracture risk, we found that bisphosphonates may reduce non-vertebral fracture risk among NH residents with a history of prior fracture or who are relatively independent in ADLs, but not necessarily among residents without a prior fracture or with severe functional impairment.[22]

Concurrent with reports about rare adverse events, especially among patients at low risk of fracture, bisphosphonate use declined by over 50 percent from 2008 to 2012.[49] The declines in bisphosphonate use have raised concerns that patients who need pharmacologic treatment are not receiving it regardless of fracture risk. These concerns about underuse extend to older, frail adults, including those residing in a NH, and our findings suggest that even among NH residents, the potential benefits may outweigh risks.

Since this study is observational, we cannot rule out the possibility of confounding. However, several factors support the robustness of our findings. Our linked clinical and administrative databases provide detailed patient information beyond what is captured in administrative claims alone while allowing for generalization of the results to a large population of frail, older adults. We also obtained excellent balance in baseline covariates across treatment groups and consistent results using several analytic approaches. Finally, the lack of an observed effect on the negative control outcome of heart failure suggests that confounding is less likely to be a major concern.

We were unable to compare oral and intravenous routes of bisphosphonate administration due to the very small number of intravenous users. Oral medications are often crushed and given with applesauce in the NH, a practice that would diminish the absorption of bisphosphonates. It remains possible that we would have seen a stronger effect with intravenous than oral bisphosphonates. We found the effects of bisphosphonates on fracture were larger when we considered an “as-treated” approach, which accounted for the time the

patient remained on drug (Supplementary Table S5). However, the as-treated estimand is more susceptible to bias due to informative censoring.

Calcium and vitamin D supplement use is not included in Medicare Part D claims. These supplements decrease the risk of fracture in the NH setting.[50] It is unlikely that use differed between the bisphosphonate and calcitonin groups. Nonetheless, future work should attempt to address this limitation.

Although atypical femur fracture and non-esophagitis gastrointestinal events are important safety outcomes of interest, we were unable to study them because validated definitions of the events are unavailable. Vertebral fractures were similarly unexamined. We were also interested in studying functional decline, but unfortunately did not have sufficient MDS data after treatment initiation. Finally, esophagitis was likely underascertained using our definition based on hospital claims data since esophagitis may be recognized by NH staff and addressed without hospitalization. Similarly, non-vertebral fractures may have been underascertained since they are sometimes treated in emergency departments without hospitalization. Underascertainment of both outcomes was likely non-differential by osteoporosis treatment group and unlikely to result in bias, but may have reduced statistical power to detect effects.

Conclusions

Use of bisphosphonates resulted in a modest reduction in hip fracture among older NH residents. At the same time, use of these agents did not meaningfully impact non-vertebral fracture or severe esophagitis outcomes. Bisphosphonates are a key intervention to consider to reduce hip fracture risk in frail, older adults.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflict of Interest Disclosures:

Elements of Financial/Personal Conflicts	A.R.Z.		T.Z.		Y.L.		K.W.M.		L.A.D.	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Employment or Affiliation		X		X		X		X		X
Grants/Funds		X		X		X		X		X
Honoraria		X		X		X		X		X
Speaker Forum		X		X		X		X		X
Consultant		X		X		X		X		X
Stocks		X		X		X		X		X
Royalties		X		X		X		X		X
Expert Testimony		X		X		X		X		X
Board Member		X		X		X		X		X
Patents		X		X		X		X		X
Personal Relationship		X		X		X		X		X

Elements of Financial/Personal Conflicts	D.P.K.		V.M.		S.D.B.	
	Yes	No	Yes	No	Yes	No
Employment or Affiliation		X		X		X
Grants/Funds		X		X		X
Honoraria		X	X			X
Speaker Forum		X		X		X
Consultant		X	X			X
Stocks		X	X			X
Royalties	X			X	X	
Expert Testimony		X		X		X
Board Member		X		X		X
Patents		X		X		X
Personal Relationship		X		X		X

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Impact Statement:

We certify that this work is novel. It is the first nationally representative examination of U.S. nursing home residents to provide direct evidence of the efficacy and safety of bisphosphonates in frail, older adults with multiple comorbidities, and can be used to inform prescribing and improve the quality of care for the large global population of frail, older adults who stand to benefit from treatment with bisphosphonates.

Figure 1. Cumulative Incidence Function Plots by Treatment Group for Outcome Events. Panel A represents hip fracture events. Panel B represents non-vertebral fracture events. Panel C represents esophagitis events. The blue curves represents calcitonin users and the red curves represent bisphosphonate users. Cumulative incidence functions in all figures account for the competing risk of mortality.

Figure 2. Subgroup Analyses of the Effect of Bisphosphonates versus Calcitonin on Hip Fracture Events.

P values are for effect modification.

Figure 3. Subgroup Analyses of the Effect of Bisphosphonates versus Calcitonin on Non-vertebral Fracture Events.

P values are for effect modification.

Table 1.Characteristics^a of Bisphosphonate Users and Calcitonin Users Before and After Propensity Score Matching.

Characteristics	% ^b			
	Before Matching		After Matching	
	BP (n=17,753)	CA (n=5,348)	BP (n=5,209)	CA (n=5,209)
Age, mean (SD), years	83.4 (7.8)	85.5 (7.8)	85.2 (7.7)	85.3 (7.8)
Female sex	84.6	87.4	86.8	87.4
White race	80.2	88.2	88.7	88.0
High school completion	45.2	46.7	46.8	46.3
Time between becoming long-stay resident and index date, mean (SD), days	303.9 (265.0)	292.8 (262.6)	290.0 (252.0)	293.2 (264.3)
Cognitive function				
Intact to mild impairment (CPS 0-2)	50.2	46.7	47.9	47.6
Moderate impairment (CPS 3-4)	44.3	46.4	45.7	45.9
Severe impairment (CPS 5)	5.7	6.7	6.4	6.5
Number of activities of daily living with functional independence (out of 6) ^c				
4-5	10.2	8.6	8.3	8.8
2-3	14.3	12.8	12.8	13.0
0-1	75.4	78.6	78.9	78.3
Moderate to severe instability	8.9	11.6	11.0	11.4
Do not resuscitate order	49.1	60.0	59.7	59.6
Do not hospitalize order	1.8	2.4	2.1	2.3
History of falls	47.6	50.6	50.7	51.0
Comorbidities				
Number of comorbidities, mean (SD)	10.1 (3.5)	10.7 (3.6)	10.8 (3.6)	10.8 (3.5)
Osteoporosis	14.2	19.0	18.0	18.5
Arthritis	37.5	41.5	42.5	41.6
Diabetes	31.4	30.0	29.9	30.4
Bone disorder	1.3	1.6	1.4	1.6
Renal disease	6.1	8.9	8.8	8.9
Dual-energy X-ray absorptiometry	19.4	6.5	6.7	6.6
Number of medications, mean (SD)	12.4 (4.9)	13.0 (5.2)	12.9 (5.0)	13.0 (5.2)
Oral glucocorticoids	17.9	19.9	20.1	20.1
Proton pump inhibitors	46.8	53.8	53.4	53.4
Loop diuretics	41.1	46.4	47.1	46.3
Opioids	25.1	33.4	32.8	33.3
Non-benzodiazepine hypnotics	13.3	12.4	12.5	12.8
Number of physician visits, mean (SD)	3.1 (4.0)	2.9 (3.9)	2.9 (3.9)	3.0 (3.9)
Number of hospitalizations, mean (SD)	1.1 (1.4)	1.2 (1.5)	1.2 (1.5)	1.2 (1.5)

Abbreviations: BP, bisphosphonates; CA, calcitonin; SD, standard deviation.

^a A complete list of variables is provided in Supplementary Table S3 and a complete Table 1 with additional characteristics available in Supplementary Table S4;

^b Percentages unless otherwise noted;

^c No residents were independent in all 6 activities of daily living.

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Table 2.

Effect of Bisphosphonates versus Calcitonin on Outcomes Before and After Propensity Score Matching.

	P Score Matched	Events / n		PY		Risk		HR (95% CI)	Absolute difference in RMST ^a (95% CI)
Outcome		BP	CA	BP	CA	BP	CA		
Hip Fracture	No	910 / 17,753	308 / 5,348	50,056	12,790	5.13	5.76	0.78 (0.68 to 0.88)	33.93 (16.14 to 51.72)
	Yes	267 / 5,209	301 / 5,209	12,740	11,781	5.13	5.78	0.83 (0.71 to 0.98)	28.39 (6.02 to 50.76)
Non-vertebral Fracture	No	1,554 / 17,753	482 / 5,348	46,050	11,750	8.18	8.47	0.84 (0.76 to 0.94)	33.82 (12.07 to 55.58)
	Yes	430 / 5,209	444 / 5,209	12,491	11,537	8.25	8.52	0.91 (0.80 to 1.03)	21.16 (−5.80 to 48.11)
Esophagitis	No	390 / 17,753	94 / 5,348	50,989	13,107	2.20	1.76	1.08 (0.86 to 1.35)	−2.90 (−13.69 to 8.10)
	Yes	108 / 5,209	91 / 5,209	13,009	12,070	2.07	1.75	1.11 (0.84 to 1.47)	−3.87 (−17.72 to 9.98)

Abbreviations: PY, person-years; HR, hazard ratio; CI, confidence interval; P score, propensity score; BP, bisphosphonates; CA, calcitonin; RMST, restricted mean survival time.

^aThe absolute difference in restricted mean survival time is interpretable as the average gain or loss in event-free days due to bisphosphonates versus calcitonin during a 6-year follow-up period; for example, residents who initiated bisphosphonates instead of calcitonin in the matched cohort would increase the time they went without having a hip fracture by 28.39 days on average over a 6-year follow-up period.