Effect of Bisphosphonates on Fracture Outcomes Among Frail Older Adults

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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, nonvertebral fractures, and severe esophagitis among frail, older adults.

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

SETTING: US nursing homes (NHs).

PARTICIPANTS: Long-stay NH residents 65 years and older 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, nonvertebral fracture, and esophagitis outcomes were measured using part A claims. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated, controlling for over 100 baseline characteristics.

RESULTS: The matched cohort included 5209 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 (SD = 1.7) years, 568 residents (5.5%) had a hip fracture, 874 (8.4%) had a nonvertebral fracture, and 199 (1.9%) had a hospitalized esophagitis event. Users of bisphosphonates were less likely than calcitonin users to experience hip fracture (HR = 0.83; 95% CI = 0.71-0.98), with an average gain in time without fracture of 28.4 days (95% CI = 6.0-50.8 days). Bisphosphonate and calcitonin users had similar rates of nonvertebral fracture (HR = 0.91; 95% CI = 0.80-1.03) and esophagitis events (HR = 1.11; 95% CI = 0.84-1.47). The effects of bisphosphonates on fractures and esophagitis were generally homogeneous 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 nonvertebral fracture or severe esophagitis. **J Am Geriatr Soc 67:768–776, 2019.**

Key words: bisphosphonates; hip fracture; nonvertebral fracture; nursing homes; Medicare

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 United States 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

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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 nonvertebral 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] provide 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 or older who became a long-stay resident (longer than 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 residents 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 (eg, 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 to nonuse 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 weak effect on nonvertebral 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 vs calcitonin on fracture risk was measured regardless of subsequent treatment discontinuation or switching among treatment groups (ie, intention to treat).[14,15]

Outcomes

The outcomes were hospitalized (1) hip fracture, (2) nonvertebral fracture, and (3) esophagitis. Each outcome was defined using previously validated *International Classification of Diseases, 9th Revision, Clinical Modification* codes in the primary or secondary position on inpatient claims.[17–20] In validation studies, the positive predictive value was 98% for the hip fracture definition and 95% to 96% for nonvertebral 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 (ie, potential confounders) or proxies of common causes of treatment and outcomes were prespecified, 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 (ie, the probability of receiving bisphosphonates vs calcitonin,

conditional on covariates). Propensity scores were estimated using a logistic regression model. We limited our main analyses to the complete cases (greater than 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 five-to-one 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 vs 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 (younger than 85 years vs 85 years or older), sex (male vs female), race (white vs nonwhite), prior fracture, prior fall, cognition (cognitive performance score, 0-2 vs 3-5), physical functioning (activity of daily living [ADL] score, 0-13 vs 14-28), cancer, and estimated fracture risk (Fracture Risk Assessment in Long-Term Care [FRAiL] score,[22] below median [less than 5.3%] vs 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-, 3-, and 6-year risk differences with 95% CIs calculated using the nonparametric 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 $P < .05$ 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 women [85.3%] and 3614 men [14.7%]; mean [SD] age = 84 [8 years; 51% with moderate-to-severe cognitive impairment) included 18,869 bisphosphonate users and 5702 calcitonin users (Supplementary Figure S1). Before matching, bisphosphonate users were more likely to be younger, female, and nonwhite, 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 5209 new bisphosphonate users and an equal number of new calcitonin users (Table 1). Mean (SD) age was 85 (8) years; 9071 were women (87.1%), and 1347 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%) experienced a nonvertebral fracture; and 199 (1.9%) experienced esophagitis. There were 8189 (78.6%) deaths overall during follow-up, and 4024 (77.3%) of bisphosphonate users and 4165 (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 = 0.71-0.98) 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 = 6.0-50.8) 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 nonvertebral fracture before propensity score matching (HR = 0.84; 95% CI = 0.76-0.94), though this result was highly compatible with chance after matching (HR = 0.91; 95% CI = 0.80-1.03) (Table 2; Figure 1B).

Bisphosphonate vs calcitonin use had no significant effect on hospitalized esophagitis events before matching (HR = 1.08; 95% CI = 0.86-1.35) or after matching (HR = 1.11; 95% CI = 0.84-1.47) (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

Table 1. Characteristics of BP and CA Users Before and After Propensity Score Matching[a]

Characteristics	% of Each Group[b]			
	Before Matching		After Matching	
	BP (n = 17,753)	CA (n = 5348)	BP (n = 5209)	CA (n = 5209)
Age, mean (SD), y	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), d	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
No. of activities of daily living with functional independence (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				
No. 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
No. 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
Nonbenzodiazepine hypnotics	13.3	12.4	12.5	12.8
No. of physician visits, mean (SD)	3.1 (4.0)	2.9 (3.9)	2.9 (3.9)	3.0 (3.9)
No. of hospitalizations, mean (SD)	1.1 (1.4)	1.2 (1.5)	1.2 (1.5)	1.2 (1.5)

Abbreviations: BP, bisphosphonate; CA, calcitonin; CPS, cognitive performance scale.

[a]A complete list of variables is provided in Supplementary Table S3, and a complete Table 1 with additional characteristics is available in Supplementary Table S4.

[b]Data are given as percentage unless otherwise noted.

[c]No residents were independent in all six activities of daily living.

other outcomes. There was no intention to treat (ITT) effect of bisphosphonates on the negative control outcome of heart failure after propensity score matching (HR = 0.97; 95% CI = 0.87-1.07) (Supplementary Table S6). Risk difference and NNH/NNT 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 nonvertebral (Figure 3) fracture. Bisphosphonate use may have been associated with a reduction in nonvertebral 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 nonsignificant (Figure 3). The effect of bisphosphonates vs 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 nonwhite 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 nonvertebral 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.

Table 2. Effect of BPs vs CA on Outcomes Before and After Propensity Score Matching

Outcome	Propensity Score Matched	Events/n		PY		Risk		HR (95% CI)	Absolute Difference in RMST (95% CI)[a]
		BP	CA	BP	CA	BP	CA		
Hip fracture	No	910/17,753	308/5348	50,056	12,790	5.13	5.76	0.78 (0.68 to 0.88)	33.93 (16.14 to 51.72)
	Yes	267/5209	301/5209	12,740	11,781	5.13	5.78	0.83 (0.71 to 0.98)	28.39 (6.02 to 50.76)
Nonvertebral fracture	No	1554/17,753	482/5348	46,050	11,750	8.18	8.47	0.84 (0.76 to 0.94)	33.82 (12.07 to 55.58)
	Yes	430/5209	444/5209	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	94/5348	50,989	13,107	2.20	1.76	1.08 (0.86 to 1.35)	−2.90 (−13.69 to 8.10)
	Yes	108/5209	91/5209	13,009	12,070	2.07	1.75	1.11 (0.84 to 1.47)	−3.87 (−17.72 to 9.98)

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

[a]The absolute difference in RMST is interpretable as the average gain or loss in event-free days due to BPs vs CA during a 6-year follow-up period; for example, residents who initiated BPs instead of CA 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.

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 vs placebo.[38] After 2 years of 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 et al, 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) vs placebo.[38] After 2 years of follow-up, there were numerically fewer vertebral fractures in women receiving zoledronic acid as compared with placebo (6 vs 8), although the total number of fractures was greater in the zoledronic acid group (18 vs 15). Of note, a trial randomizing 514 older NH residents to zoledronic acid or placebo is planned (ClinicalTrials.gov Identifier: NCT02589600) 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,[42,43] though these estimates were imprecise and not directly representative of frail adults or NH residents. In the Fracture Intervention Trial comparing alendronate vs placebo among 3658 community-dwelling postmenopausal women, the NNT was 189 over 2 years of follow-up in the oldest subgroup (patients aged 75-85 years), 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 small. Nevertheless, given the mortality and expenses associated with a single hip fracture, it may be reasonable to treat at-risk residents with a 1-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] 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 nonvertebral fracture risk, we found that bisphosphonates may reduce nonvertebral 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% from 2008 to 2012.[49] The declines in bisphosphonate use have raised concerns that patients who need pharmacologic treatment are not

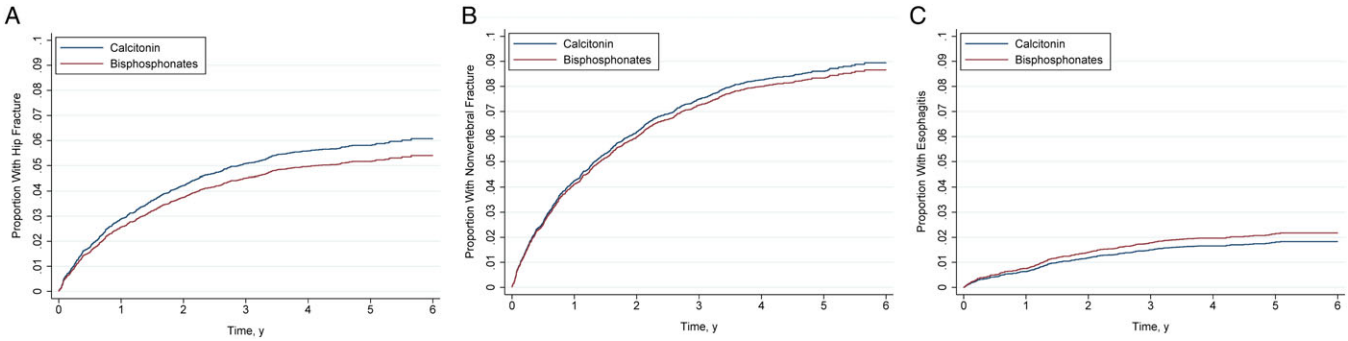

Figure 1. Cumulative incidence function plots by treatment group for outcome events. (A) Hip fracture events. (B) Nonvertebral fracture events. (C) Esophagitis events. The blue curves represents calcitonin users, and the red curves represent bisphosphonate users. Cumulative incidence functions in all figures account for the competing risk of mortality.

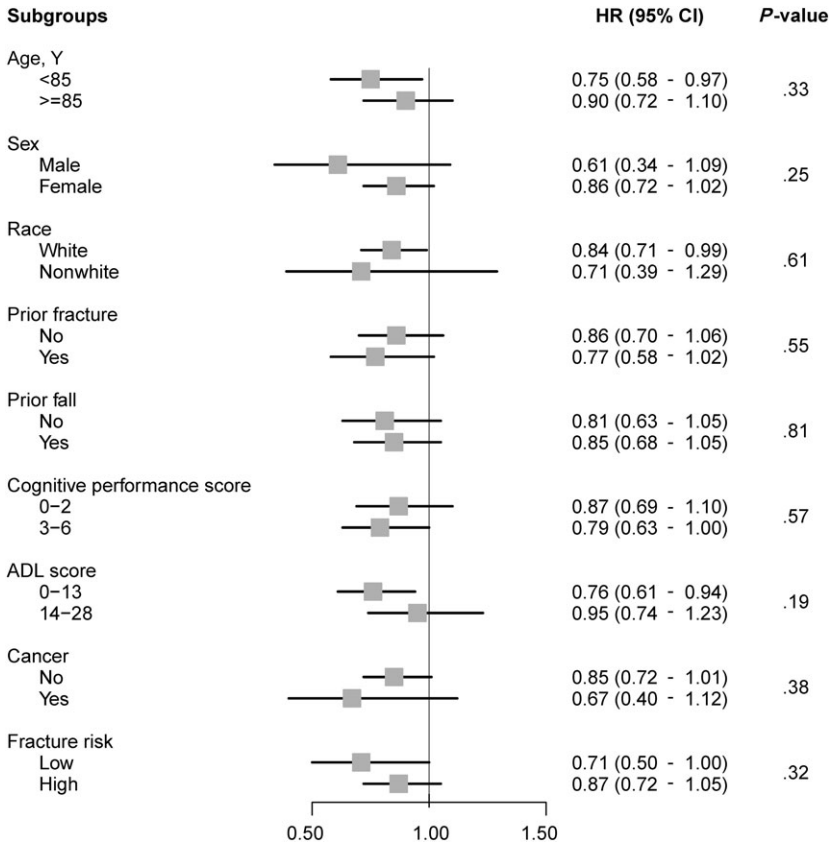

Figure 2. Subgroup analyses of the effect of bisphosphonates vs calcitonin on hip fracture events. *P* values are for effect modification. ADL, activity of daily living; CI, confidence interval; HR, hazard ratio.

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 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

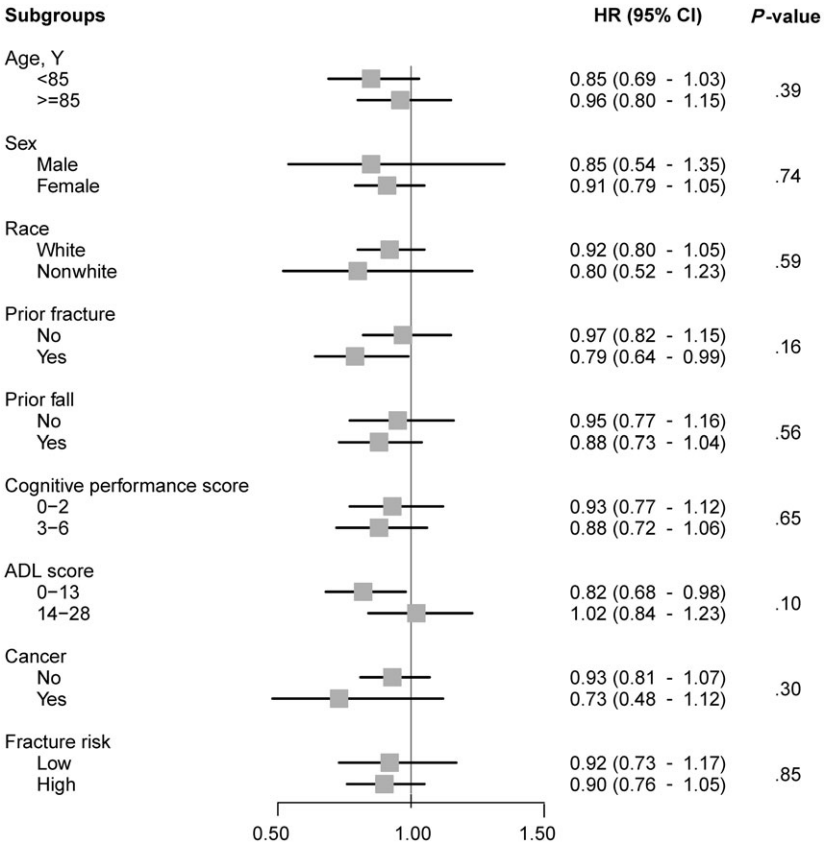

Figure 3. Subgroup analyses of the effect of bisphosphonates vs calcitonin on nonvertebral fracture events. *P* values are for effect modification. ADL, activity of daily living; CI, confidence interval; HR, hazard ratio.

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 nonesophagitis 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 unexaminable. 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, nonvertebral fractures may have been underascertained since they are sometimes treated in emergency departments without hospitalization. Underascertainment of both outcomes was likely nondifferential 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 nonvertebral fracture or severe esophagitis outcomes. Bisphosphonates are a key intervention to consider to reduce hip fracture risk in frail, older adults.

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Conflicts of Interest: 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.'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 the 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 to $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 to 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. serves as an author for the "Falls" chapters in UpToDate and receives royalties from Wolters Kluwer for this.

Author Contributions: Drs. Zullo and Berry had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analyses. *Study concept and design*: Berry, Kiel, Mor, Zullo. *Acquisition, analysis, or interpretation of the data*: Zullo, Lee, Zhang, McConeghy, Daiello, Kiel, Mor, Berry. *Drafting of the manuscript*: Zullo, Berry. *Critical revision of the manuscript for important intellectual content*: Zullo, Zhang, Lee, McConeghy, Daiello, Kiel, Mor, Berry. *Statistical analysis*: Zullo, Zhang, Lee. *Obtained funding*: Berry, Zullo, Mor. *Administrative, technical, or material support*: Berry, Zullo, Kiel, Mor. *Study supervision*: Berry.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Supplementary Figure S1. Study cohort flow diagram.

Supplementary Figure S2. Stability analyses to determine if main results were robust to various decisions about estimation.

Supplementary Figure S3. Subgroup analyses of the effect of bisphosphonates vs calcitonin on esophagitis events.

Supplementary Table S1. Summary of the Protocol of the Hypothetical Target Trial We Emulated to Compare Bisphosphonates vs Calcitonin Among Older Nursing Home Residents

Supplementary Table S2. List of Medications Captured in the Analyses

Supplementary Table S3. Covariates Included in the Propensity Score and Standardized Differences Before and After Propensity Score Matching

Supplementary Table S4. Characteristics of Bisphosphonate Users and Calcitonin Users Before and After Propensity Score Matching (Full Table)

Supplementary Table S5. As-Treated Effect of Bisphosphonates vs Calcitonin on Outcomes Before and After Propensity Score Matching

Supplementary Table S6. Effect of Bisphosphonates vs Calcitonin on the Negative Control Outcome of Heart Failure Before and After Propensity Score Matching

Supplementary Table S7. Risk Differences and Numbers Needed to Treat and Harm for the Effect of Bisphosphonates vs Calcitonin on Outcomes Before and After Propensity Score Matching