Nitrogen-containing bisphosphonates are associated with reduced risk of pneumonia in patients with hip fracture

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Running title: Bisphosphonates reduced risk of pneumonia

Word count: 230 (Abstract); 2995 (Main text)

Disclosure

All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr. Cheung and Prof Wong report receipt of research funding from Amgen, the Hong Kong Research Grants Council, and the Hong Kong Health and Medical Research Fund. Prof Wong has also received funding from Pfizer. BMS, Bayer, Novartis and Janssen. Dr. Kiel has received stipends for serving on a scientific advisory board for Solarea Bio, has received grants to his institution from the Dairy Council and Radius Health. He receives royalties for publication from Wolters Kluwer for UpToDate. No other disclosures were reported.

Abstract

Objective To study the risk of pneumonia and pneumonia mortality among patients receiving nitrogen-containing bisphosphonates (N-BPs), non-N-BPs anti-osteoporosis medications, and no anti-osteoporosis medications after hip fracture.

Methods This is a historical cohort study using a population-wide database. Patients with first hip fracture during 2005-2015 were identified and matched by time-dependent propensity score. The cohort was followed until December 31 2016 to capture any pneumonia and pneumonia mortality. Hazard ratios (HR) and 95% confidence intervals (CI) were estimated using Cox-proportional hazards regression. Absolute risk differences (ARD) and number needed to treat (NNT) were calculated.

Results This study identified 54,047 patients with hip fracture. Of these, 4,041 patients who received N-BPs and 11,802 without anti-osteoporosis medication were propensity score matched. N-BPs was associated with a significantly lower risk of pneumonia compared with no treatment (6.9 vs 9.0 per 100 person-years; HR 0.76, 95% CI0.70-0.83), resulting in an ARD of 0.02 and NNT of 46. A similar association was observed with pneumonia mortality (HR 0.65, 95% CI 0.56-0.75). When N-BPs were compared with non-N-BPs anti-osteoporosis medications, the association remained significant.

Conclusions N-BPs were associated with lower risks of pneumonia and pneumonia mortality. N-BP may be a new non-vaccine based medication to reduce pneumonia incidence in high risk groups.

Keywords: antiresorptives, osteoporosis, epidemiology, general population studies

Introduction

Nitrogen-containing bisphosphonates (N-BPs) are widely used in the treatment of postmenopausal osteoporosis, with alendronate being the first-line medication in many countries. Early studies have suggested potential beneficial effects of alendronate and related N-BPs on the lung. A pharmacokinetic study showed the highest concentration of alendronate in the trachea among all non-bone tissues studied and it was retained in the trachea >60 days after a single or 7-day repeated intravenous administration.(1) Alendronate was still detected in the trachea with a concentration of 607 ng/ml (vs 1370 ng/ml detected in vertebra) seventy-two hours after oral ingestion.(2) Moreover, alendronate targets the same pathway as statins. A previous animal study and a recent randomized controlled trial (RCT) showed that statins possess immunomodulatory effects(3) and improve pneumonia survival(4).

Based on of the above evidence, we hypothesized that N-BP could protect humans from pneumonia and its associated mortality. To test this hypothesis, we conducted a real-world population-based propensity score (PS) matched cohort study in hip fracture patients, in which pneumonia was the leading cause of death.(5) The risk of incident pneumonia and pneumonia mortality in hip fracture patients receiving N-BPs, compared with no anti-osteoporosis medication or non-N-BPs anti-osteoporosis medications, was studied.

Materials and Methods

Data source

Data was collected from the Clinical Data Analysis and Reporting System (CDARS), an electronic medical database managed by the HKHA. HKHA is a public healthcare provider, serving >80% of hospital admissions in Hong Kong. CDARS is a centralized database developed for research and audit. It includes anonymized records of demographics, admission, prescription, diagnosis, procedures, laboratory tests results, and deaths. The database has been widely used in population-based studies(5, 6) and specifically validated for bone fractures studies.(7)

Study cohort

We identified a historical study cohort using CDARS. Patients aged≥50 years who were admitted via an emergency room between January 1 2005 and December 31 2015, with an incident hip fracture (ICD-9 code 820.XX) were included. To reduce selection bias and/or competing risk of death, we excluded patients who had i) previous exposure to anti-osteoporosis medications since 1993 when data were first available in CDARS; ii) prolonged length of stay (LOS) after hip fracture, defined as >60 days according to the general LOS of patients with hip fracture in Hong Kong(8). , as patients with prolonged LOS might be physically unfit to receive anti-osteoporosis medications; or iii) history of cancer since bone targeting agents are often prescribed. All patients in the study cohort were followed until December 31 2016 (end of study) to allow at least one-year of follow-up.

Exposure and outcomes

Patients were classified as "N-BPs-exposed" if they had a prescription record of any N-BPs, including alendronate, ibandronate, risedronate, and zoledronate, before the end of study.

Bisphosphonates can accumulate in the skeleton(9) and their residual effects after treatment withdrawal can be sustained up to 7 years.(10) Due to the above characteristics and to emulate the "intention-to-treat" principle, the patients were considered exposed to the drug if they received any treatment with bisphosphonates until the end of follow-up.

In the primary analysis, we compared patients treated with N-BPs (N-BPs-exposed) to patients without any anti-osteoporosis medication treatment (non-exposed). In the secondary analysis, we compared patients treated with N-BPs to patients treated with non-N-BP anti-osteoporosis medications with different mechanism-of-actions, namely denosumab, raloxifene, salcatonin, strontium ranelate, and teriparatide.

The outcomes of interest were pneumonia incidence and death (pneumonia mortality). Diagnosis of pneumonia was defined as in-patient/out-patient records coded with ICD-9 codes 480-487.0. Pneumonia mortality was defined by a cause of death with ICD-10 codes J12-J18.

Propensity Score matching

Propensity scores (PS) were used to reduce potential confounding by non-randomized treatment allocation.(11) Propensity score was defined as a conditional probability of receiving certain treatment given a patient's characteristics. Details and covariates used to estimate PS are provided in Supplementary Method and Supplementary Table S1. Immortal time bias that favours the treatment group might arise due to the differences in follow-up start day between patients in non-

exposed and N-BPs-exposed groups. To address the bias, we adopted a time-dependent PS matching approach, where N-BPs-exposed patients were matched with patients who were not yet exposed to N-BPs at the particular time point, allowing the comparison groups to be followed from the same starting point.(12) Details of the time-dependent PS matching are described in the Supplementary Methods. (13) To reduce any unmeasured confounding, PS trimming was performed before matching, in which patients with treatment status contrary to the prediction, i.e. patients with PS<5^{th} percentile of treated or >95^{th} percentile of untreated, were excluded. (14)

Given that the exposure status is time-dependent, a patient was considered as non-exposed until the initial prescription of N-BP. In the primary analysis, each N-BPs-exposed patient was matched with up to three non-exposed patients using sequential greedy matching(15) with a caliper of 0.2 standard deviations (SD), without replacement. In the secondary analysis, each patient in the non-N-BP anti-osteoporosis medication group was matched with up to three patients in the N-BPs-exposed group, without replacement, since more patients were treated with N-BPs than non-N-BP anti-osteoporosis medications. To assess the quality of matching, the absolute standardized differences (ASD) in covariates between treatment groups were estimated. ASD<0.1 was considered as well-balanced matching.(16) Any covariate with ASD≥0.1 was further adjusted in the regression analysis.

Patients were followed from the index date until the occurrence of a pneumonia event, switch to another anti-osteoporosis medication, death, or end of study, whichever occurred first. The index date in N-BP-exposed patients was the date of first prescription while the index date in non-exposed patients was matched with N-BPs-exposed patients.

Statistical analysis

Continuous variables were presented as mean±SD and categorical variables as frequency (percentage). Incidence rates per 100 person-years and 95% confidence intervals (CIs) were estimated using Poisson distribution. Time-to-event analysis was used to evaluate the association of N-BPs with outcomes. Hazard ratios (HRs) and 95% CIs were estimated using Cox proportional hazards regression models stratified on the matched pairs. Kaplan–Meier curves comparing treatment groups were plotted and tested using a stratified log-rank test on matched pairs. The absolute risk difference (ARD) between treatment groups was estimated using the formula (incidence rate ratio – 1) x incidence rate of event in non-exposed group, where incidence rate ratio was interpreted as HR, given the large sample size. The number needed to treat (NNT) was calculated as the reciprocal of ARD.

Additional analyses

Subgroup analyses were performed by sex and history of pneumococcal/seasonal influenza vaccination. Sensitivity analysis was conducted to detect any residual and unmeasured confounding. First, we excluded patients receiving late treatment (start of first treatment>180 days from the time of discharge from hip fracture). Since a longer time from hip fracture is associated with a lower pneumonia risk, patients with delayed treatment were excluded to prevent bias. The 180 days cut-off was used because mortality of hip fracture stabilized after 180 days.(5) Second, we repeated the analysis in the unmatched cohort using inverse probability of treatment weighting (IPTW). PS-matching excluded unmatched subjects in the analysis, limiting the sample size and

generalizability of the study. Conversely, IPTW retains all subjects in the study cohort and overcomes the limitation in PS-matching. Details of IPTW and calculation of the weights using PS were discussed elsewhere.(17) In this study, we conducted IPTW using stabilized weights with truncation at 5%. Finally, the E-value(18, 19) was also computed to further evaluate the robustness of the findings to unmeasured confounding.(20)

R was used for all statistical analyses. A two-sided p-value<0.05 was considered significant.

Results

Baseline characteristics

We identified 54,047 patients from the database. Among the 43,349 patients included after screening (Figure 1), 6,467 (14.9%) were prescribed anti-osteoporosis medication by the end of study. In the primary analysis, 4,041 N-BPs-exposed patients were matched with 11,802 non-exposed patients. The covariates were well-matched (ASD<0.1) except for the year of index date, frequency of in-patient admissions, and the use of anticoagulants and nonsteroidal anti-inflammatory drugs in the past 180 days (Table 1), which were later adjusted in the analysis. In the secondary analysis, 1,284 N-BP exposed patients were matched with 507 non-N-BP anti-osteoporosis medications exposed patients (166 on strontium ranelate, 161 on salcatonin, 135 on denosumab, 38 on teriparatide, and 7 on raloxifene). All covariates were well-matched (Supplementary Table S2). The Kaplan–Meier curves between treatment groups showed significant difference in the pneumonia events (Figure 2).

N-BPs and risk of pneumonia

The median follow-up time was 2.7 years (interquartile range 1.3 to 5.1 years). The incidence of pneumonia was 9.0 and 6.9 per 100 patient-years for the non-exposed and N-BPs-exposed groups, respectively (Table 2). N-BPs were associated with a reduced risk of incident pneumonia (HR 0.76, 95% CI 0.70 to 0.83; Table 2), with an ARD of 0.02 (95% CI 0.03 to 0.02), and 46 (95% CI 37 to 65) patients were required to treat to prevent one pneumonia. Similar significant findings were observed for alendronate exposure (Table 2).

No significant interaction was observed for N-BPs with gender and vaccination, and subgroup analyses revealed similar findings (Supplementary Table S3). In the sensitivity analyses (Supplementary tables S4), late treatment and IPTW analysis revealed similar findings. The E-value for point estimate and upper confidence limit was 1.96 (1.7).

N-BPs and risk of pneumonia mortality

The pneumonia mortality was 3.5 and 2.3 per 100 patient-years for the non-exposed and N-BPs-exposed groups, respectively (Table 2). N-BPs were associated with a reduced risk of pneumonia mortality (HR 0.65, 95% CI 0.56 to 0.75; Table 2). Similar significant findings were observed for alendronate exposure (Table 2). No significant interaction was observed for N-BP with gender and vaccination on pneumonia mortality (Supplementary Table S3). Similar results were observed in the subgroup (Supplementary Table S3) and sensitivity analyses (Supplementary Tables S4). The E-value for point estimate and upper confidence limit was 2.45 (2).

N-BPs vs. non-N-BP anti-osteoporosis medications

To avoid confounding by indication, non-N-BP anti-osteoporosis medications was considered as the comparator. Similarly, the association of N-BPs was significant (pneumonia: HR 0.68, 95% CI 0.53 to 0.87; pneumonia mortality: HR 0.60, 95% CI 0.41 to 0.89; Table 3). Using the IPTW method with maintained sample size, significant associations of N-BPs with reduced risk of pneumonia incidence and mortality were observed (pneumonia: HR 0.52, 95% CI 0.44–0.61; pneumonia mortality: HR 0.38, 95% CI 0.3–0.47; Supplementary Table S4).

Discussion

This is the first real-world population-based study using a large electronic clinical database to examine the potential effect of N-BPs on post-hip fracture pneumonia risk. Patients prescribed N-

BPs had a significantly reduced pneumonia risk and mortality when compared with those without any treatment or with non-N-BP anti-osteoporosis medications. The effect was robust in various sensitivity and subgroup analyses.

Potential mechanisms

This hypothesis-testing study was based on evidence suggesting that N-BPs may have similar effects on both alveolar macrophages and osteoclasts, cells that share the same lineage, and thus may influence i the pathogenesis of pneumonia characterized by lung parenchyma inflammation. Alveolar macrophages play an important antibacterial role in defending against pneumonia by early phagocytosis of pathogens and subsequent induction of apoptosis to minimize inflammation.(21) A clinical study showed that N-BP reduced macrophage lineage cells(22) through the reduction of mcl-1 expressions in both macrophages(23) and osteoclasts(24), which might subsequently reduce inflammation(21). The pharmacology(21, 24) and pharmacokinetics(1, 2) of N-BPs also make it a potential drug for pneumonia as previously mentioned. N-BP (pamidronate) expands human Vγ9Vδ2 T-cell populations in humanized mice, kills influenza -infected cells, inhibits *in vitro* influenza viral replication, and subsequently reduces the severity of influenza infection and the associated mortality.(25) Moreover, both N-BP and statins target the same pathway, and possess similar anti-inflammation and immunomodulatory effects.(3, 26) In a recent RCT, statin improved neutrophil function and hospital-free survival in pneumonia.(4) Furthermore, that study also proposed that N-BP (zoledronate) could maintain physiological reserve, thus enhancing the ability to recover from acute illnesses.(27) Together with the current study, this evidence suggested N-BPs as a new promising drug class in reducing risk of pneumonia and its associated mortality.

Comparison with other studies

Our study is in agreement with a post-hoc analysis(27) of HORIZON Recurrent Fracture Trial, which demonstrated that zoledronate reduced pneumonia mortality by ~50% after a mean follow-up of 2 years. Similarly, we observed HRs of 0.65 in N-BPs group at a 3-year (median) follow-up for pneumonia mortality, respectively. Although the post-hoc analysis of the RCT showed only a slightly lower incidence of pneumonia in the zoledronate group (5.5% in zoledronate group vs. 5.6% in placebo group), such a discrepancy could be due to the highly selected patients in the HORIZON RCT, which excluded patients who were unwilling/unable to take oral bisphosphonate and had life expectancy<1 year as judged by the investigators. Patients with high risk of pneumonia might be excluded, leading to reduced statistical power. Moreover, the self-reported pneumonia incidence was subjected to under-diagnosis, loss of follow-up, and recall and misclassification bias, resulting in a bias towards the null hypothesis. Conversely, the larger sample size of the current study has increased the power to detect differences with statistical significance. Also, we used the clinical diagnosis of pneumonia by physicians, which is more accurate and less biased. It should be noted that our study included mainly alendronate-exposed patients (81.6%); however given that alendronate and zoledronate have the same pharmacology with different potency(28), it is possible that alendronate could have similar effects on reducing pneumonia, which is supported by our findings. Further studies investigating the link between alendronate and pneumonia are warranted.

Previous RCTs and observational studies have suggested 10% to 60% reduction of all-cause mortality by bisphosphonates (29-31) Among these studies, only a few reported the cause of death

(30) or the risk of pneumonia mortality(31). Apart from the post-hoc analysis of the HORIZON Recurrent Fracture Trial as previously mentioned, a prospective study involving 78 bisphosphonates users (63 on alendronate) and 1,923 non-users has reported a reduced risk of death due to infection (including pneumonia) but the association did not reach statistical significance (HR 0.64, 95%CI 0.35-1.19, p = 0.16).(31) Indeed, the point estimate reported in this study is similar in magnitude to our finding; however the lack of statistical significance possibly could be due to the lack of power with a small sample. Therefore, more studies on the effect of N-BPs on cause-specific mortality are warranted. On the other hand, a recent meta-analysis of RCTs reported no association between bisphosphonates and overall mortality.(32) This meta-analysis of 38 RCTs included patients with osteoporosis, osteopenia, and osteoporotic fractures. Indeed, if RCTs of patients with osteoporotic fractures was selected, a reduced risk of mortality (pooled risk ratio 0.79; 95% CI 0.65 – 0.95; I^2 = 0%) would be observed. Although the pooled risk ratio was largely driven by one RCT which studied zoledronate, as mentioned previously, it is possible that alendronate would have similar effects as zoledronate. In addition, there is a longstanding debate that RCTs excluding patients with chronic health conditions result in a healthier cohort that is unrepresentative of the real-world setting. (33) Bisphosphonate studies are susceptible to such bias because in clinical settings, the drugs are commonly used in old patients with multiple chronic diseases. The effect of bisphosphonates in reducing mortality might be more pronounced in higher-risk groups e.g. patients with osteoporotic fractures, or critically ill patients(34) than lower-risk groups. We, therefore, suggest the inclusion of high-risk patients in future anti-osteoporosis treatment RCTs.

Since frail patients would be less likely to receive anti-osteoporosis medications after hip fracture, bias in the prescribing of treatment could exist. As shown in Table 1, N-BPs exposed patients in the pre-matched cohort generally had less comorbidity compared with the non-exposed group. We, therefore, used patients receiving non-N-BP anti-osteoporosis medications as a comparator. A significant reduced risk of pneumonia and pneumonia mortality was still observed. On the other hand, patients receiving medication treatment could be wealthier and thus could get a better medical care, resulting in a lower risk of infections and mortality. Nonetheless, such bias should be minimal because the cost of N-BPs are highly subsidized in Hong Kong and also we used non-N-BP anti-osteoporosis medications, which are more expensive than N-BPs, as a comparator. In addition, the analyses were repeated using injury or trauma hospitalization as a negative control outcome.(35) No significant association was observed (Supplementary Table S5), suggesting minimal confounding bias.

Clinical implication

Currently, vaccination is the only medication that can prevent pneumonia. In our subgroup analysis, we showed that N-BPs were associated with reduced pneumonia risk and mortality, regardless of the vaccination status. N-BPs could therefore confer additional protection against pneumonia to compensate for the reported shortage and low acceptance of vaccine, as well as the high cost of large-scale vaccination program. Drug repositioning of N-BPs as a pneumonia-prevention drug, especially in high-risk groups (e.g. patients with osteoporosis), may be of public health importance. The multiple benefits of using N-BPs in hip fracture patients may help to promote the use of these medications, especially in light of the fact that anti-osteoporosis medications are under-utilized.(36) Given the potential importance of N-BPs, further investigation or a RCT is warranted.

Strengths and limitations

Our study has several strengths. A clinical database capturing most records with high validity(37) was used to conduct this population-based study to provide ample power for association detection. We also used non-N-BP anti-osteoporosis medications as a comparator to minimize confounding by indication. The finding is likely generalizable to hip fracture patients, who are susceptible to pneumonia.

Limitations of the study included the unavailability of data regarding infection type. There might also be competing risk of death. However, such effect should be minimal since pneumonia is the top leading cause of death and similar results were observed using competing risk regression (data not shown). In addition, there might be potential residual confounding. Nonetheless, the calculated E-values of incident pneumonia and pneumonia mortality were greater than any risk factors included in the PS model (Supplementary Table S6), suggesting the presence of unmeasured confounding that could overcome the effect of N-BPs treatment observed was unlikely. Moreover, our previous study has revealed association between N-BP and reduced risk of myocardial infarction(5) and the association was subsequently observed in a large-scale RCT of zoledronate.(38) Such external and independent validation in RCT provided a strong support for the validity and causality of our findings. Besides, further studies are required to determine if the results are generalizable to other disease groups.

Conclusion

Among patients with hip fracture, the use of N-BPs was associated with a lower risk of pneumonia and associated mortality when compared to non-N-BP anti-osteoporosis or no anti-osteoporosis medication use. Future RCTs may be warranted to further validate the findings.

Contributors: C.W.S., D.P.K., R.B.H., C.L.C. designed the study. C.W.S. and C.L.C. collected data and conducted data analysis. C.W.S., D.P.K., R.B.H., W.C.L., A.W.K., I.C.W., C.L.C. interpret the data. C.W.S. and C.L.C. drafted the manuscript. C.W.S., D.P.K., R.B.H., W.C.L., G.H.L., A.W.K., I.C.W., C.L.C. revised the manuscript. All authors approved final version of manuscript. C.L.C. takes responsibility for the integrity of the data analysis.

Acknowledgements: None

Funding: None

Ethical approval: The study protocol was approved by the institutional review boards of the University of Hong Kong and Hong Kong Hospital Authority (HKHA); Reference: UW17-364.

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459 **Figure Legends**

460 Figure 1. Screening flow chart of the study cohort

461 Figure 2. Kaplan–Meier curves comparing treatment groups for a) incident pneumonia and b)

462 pneumonia mortality. (p-value tested with stratified log-rank test on matched pairs)

463 Table 1. Baseline characteristics of the study population before and after propensity score matching, patients treated with N-BPs compared with no

464 treatment

	Pre-matched cohort			Matched cohort		
	Non-exposed	N-BPs exposed	ASD	Non-exposed	N-BPs exposed	ASD
Subject, n (%)	37542	5807		11802	4041	
Male, n (%)	12178 (32.4)	1229 (21.2)	0.26	2791 (23.6)	928 (23.0)	0.02
Age, mean (SD)	81.9 (9.5)	80.0 (8.6)	0.22	80.3 (9.8)	80.3 (8.4)	<0.01
50-69	3835 (10.2)	715 (12.3)		1617 (13.7)	446 (11.0)	
70-89	25844 (68.8)	4458 (76.8)		8314 (70.4)	3131 (77.5)	
90+	7863 (20.9)	634 (10.9)		1871 (15.9)	464 (11.5)	
Year of index date, n (%)			0.66	0		0.31
2005	3048 (8.1)	46 (0.8)		419 (3.6)	43 (1.1)	
2006	3325 (8.9)	95 (1.6)		376 (3.2)	71 (1.8)	
2007	3323 (8.9)	272 (4.7)		962 (8.2)	196 (4.9)	
2008	3555 (9.5)	350 (6.0)		1092 (9.3)	271 (6.7)	
2009	3252 (8.7)	584 (10.1)		1279 (10.8)	401 (9.9)	
2010	3201 (8.5)	808 (13.9)		1272 (10.8)	485 (12.0)	
2011	3493 (9.3)	661 (11.4)		1154 (9.8)	472 (11.7)	
2012	3487 (9.3)	564 (9.7)		1023 (8.7)	396 (9.8)	
2013	3406 (9.1)	636 (11.0)		1126 (9.5)	445 (11.0)	
2014	3662 (9.8)	762 (13.1)		1407 (11.9)	493 (12.2)	
2015	3498 (9.3)	693 (11.9)		1367 (11.6)	532 (13.2)	
2016	292 (0.8)	336 (5.8)		325 (2.8)	236 (5.8)	
Admission hospital cluster, n (%)						0.09
Hong Kong West Cluster	2842 (7.6)	409 (7.0)		1056 (8.9)	314 (7.8)	
Hong Kong East Cluster	4307 (11.5)	937 (16.1)		1925 (16.3)	596 (14.7)	
New Territories West Cluster	4562 (12.2)	307 (5.3)		650 (5.5)	227 (5.6)	
New Territories East Cluster	6252 (16.7)	1026 (17.7)		2252 (19.1)	842 (20.8)	
Kowloon West Cluster	7442 (19.8)	1309 (22.5)		2588 (21.9)	844 (20.9)	

Kowloon East Cluster	4698 (12.5)	1339 (23.1)		2190 (18.6)	858 (21.2)	
Kowloon Central Cluster	7439 (19.8)	480 (8.3)		1141 (9.7)	360 (8.9)	
Nursing home residency, n (%)	10706 (28.5)	778 (13.4)	0.38	1426 (12.1)	518 (12.8)	0.02
Seasonal influenza / Pneumococcal vaccination, n (%)	4004 (10.7)	1020 (17.6)	0.20	1683 (14.3)	637 (15.8)	0.04
Surgical operation for hip fracture, n (%)	33158 (88.3)	5650 (97.3)	0.35	11448 (97.0)	3948 (97.7)	0.04
Frequency of healthcare service in past one year, mean (SD)						
In-patient admission	1.9 (3.3)	1.5 (2.0)	0.13	1.6 (1.5)	1.4 (1.1)	0.16
Out-patient clinics	7.9 (10.1)	11.6 (11.8)	0.34	9.9 (10.5)	10.2 (9.8)	0.03
Intensive care units	0.02 (0.13)	0.01 (0.12)	0.01	0.02 (0.13)	0.01 (0.10)	0.05
Medical history, n (%)						
Coronary heart disease	5043 (13.4)	602 (10.4)	0.10	1276 (10.8)	390 (9.7)	0.04
Congestive heart failure	4147 (11.0)	445 (7.7)	0.12	908 (7.7)	287 (7.1)	0.02
Arrhythmia and conduction disorders	4917 (13.1)	592 (10.2)	0.09	1261 (10.7)	403 (10.0)	0.02
Arterial disease	1814 (4.8)	246 (4.2)	0.03	487 (4.1)	161 (4.0)	0.01
Hypertensive disease	16216 (43.2)	2584 (44.5)	0.03	5037 (42.7)	1669 (41.3)	0.03
Cerebrovascular disease	7032 (18.7)	872 (15.0)	0.10	1732 (14.7)	610 (15.1)	0.01
Chronic obstructive pulmonary disease	3829 (10.2)	531 (9.1)	0.04	998 (8.5)	328 (8.1)	0.01
Other lung diseases	7547 (20.1)	1070 (18.4)	0.04	2021 (17.1)	694 (17.2)	<0.01
Diabetes	8296 (22.1)	1356 (23.4)	0.03	2662 (22.6)	854 (21.1)	0.03
Hyperlipidemia	3473 (9.3)	681 (11.7)	0.08	1214 (10.3)	394 (9.8)	0.02
Obesity	102 (0.3)	23 (0.4)	0.02	44 (0.4)	10 (0.2)	0.02
Renal failure	2119 (5.6)	135 (2.3)	0.17	302 (2.6)	95 (2.4)	0.01
Chronic liver disease	304 (0.8)	35 (0.6)	0.03	88 (0.7)	24 (0.6)	0.02
Osteoporosis	1576 (4.2)	849 (14.6)	0.36	551 (4.7)	224 (5.5)	0.04
Fall	36431 (97.0)	5691 (98.0)	0.06	11504 (97.5)	3957 (97.9)	0.03
Other major fractures	4408 (11.7)	885 (15.2)	0.10	1584 (13.4)	560 (13.9)	0.01
Connective tissue disease	221 (0.6)	128 (2.2)	0.14	104 (0.9)	46 (1.1)	0.03
Dementia	3416 (9.1)	236 (4.1)	0.20	392 (3.3)	140 (3.5)	0.01
Thyroid disorders	1007 (2.7)	171 (2.9)	0.02	336 (2.8)	109 (2.7)	0.01

Prescription in past 180 days, n (%)						
Digoxin	1256 (3.3)	123 (2.1)	0.08	271 (2.3)	90 (2.2)	0.01
Loop diuretics	5074 (13.5)	571 (9.8)	0.12	1241 (10.5)	377 (9.3)	0.04
Other diuretics	2797 (7.5)	401 (6.9)	0.02	841 (7.1)	305 (7.5)	0.02
Anti-arrhythmics class I and II	668 (1.8)	69 (1.2)	0.05	197 (1.7)	43 (1.1)	0.05
Beta blockers	7977 (21.2)	1218 (21.0)	0.01	2538 (21.5)	823 (20.4)	0.03
Angiotensin receptor blocker/ angiotensin converting enzyme inhibitor/ renin inhibitor	8692 (23.2)	1415 (24.4)	0.03	2761 (23.4)	939 (23.2)	<0.01
Nitrates	3973 (10.6)	460 (7.9)	0.09	953 (8.1)	309 (7.6)	0.02
Calcium channel blockers	14296 (38.1)	2137 (36.8)	0.03	4204 (35.6)	1465 (36.3)	0.01
Peripheral vasodilators	701 (1.9)	56 (1.0)	0.08	119 (1.0)	35 (0.9)	0.02
Anticoagulants	2375 (6.3)	316 (5.4)	0.04	766 (6.5)	150 (3.7)	0.13
Platelet inhibitors	10405 (27.7)	1407 (24.2)	0.08	2836 (24.0)	935 (23.1)	0.02
Lipid regulating drugs	5119 (13.6)	1042 (17.9)	0.12	1804 (15.3)	694 (17.2)	0.05
Antipsychotics	4216 (11.2)	306 (5.3)	0.22	642 (5.4)	217 (5.4)	<0.01
Antidepressants	3500 (9.3)	461 (7.9)	0.05	934 (7.9)	294 (7.3)	0.02
Antidiabetic drugs	7244 (19.3)	1171 (20.2)	0.02	2290 (19.4)	784 (19.4)	<0.01
Oral corticosteroids	1677 (4.5)	313 (5.4)	0.04	506 (4.3)	161 (4.0)	0.02
Non-steroidal anti-inflammatory drugs	3360 (8.9)	589 (10.1)	0.04	1315 (11.1)	325 (8.0)	0.10
Proton pump inhibitors	4393 (11.7)	523 (9.0)	0.09	1051 (8.9)	344 (8.5)	0.01
Beta2 agonists	3831 (10.2)	488 (8.4)	0.06	901 (7.6)	304 (7.5)	<0.01
Inhaled corticosteroids	1633 (4.3)	246 (4.2)	0.01	440 (3.7)	145 (3.6)	0.01
Immunosuppressant	40 (0.1)	21 (0.4)	0.05	15 (0.1)	5 (0.1)	<0.01

N-BPs nitrogen-containing bisphosphonates

ASD Absolute standardized difference, compared with non-exposed group

467 Table 2. Risk of pneumonia in patients treated with N-BPs after hip fracture, compared with no treatment

Outcome	Group	Subject, n	Event, n	Mortality / Incidence rate, per 100 person-years	Hazard ratio[b] (95% CI)	P
Incident pneumonia	Non-exposed	11,802	3,595	9.0 (8.7-9.3)	1	-
	All N-BPs[a]	4,041	977	6.9 (6.5-7.3)	0.76 (0.70-0.83)	<0.001
	Alendronate	3,298	732	6.8 (6.3-7.3)	0.74 (0.67-0.81)	<0.001
Pneumonia mortality	Non-exposed	11,802	1,550	3.5 (3.3-3.7)	1	-
	All N-BPs	4,041	354	2.3 (2-2.5)	0.65 (0.56-0.75)	<0.001
	Alendronate	3,298	270	2.3 (2-2.6)	0.63 (0.54-0.74)	<0.001

468 a N-BPs included alendronate, ibandronate, zoledronate, and risedronateb Models were adjusted for
469 imbalanced variables (year of index date, frequency of in-patients admission , use of anticoagulants and
470 nonsteroidal anti-inflammatory drugs in the past 180 days)

471

Table 3. Risk of pneumonia in patients treated with N-BPs after hip fracture, compared with non-N-BP anti-osteoporosis medications

Outcome	Group	Subject, n	Event, n	Mortality / Incidence rate, per 100 person-years	Hazard ratio (95% CI)	P
Incident pneumonia	Non-N-BPs[b]	507	161	14 (11.9-16.3)	1	1
	All N-BPs[a]	1,284	366	8.5 (7.7-9.4)	0.68 (0.53-0.87)	0.002
	Alendronate	1,009	256	8.3 (7.3-9.3)	0.67 (0.52-0.87)	0.003
Pneumonia mortality	Non-N-BPs	507	75	5.6 (4.4-7)	1	1
	All N-BPs	1,284	139	2.9 (2.4-3.4)	0.60 (0.41-0.89)	0.01
	Alendronate	1,009	103	3.0 (2.4-3.6)	0.65 (0.42-1)	0.049

a. N-BPs included alendronate, ibandronate, risedronate, and zoledronate

b. Non-N-BP included denosumab, raloxifene, salcatonin, strontium ranelate, and teriparatide

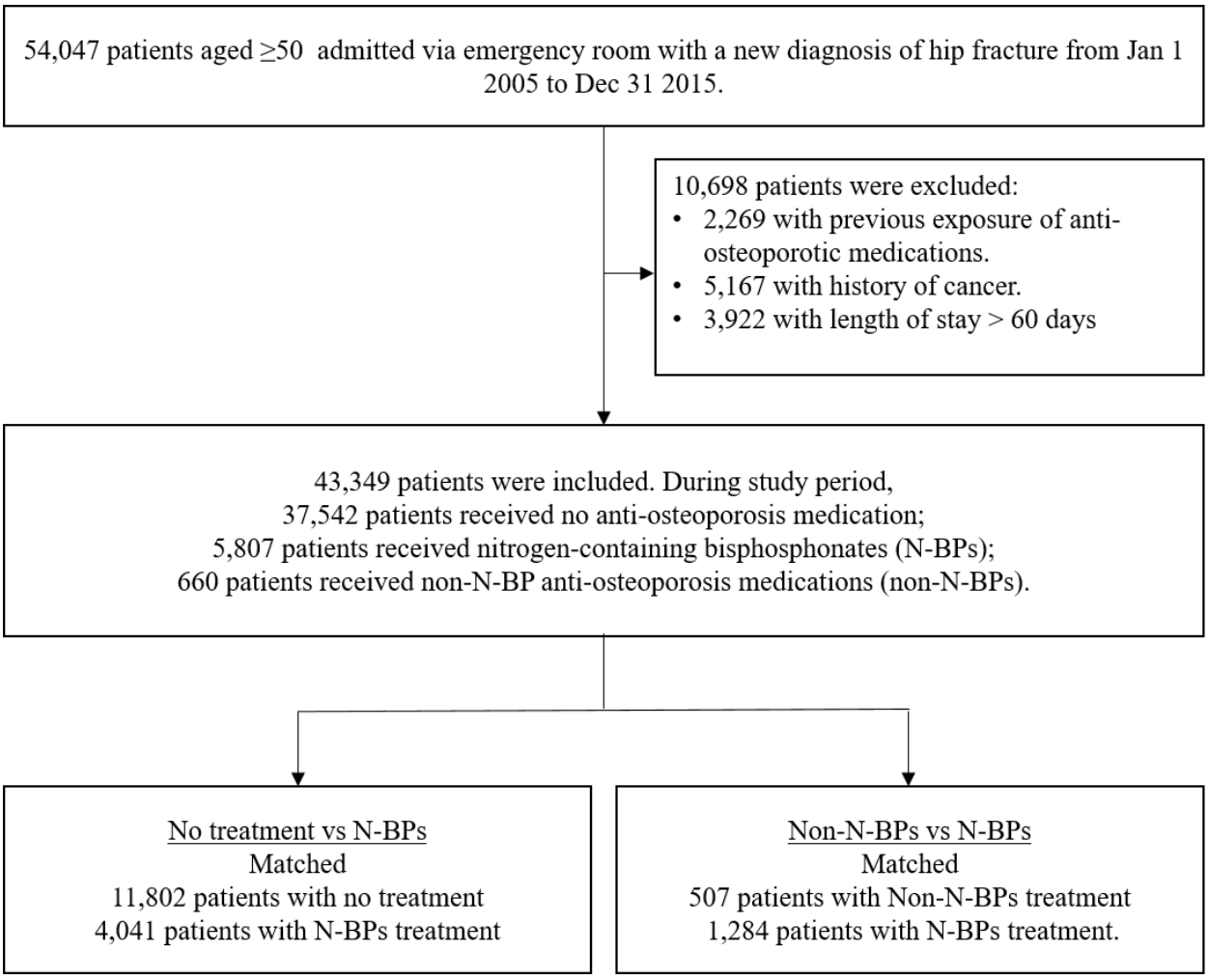

Figure 1. Screening flow chart of the study cohort

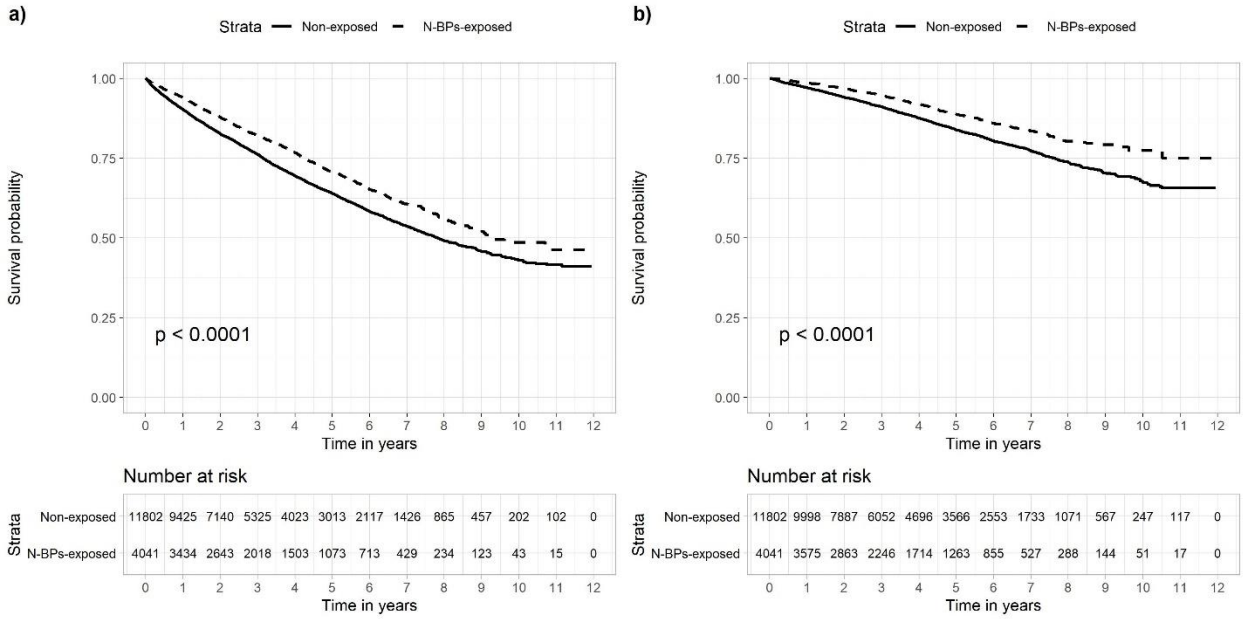

Figure 2. Kaplan–Meier curves comparing treatment groups for a) incident pneumonia and b) pneumonia mortality. (p-value tested with stratified log-rank test on matched pairs)