Association of Alendronate and Risk of Cardiovascular Events in Patients with Hip Fracture

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Abstract

The risk of cardiovascular events (CVE) with alendronate use in real-world hip fracture patients is unknown. This study aimed to investigate the risk of CVE with and without use of alendronate in patients with hip fracture. We conducted a retrospective cohort study using a population-wide database managed by the Hong Kong Hospital Authority. Patients newly diagnosed with hip fracture from 2005 through 2013 were followed until November 6, 2016. Alendronate and other anti-osteoporosis medications use during the study period were examined. We matched treated and non-treated patients based on time-dependent propensity score. The risks of cardiovascular mortality, myocardial infarction, and stroke between treatment groups were evaluated using conditional Cox regression stratified by match pairs. To examine the associations over time, outcomes were assessed at 1-, 3-, 5- and 10-years. Among 34,991 patients with newly diagnosed hip fracture, 4,602 (13.2%) received anti-osteoporosis treatment during follow-up. Physical functioning or survival prospect was not significantly different between treated and non-treated patients. 4,594 treated patients were matched with 13,568 non-treated patients. Results of Cox-regression analysis revealed that alendronate was associated with a significantly lower risk of one-year cardiovascular mortality (HR: 0.33; 95% CI: 0.17-0.65) and incident myocardial infarction (HR: 0.55; 95% CI: 0.34-0.89), whereas marginally significant reduction in risk of stroke was observed at 5- and

10-years (HR at 5-years: 0.82; 95% CI: 0.67-1; p=0.049; HR at 10-years: 0.83; 95% CI:0.69-1.01; p=0.065). The strength of the association declined over time but remained significant. Similar results were observed when all nitrogen-containing bisphosphonates were analyzed together. These findings were robust in multiple sensitivity analyses. Additional studies in other population samples and randomized clinical trials may be warranted to further understand the relationship between use of various anti-osteoporosis medication and risk of CVE in patients with hip fracture.

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Introduction

Hip fracture is a common condition that leads to great morbidity and mortality in the elderly population. One of the consequences of hip fracture is an increased risk of cardiovascular events (CVE) such as MI,[1] stroke,[2] and cardiovascular mortality.[3, 4] Thus, there is a clinical need to be aware of this increased risk of CVE among patients who sustain a hip fracture, and to intervene to reduce these life-threatening outcomes. Nonetheless there are no clinical recommendations that address this issue.

Nitrogen-containing bisphosphonates (N-BPs) are the recommended treatment for the secondary prevention of fractures in persons who have sustained a fragility fracture [5]. However, N-BPs are under-used worldwide due to patients' concerns about potential side effects.[6] Emerging evidence has suggested that N-BPs are potential cardiac-protecting agents. [7, 8] A longitudinal cohort study in women showed an association of N-BPs and decreased prevalence of cardiovascular calcification in older subjects.[7] Another randomized clinical trial demonstrated that treatment with alendronate inhibited the progression of aortic calcification after kidney transplant, compared with no treatment of bisphosphonates.[8] Animal studies found that farnesyl pyrophosphate synthase (FPPS), the molecular target of N-BPs, is involved in the pathogenesis of cardiac hypertrophy. Cardiac-specific over-expression or inhibition (using alendronate)

of FPPS in mice has been shown to result in[9] or attenuate[10] cardiac hypertrophy, respectively.

While the risk of all-cause mortality was reduced by 10-60% in patients treated with N-BPs after hip fracture,[11-13] the risk of CVE was inconclusive. A previous randomized controlled trial (RCT) and cohort study showed a trend towards reduction of cardiovascular mortality in patients treated with zoledronate[4] or risedronate[14] following a hip fracture. A recent meta-analysis of RCTs reported a lower risk of cardiovascular mortality in the use of bisphosphonates, although not statistically significant.[11] In view of these findings, further studies are needed to evaluate the role of anti-osteoporosis medication in CVE.[15] Because RCT data are limited with regard to CVE outcomes and participants in clinical trials are rarely representative of the actual patient population receiving medications, large observational studies that include methods to minimize confounding by indication may add important data complementing the randomized trials.

This population-based cohort study used data from a large territory-wide healthcare database to determine the risk of CVE in patients with hip fracture, with and without use of alendronate.

Materials and Methods

Methods

The study protocol was approved by the institutional review boards of the University of Hong Kong and Hong Kong HA.

Data source

Data was collected from the Clinical Data Analysis and Reporting System (CDARS), an electronic medical database managed by the Hong Kong HA. HA is a public healthcare provider that manages 42 hospitals and institutions, and 120 out-patient clinics, serving >80% of hospital admissions in Hong Kong. CDARS is a centralized database developed for the purposes of research and audit. It includes records of demographics, admission, prescription, diagnosis, procedures, laboratory tests, and deaths. All records are anonymized. The database has been widely used in conducting high-quality population-based studies[16, 17] and is specifically validated for study of the effects of medication on bone fractures.[18] More information about Hong Kong HA is provided in the Supplemental Methods.

Study cohort

This was a retrospective cohort study. We identified patients aged≥50 years who were admitted via an emergency room between January 1 2005 and December 31 2013 with a new diagnosis of hip fracture (ICD-9, 820.XX). Patients who survived and were discharged were included in the study cohort. To reduce selection bias and/or competing risk of death, we excluded patients who fulfilled any of the following criteria: i) previous exposure to anti-osteoporosis medications two-year preceding the index date; ii) length of stay (LOS) in hospital>60 days (Supplemental Methods). Patients with a longer length of stay may be less healthy and unable to take anti-osteoporosis medications. Inclusion of these patients could lead to substantial selection bias; and iii) history of cancer where anti-resorptive agents are often prescribed.

Exposure and outcomes

The primary drug of interest was alendronate, which is the first-line therapy for osteoporosis, following hospital discharge post-fracture. Patients were classified as "alendronate-treated" if they had at least one prescription record of alendronate before the end of the study (November 6 2016). Bisphosphonates can accumulate in the skeleton[19] and studies have reported a residual effect of alendronate after treatment withdrawal for up to 7 years[20, 21]. Therefore, once being treated, the patients were considered exposed to the drug until the end of follow-up. In a secondary analysis, we

aimed to determine whether the association was also observed for all N-BPs as a single group (including alendronate, ibandronate, risedronate, and zoledronate), and for two anti-osteoporosis medications with different mechanism-of-actions commonly prescribed in Hong Kong (>1% usage among hip fracture patients), namely strontium ranelate and salcatonin.

Primary outcomes of interest were cardiovascular mortality, incident MI, and stroke during the follow-up period. Our previous studies validated the coding of MI and stroke in CDARS with a positive predictive value (PPV) of 85.4% and 91.1% respectively.[16] In the analysis of incident CVE, patients with outcomes of interest at baseline were excluded. All outcomes were defined by ICD-10 and ICD-9 and are shown in the (Supplemental Table 1 and Table 2).

Statistical analysis

The statistical analyses were conducted by two co-authors (C.W.S. and A.Y.S.W.) independently and cross-checked for quality assurance. Continuous variables are presented as mean±standard deviation (SD) and categorical variables as percentages. Incident rates per 10,000 person-years and the 95% confident intervals (CIs) for CVE were estimated using a Poisson distribution.

Time-to-event analysis was used to evaluate the association of anti-osteoporosis medication with outcomes. Since there may have been a delay in prescribing alendronate, immortal time bias was possible. Such bias, which would favor the treatment group, has been discussed elsewhere. [22, 23] To address this issue, a time-dependent propensity score matching was used [24, 25], which matches a patient treated at time *t* (defined as number of days from the date of discharge to first treatment) to another patient who had not received treatment yet at time *t* based on the propensity score (PS) at time *t*. The matched pair was followed from time *t* until the occurrence of an event, switch to another anti-osteoporosis medication, death, or study end (November 6 2016), whichever occurred first. Using this approach, treated and non-treated groups were followed at the same starting point (time *t*), which has been shown to be a superior approach to control immortal time bias.[26] As exposure to treatment is time-dependent, propensity scores at different time points were estimated using Cox regression with time-dependent covariates. Details are provided in Supplemental Methods and the list of covariates used in the PS model is shown in Supplemental Table 2. Each treated patient was matched with up to 3 non-treated patients using sequential greedy matching with a caliper of 0.2 standard deviation. Those who failed to match with a non-treated patient were excluded. To assess the quality of matching, absolute

standardized differences (ASD) in covariates between treatment groups were estimated. After matching, all covariates had an ASD <0.25 (Table 1), indicating that the covariates were well balanced [27]. Survival rate or disease-free survival rates of CVEs were plotted using the Kaplan-Meier method. [28] Hazard ratios (HRs) and 95% confidence intervals (CI) were estimated using a conditional Cox proportional hazard model stratified by the matched pairs. To examine the association of treatment and risk of CVEs over time, follow-up for 1, 3, 5, and 10 years was reported.

Sensitivity analysis was conducted to investigate any residual and unmeasured confounding. First, the risk of CVE is expected to be the highest close to the time of hip fracture. Thus, patients with late treatment would have a much lower risk of CVE at the time of treatment, leading to bias towards any protective effect of treatment. We, therefore, performed a sensitivity analysis by excluding patients with late treatment, defined as the start of first treatment over 180 days from the time of discharge. The cut-off 180 days was used because we observed that mortality of hip fracture stabilized after 180 days (Figure 1). In addition, patients with a short exposure of the drug would likely not have the beneficial effect of treatment. Therefore, another sensitivity analysis that excluded patients with treatment duration less than 30 days was conducted. For some very frail hip fracture patients, pharmacologic treatment may be perceived as non-

beneficial. Such practice may result in treatment of the subpopulation thought to have better survival prospects and long-term benefits in physical functioning. Thus, we performed a validation study to evaluate if those patients receiving treatment would have better survival prospects and physical functioning. Details are provided in the Supplemental Methods. Subgroup analysis was performed to evaluate the risk of outcomes by gender, history of cardiovascular disease (CVD; ICD9 390-495 Diseases of the circulatory system), history of diabetes, and type of surgical procedure for hip fracture.

R and SAS (version 9.3; SAS institute, Inc) were used for all statistical analyses. A two-sided p-value<0.05 was considered significant.

Results

Baseline characteristics

Between January 1 2005 and December 31 2013, 46,253 patients aged ≥50 years were admitted via the emergency room with a new diagnosis of hip fracture. The top three causes of mortality in the first year following hip fracture are shown in Figure 1. The risk of cardiovascular mortality was the highest in the first month after hip fracture (22.2%), and dropped to 11.6% after one year. Nonetheless, risk of pneumonia- and

cancer-mortality increased continuously.

Among 34,991 patients included in the final cohort (Figure 2), 2,868 (8.2%) were prescribed anti-osteoporosis medication in the first year, and 4,602 (13.2%, treated group) by study end date. The mean age of the cohort was 82±9.3 years and 24,337 patients (69.6%) were female. After PS-matching, 4,594 patients in the treatment group were matched with 13,568 non-exposed patients. The median (interquartile range, IQR) follow-up times in non-exposed and treated groups were 1,076 (1,349) days and 1,446 (1,371) days, respectively. Among the treated patients, 3,081 patients (67.1%) exposed to alendronate (98% of patients treated weekly and 2% treated daily). Of these alendronate-treated patients, over 60% were prescribed the drug in the first year with a mean±SD starting time of 100 (93.5) days after hip fracture. Compared to those patients who were not on treatment, the patients receiving treatment was not associated with better physical functioning or survival prospect, with an odds ratio of 1.01 (95% CI: 0.41-2.50); P=0.98. Survival curves of alendronate treatment and risk of CVEs are presented in Figure 3.

Alendronate and risk of CVE

At one-year follow up, the incidence of cardiovascular mortality was 108.9 and 34.7

per 10,000 patient-years for the non-treated and alendronate-treated groups, respectively (Table 2). Alendronate was associated with a reduced risk of one-year cardiovascular mortality (HR: 0.33; 95% CI: 0.17-0.65; P=0.001) and incident MI (HR: 0.55; 95% CI: 0.33-0.89; P=0.014). For incident stroke, a marginally significant reduction in risk was observed at 5-years (HR: 0.82; 95% CI: 0.67-1.00; p=0.049) and 10-years (HR: 0.83; 95% CI: 0.69-1.01; p=0.065) (Table 2). The protective association of alendronate and CVEs declined over time but remained statistically significant. Sensitivity analyses, (Supplemental Table 3 and Table 4) revealed similar findings. In a subgroup analysis of only, women, BP use was associated with a reduced risk of cardiovascular mortality and incident MI, in a trend similar to the primary analysis, whereas in men there was association with cardiovascular mortality but not with incident MI. For incident stroke, association was not observed in both sex. (Table 4),

Other anti-osteoporosis medications and risk of CVE

In a secondary analysis, similar but statistically more significant findings were observed for all N-BPs exposures (Table 2). Salcatonin had no association with CVEs at one-year follow up (Table 3) but significant increased risks of incident MI at 5-years (HR 2.0; 95% CI: 1.16-3.46; P=0.013) and at 10-years follow up were observed (HR 2.0; 95% CI: 1.17-3.41; P=0.011). Strontium ranelate showed no association with CVEs.

Sensitivity analysis revealed similar findings (Supplemental Table 3 and Table 4).

Discussion

This is the first population-based study using a large electronic clinical patient record database to examine the risk of major CVE in hip fracture patients with and without alendronate treatment. Patients prescribed alendronate treatment versus non-treatment had a significantly reduced risk of CVE. The association could endure for ten years after fracture and was robust in various sensitivity analyses. Nonetheless, it appeared that the protective association was not evident for other classes of anti-osteoporosis treatment.

Hip fracture is often under-treated with anti-osteoporosis medication, which is the worldwide experience. In the current study, only 13.2% of patients received anti-osteoporosis medication following hip fracture. Notably, we showed that post-hip fracture use of alendronate reduced cardiovascular mortality. This highlights the importance of initiating alendronate treatment after hip fracture.

Our findings were contrary to some studies where anti-osteoporosis treatment was associated with an increased CVE risk, one of the reasons for the “Crisis in the

Treatment of Osteoporosis".[29] Treatment with bisphosphonates has been associated with an increased risk of MI in patients with a history of fracture.[30] The population in that study was mainly male veterans (>95%), which could explain the discrepancy with our results. Indeed, the current study showed increased risk of incident MI in men but the association was not significant probably due to the relatively small numbers of men in the cohort.

A recent meta-analysis of RCTs on treatment of bisphosphonates reported a decreased risk of cardiovascular mortality but the association was not significant (pooled risk ratio: 0.81; 95% CI 0.64-1.02).[11] The magnitude of effect sizes that we observed differed from those reported in the RCTs. Overestimation of treatment effect in PS-based observational studies is commonly reported.[31, 32] One possible reason for the discrepancy is the difference in the study populations. In the meta-analysis, four out of ten trials targeted patients with cancer, whereas our cohort excluded these patients. Nevertheless, although PS matching has minimized the confounding in observational studies, selection bias due to unmeasured factors may still exist. For example, we cannot evaluate drug adherence by the patients, which is a common limitation of health care database research. Therefore, bias due to a "healthy adherer effect"[33] cannot be ruled out. In RCTs, intention-to-treat analysis is a common approach to address bias

due to participants being lost-to follow up. However, some reviews suggested that this approach might underestimate treatment effect, resulting in larger discrepancies between RCTs and observational studies.[34, 35] On the other hand, no association of treatment and incident MI was shown in the meta-analysis. The studies included in the meta-analysis had different follow up periods ranging from 1 to 15 years. However, the current study showed that the protective association of treatment and CVEs declined over time. Such findings suggest that the studies with long follow-up periods in the meta-analysis may dilute the association, leading to the discrepancy of findings between the meta-analysis and the current study.

One RCT of zolendronate showed reduction of mortality after hip fracture only after the first year,[36] which was contrary to our findings. In the current study, most of the patients were treated with alendronate while only small number of cases were treated with other N-BPs. We cannot rule out the possibility that the protective association of alendronate and other N-BPs on the risk of CVE are different, even though they belong to the same drug class. Given the relatively small number of zolendronate users and other N-BPs, we were not able to test this hypothesis. Further study with larger sample size of N-BPs is warranted.

Confounding by indication affects the validity of pharmacoepidemiology studies, thus we performed an analysis to evaluate if the cardiac-protective association was observed for two other anti-osteoporosis medications with a different mechanism-of-action. These medications were associated with a non-significant or non-robust increased CVE risk (Table 3), especially for strontium ranelate that has been shown to be associated with increased CVE risk. Such a finding could be due to our limited sample size, or the null association, which was reported in two large population-wide studies.[37, 38] In addition, patients with short-term or late treatment may bias the effect of treatment because short exposure of the drug would have little beneficial effect on CVEs and patients with late treatment would have a much lower risk of CVE at the time of treatment. To address the bias, we excluded these patients in the sensitivity analysis and the results remained robust. Furthermore, we showed that the prescription of bisphosphonate did not differ according to the physical functioning of the patients, suggesting that the observed association with alendronate was not due to better patient-care, survival prospect, or physical functioning.

The association of alendronate and reduced risk of CVEs could be explained by the extra-mineral and skeletal effect of N-BPs. N-BPs target FPPS in the mevalonate pathway that belongs to the same pathway as statins. Thus N-BPs have a cholesterol-

lowering effect.[39] Bisphosphonates can also modulate ion channels in cardiac myocytes,[40, 41] regulate and inhibit vessel pathogenesis,[42] and has an anti-inflammatory effect.[43] Animal studies have shown that N-BPs attenuate diastolic dysfunction following MI,[44] improve cardiac properties, and reduce severity of CVE.[9, 10]

The current study has important clinical implications. It is well established that there is a world-wide crisis in the treatment of osteoporosis,[29] due to patients' awareness of the potential side effects. This leads to under-use of the treatment in hip fracture patients, even though multiple clinical guidelines recommend the use. If our findings are further validated, optimal uptake of anti-osteoporosis medication can be encouraged. In addition, our study has important implications for RCT design. RCT of new anti-osteoporosis agents often use alendronate as a comparator, e.g. the RCT of romosozumab.[45] FDA has recently requested more data before reaching to decision on whether to approve the osteoporosis drug romosozumab, due to the excess cardiovascular adverse events in the romosozumab arm compared with the alendronate arm.[46] In light of these important deliberations, our results provide evidence that such differences in cardiovascular adverse events could be potentially related to protective association of alendronate, rather than an increase in cardiovascular adverse events

related to romosozumab use.

Our study has several strengths. To the best of our knowledge, this is the first large contemporary analysis of real-world clinical practice to compare the risk of CVE among hip fracture patients with and without anti-osteoporosis treatment, and complements results from RCTs. All records in the CDARS were validated with high accuracy,[47] and is a powerful platform from which to conduct large-scale, post-marketing, drug surveillance studies.[16, 17, 48, 49] This study was also carefully designed. Patients with previous exposure to anti-osteoporosis treatment were excluded to avoid a residual effect of treatment. Similarly, patients with history of hip fracture and cancer were excluded. Using a time-dependent PS matching method, the potential confounding factors between treated and untreated groups were minimized, and we included multiple sensitivity analyses to further reduce the confounding bias. Immortal bias due to delay of treatment was adjusted using the robust method.[23]

There were several limitations in the current study. First, similar to other studies utilised healthcare record, over-the-counter products by a non-HA pharmacy are not captured by the CDARS. Nonetheless, patients with chronic diseases who require long-term treatment commonly use the service of HA because the medication cost is highly

subsidized. Therefore, the impact of uncaptured medications should be minimal. Second, although we excluded patients with prescription records two-year prior to hip fracture, the residual effect of anti-osteoporosis medication may exceed this time although the effect should be minimal. Third, the effect of bone mineral density (BMD) on CVE is unknown. One would expect that patients with a lower BMD would be likely to be prescribed anti-osteoporosis treatment. Nonetheless, it is known that low BMD is associated with higher CVE risk. Therefore, even if BMD affects treatment decisions, it would have led to under-estimation, not over-estimation, of the treatment effect. Fourth, data were not available on body mass index, blood pressure, blood lipids and smoking, which are risk factors for CVEs. To address the concern, we included the diagnoses of overweight and obesity, hypertensive diseases, and hyperlipidaemia in the PS model as surrogate markers of these factors. However, residual bias is still a possible. Similarly, other potential confounding factors are not captured in CDARS, such as emigration, vitamin D and calcium supplementation use. However, it is expected that these confounding factors may not confer large effects on the clinical outcomes, especially in a short period of time (e.g. 1-year cardiovascular mortality, MI, and stroke).

In conclusion, osteoporosis is under-treated among hip fracture patients. The use of alendronate was associated with a reduced risk of cardiovascular mortality, MI and

stroke. If the results are further validated, the initiation of alendronate treatment in patients with hip fracture is encouraged.

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Figure Legends

Figure 1. Trend in top 3 cause of death after hip fracture.

Figure 2. CONSORT flow diagram of the study

Figure 3 Survival curves of the association of alendronate and risk of CVE

Table 1. Baseline characteristics of the study population before and after propensity score matching

	Pre-matched cohort					Matched cohort				
	Non-exposed	Any osteoporosis medication-exposed		Alendronate-exposed		Non-exposed	Any osteoporosis medication-exposed		Alendronate-exposed	
			Absolute SD^, %		Absolute SD^, %			Absolute SD^, %		Absolute SD^, %
Subject, n	34,940	4602		3,086		13568	4594		3081	
Male, n (%)	10,648 (30.5)	915 (19.9)	24.6	628 (20.3)	23.4	2859 (21.1)	915 (19.9)	2.9	628 (20.4)	0.3
Age, mean (SD)	81.6 (9.4)	80.7 (8.7)	10.3	80.0 (8.8)	18.0	79.9 (9.7)	80.7 (8.7)	8.6	80.0 (8.8)	0.1
50-69, n (%)	3,594 (10.3)	502 (10.9)		384 (12.4)		1865 (13.7)	502 (10.9)		384 (12.5)	
70-89	24,636 (70.5)	3480 (75.6)		2,355 (76.3)		9807 (72.3)	3472 (75.6)		2350 (76.3)	
90+	6,710 (19.2)	620 (13.5)		347 (11.2)		1896 (14.0)	620 (13.5)		347 (11.3)	
Year of index date, n (%)			83.5		86.7			63.2		62.1
2005	3,309 (9.5)	45 (1.0)		34 (1.1)		576 (4.2)	45 (1.0)		34 (1.1)	
2006	3,613 (10.3)	120 (2.6)		74 (2.4)		855 (6.3)	120 (2.6)		74 (2.4)	
2007	3,704 (10.6)	206 (4.5)		122 (4.0)		1113 (8.2)	206 (4.5)		122 (4.0)	
2008	3,995 (11.4)	334 (7.3)		165 (5.3)		1528 (11.3)	334 (7.3)		165 (5.4)	
2009	3,967 (11.4)	611 (13.3)		360 (11.7)		2002 (14.8)	610 (13.3)		360 (11.7)	
2010	3,870 (11.1)	788 (17.1)		552 (17.9)		2149 (15.8)	785 (17.1)		550 (17.9)	
2011	4,082 (11.7)	597 (13.0)		466 (15.1)		1786 (13.2)	597 (13.0)		466 (15.1)	
2012	4,011 (11.5)	548 (11.9)		382 (12.4)		1680 (12.4)	547 (11.9)		382 (12.4)	
2013	3,958 (11.3)	608 (13.2)		456 (14.8)		1670 (12.3)	607 (13.2)		455 (14.8)	

2014	431 (1.2)	414 (9.0)		278 (9.0)		209 (1.5)	414 (9.0)		278 (9.0)	
2015	0 (0.0)	201 (4.4)		119 (3.9)		0 (0.0)	201 (4.4)		119 (3.9)	
2016	0 (0.0)	130 (2.8)		78 (2.5)		0 (0.0)	128 (2.8)		76 (2.5)	
Medical history, n (%)										
Coronary heart disease	4,174 (11.9)	503 (10.9)	3.2	308 (10.0)	6.3	1362 (10.0)	502 (10.9)	2.9	308 (10.0)	0.2
Congestive heart failure	3,569 (10.2)	412 (9.0)	4.3	228 (7.4)	10	1017 (7.5)	409 (8.9)	5.1	227 (7.4)	<0.001
Cerebrovascular disease	5,586 (16.0)	649 (14.1)	5.3	420 (13.6)	6.7	1799 (13.3)	649 (14.1)	2.5	420 (13.6)	2
Hypertensive disease	14,059 (40.2)	2045 (44.4)	8.5	1,355 (43.9)	7.4	5570 (41.1)	2041 (44.4)	6.8	1353 (43.9)	4.6
Arrhythmia and conduction disorders	4,127 (11.8)	529 (11.5)	1	322 (10.4)	4.4	1391 (10.3)	528 (11.5)	4	321 (10.4)	0.5
Arterial disease	1,535 (4.4)	185 (4.0)	1.9	120 (3.9)	2.5	474 (3.5)	184 (4.0)	2.7	119 (3.9)	1.6
Chronic obstructive pulmonary disease	3,308 (9.5)	464 (10.1)	2.1	299 (9.7)	0.8	1223 (9.0)	462 (10.1)	3.6	298 (9.7)	2
Diabetes	7,273 (20.8)	1,069 (23.2)	5.8	721 (23.4)	6.1	2956 (21.8)	1067 (23.2)	3.4	720 (23.4)	2.3
Chronic liver disease	250 (0.7)	32 (0.7)	0.2	20 (0.6)	0.8	71 (0.5)	32 (0.7)	2.2	20 (0.6)	<0.1
Renal failure	1,719 (4.9)	151 (3.3)	8.3	86 (2.8)	11.1	346 (2.6)	149 (3.2)	4.1	85 (2.8)	1.4
Connective tissue disease	232 (0.7)	95 (2.1)	12.1	68 (2.2)	13	167 (1.2)	89 (1.9)	5.7	64 (2.1)	7
Dementia	2,864 (8.2)	218 (4.7)	14.1	124 (4.0)	17.5	519 (3.8)	216 (4.7)	4.3	123 (4.0)	1.7
Paget's disease of bone	9 (0.0)	0 (0.0)	2.3	0 (0.0)	2.3	0 (0.0)	0 (0.0)	-	0 (0.0)	-
Osteoporosis	1,628 (4.7)	623 (13.5)	31.2	386 (12.5)	28.3	1036 (7.6)	618 (13.5)	19	383 (12.4)	14.3
Fall	34,007 (97.3)	4,519 (98.2)	5.9	3,025 (98.0)	4.6	13288 (97.9)	4511 (98.2)	1.9	3020 (98.0)	<0.001
Other major fractures	3,477 (10.0)	661 (14.4)	13.5	414 (13.4)	10.8	1703 (12.6)	661 (14.4)	5.4	414 (13.4)	1.6
Obesity	58 (0.2)	11 (0.2)	1.6	9 (0.3)	2.6	21 (0.2)	11 (0.2)	1.9	9 (0.3)	2.4

Hyperlipidaemia	2,716 (7.8)	480 (10.4)	9.2	336 (10.9)	10.7	1256 (9.3)	479 (10.4)	3.9	336 (10.9)	<0.1
Thyroid disorders	799 (2.3)	127 (2.8)	3	72 (2.3)	0.3	318 (2.3)	127 (2.8)	2.7	72 (2.3)	0.1
Number of outpatient visits in past one year, mean±SD	8.0 (10.2)	13.9 (12.7)	51.3	13.9 (12.6)	51.5	8.1 (10.8)	13.9 (12.7)	49.8	13.9 (12.6)	49.8
Prescription in past 180 days, n (%)										
Digoxin	1,322 (3.8)	132 (2.9)	5.1	67 (2.2)	9.5	378 (2.8)	132 (2.9)	0.5	67 (2.2)	3.2
Loop diuretics	5,373 (15.4)	646 (14.0)	3.8	399 (12.9)	7	1792 (13.2)	643 (14.0)	2.3	397 (12.9)	1.3
Other diuretics	3,118 (8.9)	395 (8.6)	1.2	258 (8.4)	2	1316 (9.7)	393 (8.6)	4	257 (8.3)	4.5
Anti-arrhythmics class I and II	718 (2.1)	75 (1.6)	3.2	41 (1.3)	5.6	263 (1.9)	75 (1.6)	2.3	41 (1.3)	5
Beta blockers	8,676 (24.8)	1,176 (25.6)	1.7	770 (25.0)	0.3	3674 (27.1)	1170 (25.5)	3.7	765 (24.8)	5.5
Angiotensin receptor blocker/ angiotensin converting enzyme inhibitor/ renin inhibitor	9,395 (26.9)	1372 (29.8)	6.5	912 (29.6)	5.9	3925 (28.9)	1370 (29.8)	2	910 (29.5)	<0.001
Nitrates	4,216 (12.1)	505 (11.0)	3.4	315 (10.2)	5.9	1558 (11.5)	504 (11.0)	1.6	315 (10.2)	4.1
Calcium channel blockers	15,302 (43.8)	2,078 (45.2)	2.7	1,385 (44.9)	2.2	6112 (45.0)	2073 (45.1)	0.2	1382 (44.9)	2
Peripheral vasodilators	742 (2.1)	57 (1.2)	6.9	41 (1.3)	6.1	158 (1.2)	56 (1.2)	0.5	40 (1.3)	2.5
Anticoagulants	2,657 (7.6)	310 (6.7)	3.4	224 (7.3)	1.3	1176 (8.7)	307 (6.7)	7.5	222 (7.2)	5.9
Platelet inhibitors	11,037 (31.6)	1,425 (31.0)	1.3	916 (29.7)	4.1	4117 (30.3)	1421 (30.9)	1.3	914 (29.7)	2.1
Lipid regulating drugs	5,431 (15.5)	995 (21.6)	15.7	688 (22.3)	17.3	2681 (19.8)	993 (21.6)	4.6	687 (22.3)	5.1
Antipsychotics	4,327 (12.4)	302 (6.6)	20	195 (6.3)	20.9	918 (6.8)	302 (6.6)	0.8	195 (6.3)	0.2

Antidepressants	3,796 (10.9)	494 (10.7)	0.4	289 (9.4)	5	1400 (10.3)	492 (10.7)	1.3	288 (9.3)	4
Insulins	2,598 (7.4)	300 (6.5)	3.6	205 (6.6)	3.1	1018 (7.5)	299 (6.5)	3.9	205 (6.7)	3.7
Antidiabetic drugs	7,193 (20.6)	1,066 (23.2)	6.2	733 (23.8)	7.6	3206 (23.6)	1065 (23.2)	1.1	733 (23.8)	1.3
Oral corticosteroids	1,894 (5.4)	335 (7.3)	7.6	221 (7.2)	7.2	796 (5.9)	331 (7.2)	5.4	219 (7.1)	4.8
Non-steroidal anti-inflammatory drugs	3,860 (11.0)	638 (13.9)	8.5	400 (13.0)	5.9	1981 (14.6)	633 (13.8)	2.4	396 (12.9)	5.8
Surgical operation after hip fracture	31,341 (89.7)	4,451 (96.7)	28.2	2,995 (97.1)	29.9	12971 (95.6)	4443 (96.7)	5.8	2990 (97.0)	5.2
Residency in nursing home	9,062 (25.9)	469 (10.2)	41.8	307 (9.9)	42.6	1654 (12.2)	469 (10.2)	6.3	307 (10.0)	5

^Absolute standardized difference compared with non-exposed group

Table 2. Risk of CVE with N-BPs*

Group	Subject, n	Event, n	Mortality / Incidence rate, per 10,000 person-years	Hazard ratio (95% CI)	P
			1-year		
Cardiovascular mortality					
Non-exposed	13,568	130	108.9 (91-129.3)	1	-
Alendronate	3,081	10	34.7 (16.6-63.7)	0.33 (0.17-0.65)	0.001
All N-BPs*	3,778	13	37 (19.7-63.2)	0.35 (0.20-0.63)	<0.001
Incident MI^					
Non-exposed	12,708	151	135.3 (114.5-158.6)	1	-
Alendronate	2,998	20	71.4 (43.6-110.3)	0.55 (0.34-0.89)	0.014
All N-BPs	3,679	22	64.4 (40.3-97.4)	0.51 (0.32-0.81)	0.004
Incident stroke#					
Non-exposed	10,188	229	257.1 (224.9-292.7)	1	-
Alendronate	2,696	49	194.6 (144-257.3)	0.78 (0.56-1.08)	0.133
All N-BPs	3,299	56	182.8 (138.1-237.4)	0.70 (0.52-0.95)	0.022
			3-years		
Cardiovascular mortality					
Non-exposed	13,568	301	102.7 (91.4-115)	1	-
Alendronate	3,081	36	47.3 (33.1-65.4)	0.48 (0.33-0.69)	<0.001
All N-BPs	3,778	45	48.4 (35.3-64.8)	0.47 (0.34-0.66)	<0.001
Incident MI					
Non-exposed	12,708	364	132.9 (119.6-147.3)	1	-
Alendronate	2,998	57	77.2 (58.5-100.1)	0.63 (0.47-0.85)	0.002
All N-BPs	3,679	64	71.1 (54.7-90.8)	0.58 (0.44-0.76)	<0.001
Incident stroke					
Non-exposed	10,188	526	242.5 (222.2-264.1)	1	-
Alendronate	2,696	132	199.7 (167.1-236.9)	0.88 (0.71-1.09)	0.226
All N-BPs	3,299	152	189.3 (160.4-221.9)	0.80 (0.66-0.98)	0.027
			5-years		
Cardiovascular mortality					
Non-exposed	13,568	386	99 (89.4-109.4)	1	-
Alendronate	3,081	56	53.3 (40.3-69.2)	0.55 (0.40-0.75)	<0.001
All N-BPs	3,778	69	53.5 (41.6-67.7)	0.54 (0.41-0.72)	<0.001
Incident MI					
Non-exposed	12,708	506	139 (127.2-151.7)	1	-
Alendronate	2,998	100	98.4 (80-119.6)	0.70 (0.55-0.90)	0.005
All N-BPs	3,679	121	96.9 (80.4-115.8)	0.69 (0.55-0.86)	0.001
Incident stroke					
Non-exposed	10,188	647	225.3 (208.3-243.4)	1	-
Alendronate	2,696	168	185.1 (158.2-215.3)	0.82 (0.67-1.00)	0.049
All N-BPs	3,299	198	178.5 (154.5-205.2)	0.77 (0.65-0.93)	0.006

			10-years		
Cardiovascular mortality					
Non-exposed	13,568	429	96.3 (87.4-105.8)	1	-
Alendronate	3,081	78	63.9 (50.5-79.7)	0.59 (0.44-0.79)	<0.001
All N-BPs	3,778	92	60.8 (49-74.5)	0.58 (0.44-0.75)	<0.001
Incident MI					
Non-exposed	12,708	580	139.6 (128.5-151.5)	1	-
Alendronate	2,998	123	104.2 (86.6-124.3)	0.71 (0.56-0.89)	0.004
All N-BPs	3,679	145	99.1 (83.6-116.6)	0.67 (0.54-0.83)	<0.001
Incident stroke					
Non-exposed	10,188	694	212 (196.5-228.4)	1	-
Alendronate	2,696	183	173.9 (149.6-200.9)	0.83 (0.69-1.01)	0.065
All N-BPs	3,299	220	169.6 (147.9-193.5)	0.79 (0.66-0.94)	0.008

*N-BPs included alendronate, ibandronate, risedronate, and zoledronate
Patients with history of myocardial infarction^ or stroke# were excluded from the analysis

Table 3. Risk of CVE with salcatonin and strontium ranelate

Group	Subject, n	Event, n	Mortality / Incidence rate, per 10,000 person-years	Hazard ratio (95% CI)	P
			1-year		
Cardiovascular mortality					
Non-exposed	13,568	130	108.9 (91-129.3)	1	-
Salcatonin	535	8	201 (86.8-396)	2.33 (0.89-6.10)	0.084
Strontium ranelate	167	3	206.4 (42.6-603.1)	0.69 (0.15-3.24)	0.635
Incident MI^					
Non-exposed	12,708	151	135.3 (114.5-158.6)	1	-
Salcatonin	509	9	239.4 (109.5-454.5)	1.27 (0.56-2.89)	0.562
Strontium ranelate	160	3	215.3 (44.4-629.3)	1.14 (0.28-4.66)	0.854
Incident stroke#					
Non-exposed	10,188	229	257.1 (224.9-292.7)	1	-
Salcatonin	459	11	329 (164.2-588.6)	1.64 (0.75-3.59)	0.218
Strontium ranelate	143	4	324.9 (88.5-831.8)	1.07 (0.31-3.72)	0.915
			3-years		
Cardiovascular mortality					
Non-exposed	13,568	301	102.7 (91.4-115)	1	-
Salcatonin	535	15	167.6 (93.8-276.5)	1.61 (0.82-3.15)	0.165
Strontium ranelate	167	6	166.9 (61.2-363.2)	1.26 (0.44-3.63)	0.671
Incident MI^					
Non-exposed	12,708	364	132.9 (119.6-147.3)	1	-
Salcatonin	509	21	249.2 (154.3-381)	1.84 (1.02-3.31)	0.042
Strontium ranelate	160	5	145.7 (47.3-339.9)	0.91 (0.31-2.66)	0.857
Incident stroke#					
Non-exposed	10,188	526	242.5 (222.2-264.1)	1	-
Salcatonin	459	21	282.3 (174.8-431.6)	1.40 (0.80-2.47)	0.241
Strontium ranelate	143	10	330.5 (158.5-607.9)	1.24 (0.54-2.82)	0.616
			5-years		
Cardiovascular mortality					
Non-exposed	13,568	386	99 (89.4-109.4)	1	-
Salcatonin	535	17	152.1 (88.6-243.5)	1.59 (0.83-3.03)	0.163
Strontium ranelate	167	7	141.1 (56.7-290.7)	0.98 (0.37-2.60)	0.967
Incident MI^					
Non-exposed	12,708	506	139 (127.2-151.7)	1	-
Salcatonin	509	26	247.4 (161.6-362.4)	2.00 (1.16-3.46)	0.013
Strontium ranelate	160	8	168.6 (72.8-332.3)	1.13 (0.46-2.79)	0.786
Incident stroke#					
Non-exposed	10,188	647	225.3 (208.3-243.4)	1	-
Salcatonin	459	23	248.9 (157.8-373.4)	1.25 (0.73-2.13)	0.415
Strontium ranelate	143	14	340.3 (186.1-571)	1.24 (0.54-2.82)	0.616
			10-years		

Cardiovascular mortality					
Non-exposed	13,568	429	96.3 (87.4-105.8)	1	-
Salcatonin	535	18	142.5 (84.4-225.2)	1.65 (0.87-3.12)	0.123
Strontium ranelate	167	8	137.1 (59.2-270)	1.10 (0.43-2.78)	0.841
Incident MI^					
Non-exposed	12,708	580	139.6 (128.5-151.5)	1	-
Salcatonin	509	29	243.2 (162.9-349.2)	2.00 (1.17-3.41)	0.011
Strontium ranelate	160	10	178.7 (85.7-328.6)	1.11 (0.49-2.52)	0.805
Incident stroke#					
Non-exposed	10,188	694	212 (196.5-228.4)	1	-
Salcatonin	459	25	241 (155.9-355.7)	1.29 (0.76-2.19)	0.344
Strontium ranelate	143	14	291.8 (159.5-489.6)	1.24 (0.54-2.82)	0.616

Patients with history of myocardial infarction^ or stroke# were excluded from the analysis

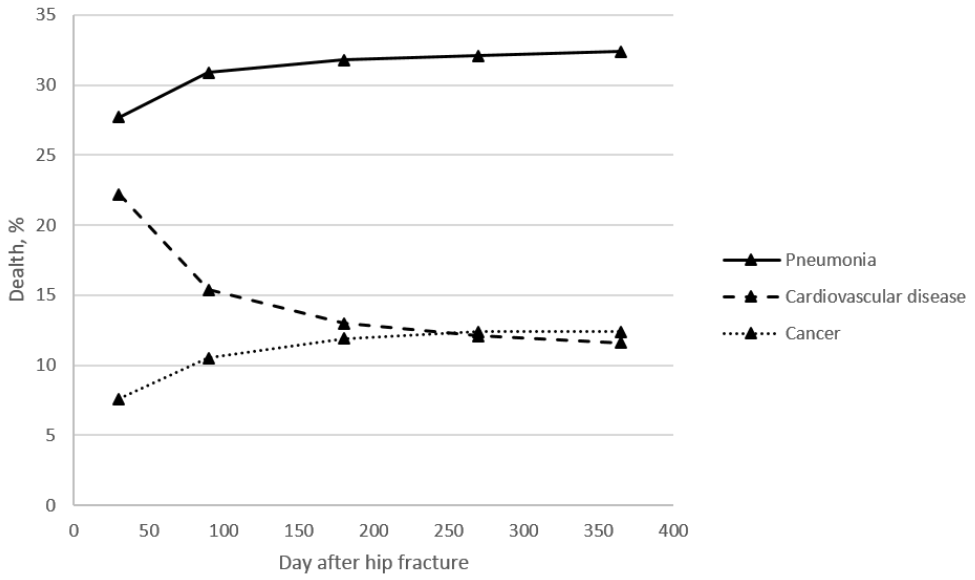
Table 4. Subgroup analysis* between alendronate treatment and CVE

Group (n)	Follow up years											
	1-year			3-years			5-years			10-years		
	Event n	Hazard ratio (95% CI)	P	Event n	Hazard ratio (95% CI)	P	Event n	Hazard ratio (95% CI)	P	Event n	Hazard ratio (95% CI)	P
Cardiovascular mortality												
Sex												
Female (2,417)	6	0.27 (0.11-0.63)	0.003	24	0.44 (0.28-0.69)	<0.001	40	0.49 (0.33-0.72)	<0.001	59	0.53 (0.36-0.76)	<0.001
Male (406)	2	0.16 (0.02-1.31)	0.088	6	0.30 (0.10-0.89)	0.03	7	0.37 (0.13-1)	0.051	9	0.38 (0.15-0.97)	0.042
History of any CVE												
No (984)	3	1.51 (0.29-7.77)	0.622	5	0.42 (0.15-1.15)	0.092	8	0.41 (0.17-0.98)	0.045	14	0.41 (0.18-0.92)	0.03
Yes (1,657)	6	0.22 (0.09-0.56)	0.002	29	0.51 (0.31-0.83)	0.007	44	0.59 (0.37-0.92)	0.019	55	0.58 (0.38-0.9)	0.016
History of diabetes												
No (2,313)	7	0.40 (0.18-0.90)	0.028	22	0.42 (0.25-0.68)	<0.001	33	0.47 (0.31-0.72)	<0.001	47	0.52 (0.35-0.78)	0.001
Yes (386)	1	0.25 (0.03-2.22)	0.215	7	0.78 (0.30-2.03)	0.603	11	0.89 (0.37-2.14)	0.796	15	0.81 (0.34-1.92)	0.639
Surgical operation												
Hip fixation (1,770)	5	0.24 (0.09-0.62)	0.003	20	0.44 (0.26-0.73)	0.002	34	0.57 (0.37-0.88)	0.011	45	0.6 (0.39-0.91)	0.018
Hip replacement (791)	4	1.19 (0.23-6.08)	0.835	10	0.61 (0.26-1.42)	0.249	13	0.47 (0.21-1.07)	0.071	20	0.58 (0.28-1.2)	0.145
Incident MI^												
Sex												
Female (2,344)	10	0.41 (0.21-0.81)	0.011	35	0.46 (0.31-0.69)	<0.001	69	0.55 (0.4-0.75)	<0.001	86	0.56 (0.41-0.75)	<0.001
Male (379)	8	1.09 (0.40-2.93)	0.865	14	1.08 (0.50-2.32)	0.845	19	1.02 (0.52-2.02)	0.954	20	1.02 (0.52-2.02)	0.954
History of any CVE												
No (984)	4	0.58 (0.18-1.88)	0.363	8	0.41 (0.18-0.91)	0.028	18	0.48 (0.26-0.89)	0.02	24	0.52 (0.29-0.94)	0.031
Yes (1,552)	12	0.53 (0.27-1.01)	0.054	42	0.64 (0.44-0.95)	0.025	70	0.7 (0.49-0.99)	0.044	82	0.68 (0.48-0.97)	0.031
History of diabetes												
No (2255)	12	0.54 (0.28-1.03)	0.06	31	0.53 (0.35-0.81)	0.003	60	0.59 (0.42-0.83)	0.002	76	0.6 (0.43-0.83)	0.002
Yes (353)	3	1.12 (0.22-5.62)	0.891	10	0.81 (0.32-2.02)	0.644	16	0.95 (0.41-2.23)	0.914	20	0.87 (0.38-2.01)	0.752
Surgical operation												
Hip fixation (1,711)	13	0.65 (0.35-1.24)	0.19	29	0.69 (0.45-1.06)	0.09	52	0.77 (0.53-1.11)	0.163	62	0.8 (0.56-1.14)	0.212
Hip replacement (752)	5	0.74 (0.21-2.6)	0.64	19	0.93 (0.50-1.72)	0.814	30	0.92 (0.53-1.57)	0.748	35	0.93 (0.55-1.57)	0.791
Incident Stroke#												
Sex												
Female (2,106)	37	0.78 (0.53-1.15)	0.207	106	0.94 (0.73-1.21)	0.635	130	0.85 (0.67-1.07)	0.164	142	0.86 (0.69-1.08)	0.2

Male (301)	7	1.18 (0.42-3.31)	0.757	17	0.77 (0.37-1.58)	0.475	22	0.76 (0.38-1.51)	0.425	23	0.72 (0.36-1.42)	0.341
History of any CVE												
No (984)	9	0.77 (0.32-1.82)	0.547	32	1.11 (0.66-1.85)	0.693	39	1.01 (0.63-1.62)	0.968	42	0.91 (0.58-1.44)	0.701
Yes (1,180)	32	0.80 (0.50-1.26)	0.327	79	0.92 (0.67-1.26)	0.604	103	0.83 (0.62-1.11)	0.202	113	0.88 (0.66-1.17)	0.381
History of diabetes												
No (2,018)	31	0.82 (0.53-1.27)	0.371	85	0.85 (0.65-1.12)	0.259	112	0.79 (0.61-1.01)	0.065	123	0.79 (0.62-1.02)	0.068
Yes (250)	5	0.39 (0.10-1.44)	0.158	17	0.87 (0.42-1.81)	0.712	22	0.9 (0.46-1.79)	0.772	25	0.96 (0.49-1.88)	0.909
Surgical operation												
Hip fixation (1,467)	27	0.87 (0.55-1.40)	0.57	64	0.76 (0.55-1.05)	0.092	81	0.67 (0.5-0.9)	0.009	90	0.68 (0.51-0.92)	0.011
Hip replacement (644)	9	0.74 (0.31-1.77)	0.498	30	0.93 (0.54-1.61)	0.799	41	0.95 (0.58-1.57)	0.849	45	0.98 (0.6-1.61)	0.95

Patients with history of myocardial infarction[^] or stroke[#] were excluded from the analysis

Figure 1 Trend in top 3 cause of death after hip fracture.



	30-day	90-day	180-day	270-day	1-year
Total deaths, n (%)	1851 (100)	4048 (100)	5971 (100)	7301 (100)	8584 (100)
Pneumonia	512 (27.7)	1249 (30.9)	1901 (31.8)	2341 (32.1)	2779 (32.4)
Cardiovascular disease	411 (22.2)	625 (15.4)	776 (13)	884 (12.1)	996 (11.6)
Cancer	141 (7.6)	425 (10.5)	708 (11.9)	908 (12.4)	1065 (12.4)

*Cardiovascular disease defined as ICD-10 codes I00-I09, I11, I13, I20-I51

Figure 2 CONSORT flow diagram of the study

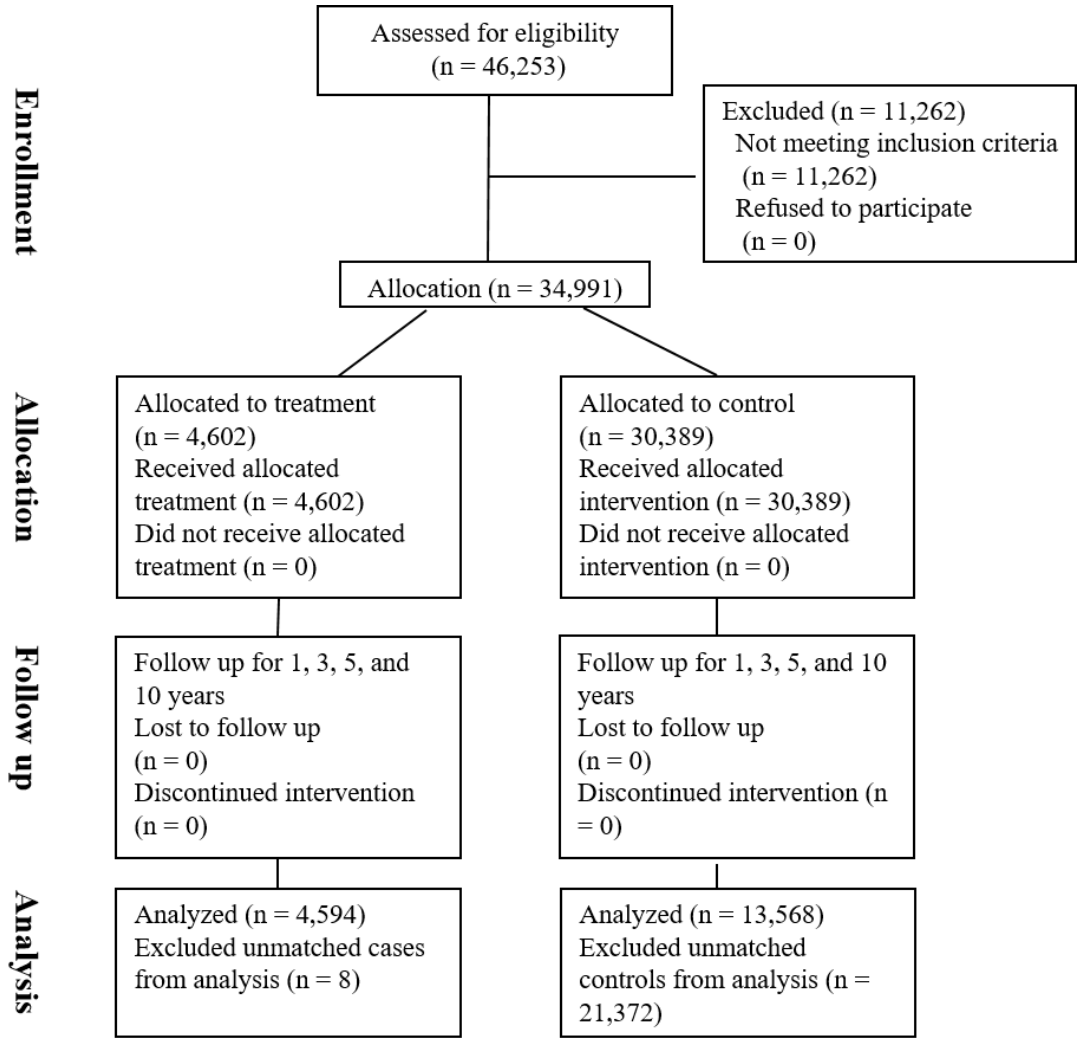
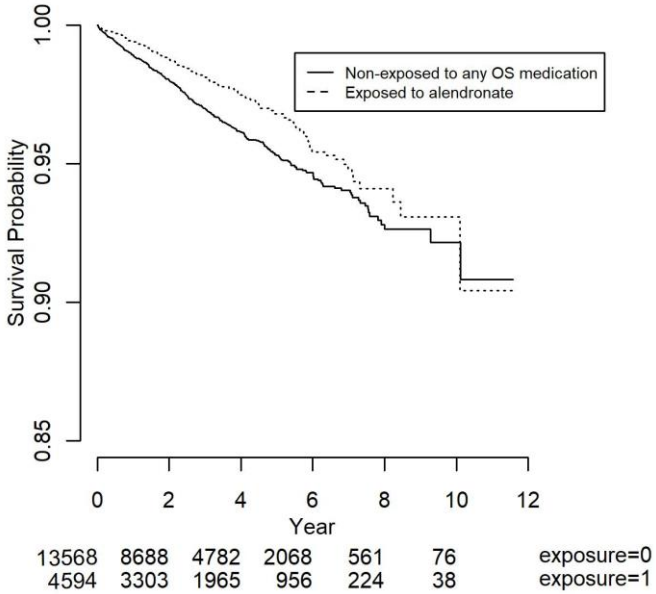
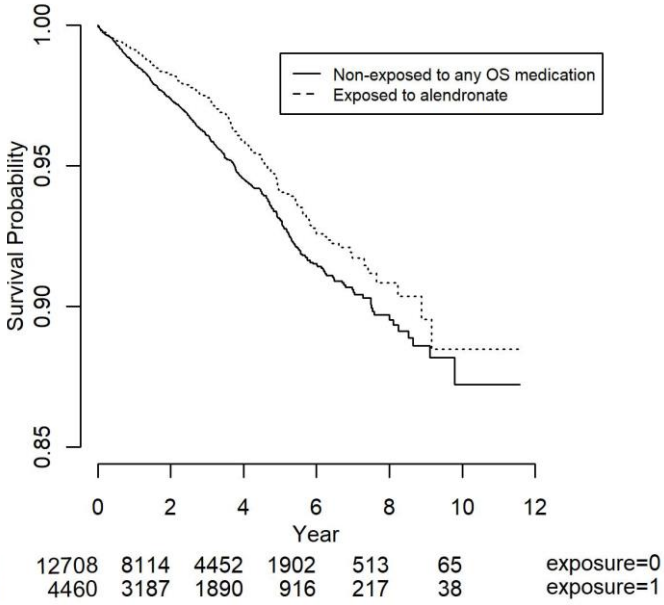


Figure 3 Survival curves of the association of alendronate and risk of CVE

a) Cardiovascular mortality



b) Incident MI



c) Incident Stroke