Mortality risk reduction differs according to bisphosphonate class

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ORIGINAL ARTICLE

Mortality risk reduction differs according to bisphosphonate class: a 15-year observational study

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Abstract

Summary In this prospective cohort of 6120 participants aged 50+, nitrogen-bisphosphonates but not non-nitrogen bisphosphonates were associated with a significant 34% mortality risk reduction compared to non-treated propensity score matched controls. These findings open new avenues for research into mechanistic pathways.

Introduction Emerging evidence suggests that bisphosphonates (BP), first-line treatment of osteoporosis, are associated with reduced risks for all-cause mortality. This study aimed to determine the association between different BP types and mortality risk in participants with or without a fracture.

Methods A prospective cohort study of users of different BPs matched to non-users by propensity score (age, gender, co-morbidities, fragility fracture status) and time to starting the BP medication from the population-based Canadian Multicentre Osteoporosis Study from nine Canadian centres followed from 1995 to 2013. Mortality risk for bisphosphonate users vs matched non-users was assessed using pairwise multivariable Cox proportional hazards models.

Results There were 2048 women and 308 men on BP and 1970 women and 1794 men who did not receive medication for osteoporosis. The relationship between BP and mortality risk was explored in three separate 1:1 propensity score-matched cohorts of BP users and no treatment (etidronate, $n = 599$, alendronate, $n = 498$, and risedronate $n = 213$). Nitrogen BP (n-BP)

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(alendronate and risedronate) was associated with lower mortality risks [pairwise HR, 0.66 (95% CI, 0.48–0.91)] while the less potent non-n-BP, etidronate, was not [pairwise HR: 0.89 (95% CI, 0.66–1.20)]. A direct comparison between n-BP and etidronate ($n = 340$ pairs) also suggested a better survival for n-BP [paired HR, 0.47 (95%CI, (95% CI, 031–0.70)] for n-BP vs. etidronate].
Conclusion Compared to no treatment, nitrogen but not non-nitrogen bisphosphonates appear to be associated with better survival.

Keywords Bisphosphonate · Fracture · Mortality risk · Osteoporosis · Prospective study

Introduction

Osteoporotic fragility fracture is highly prevalent in the general population and is associated with serious consequences. From the age of 50, 40% of women and 25% of men will sustain a fragility fracture (trauma less than or equal to a fall from standing) during their remaining lifetimes [1]. Men and women with a fracture have increased risk of further fractures [2–4] and most importantly, premature mortality [5–7]. Despite the availability of effective medications, treatment rates continue to be low with < 30% women and < 20% men with fragility fractures on validated treatments. Bisphosphonates, first-line treatment for osteoporosis world-wide [8, 9], are effective in reducing the relative risk of fracture by between 40 and 70% [10] and also appear to confer a survival benefit among patients with a fracture [11, 12] based on a randomised controlled trial (RCT) of hip fracture patients [13–15] and several cohort [16–18], registry-based studies [14, 15], and more recently in a Fracture Liaison Service setting [19]. In the RCT, hip fracture subjects given zoledronic acid had a 28% reduced mortality [11]. A meta-analysis of anti-osteoporosis medications from eight RCTs found a pooled mortality risk benefit (~ 11%) of these agents [12]. More recently, zoledronic acid was reported to reduce mortality risk by 35% [OR 0.65 (95% CI, 0.40–1.05)] over 6 years in a RCT of women with osteopenia [20].

Despite multivariate adjustment, criticism persists that, at least in cohort studies, survival benefit may relate to healthy user bias; however, RCTs with mortality as the primary outcome will likely not be conducted due to necessary large numbers, expense and particularly ethical considerations. This issue is important to resolve as, if true, it may help to increase the acceptability and uptake of urgently needed treatments [21]. A scenario in which any potential bisphosphonate-related mortality benefit could be further explored, would therefore be a cohort study that examines the effect of bisphosphonates of different chemistries expected to have different effects on all-cause mortality. Thus if a difference were found, any healthy user bias would be avoided as indications for treatment would be similar.

There are two main classes of bisphosphonates: nitrogen bisphosphonates (n-BP, e.g. alendronate, risedronate) and non-n-BP (e.g. etidronate). The newer bisphosphonates (n-BP) have a different mechanism of action and are more potent than the non-nitrogen bisphosphonates [22, 23]. The higher potency of n-BP result in a greater reduction of bone loss that would limit the resorption-related release from bone of toxic substances (e.g. lead) [24, 25]. Furthermore, several studies have suggested that n-BP may have non-bone beneficial effects such as on immune function [26, 27] (although adverse immune effects also occur [28]), endothelial function [29], systemic inflammation [30], and an antitumor effect [31].

Our hypothesis was that participants on bisphosphonates would have a better survival than those on no treatment and that the more potent nitrogen-bisphosphonate may have a greater effect than the non-nitrogen bisphosphonates. This study therefore examined the association between bisphosphonates of two different chemistries with all-cause mortality in a population-based cohort of women and men aged 50 years and older.

Methods

Subjects and setting

The study population consisted of women and men participating in the Canadian Multicentre Osteoporosis Study (CaMos), an ongoing prospective population-based study that started in 1995 with the aim to document the skeletal health of a randomly selected population of women and men aged 25 and over. All non-institutionalised Canadians who resided within 50 km of a study centre, representing ~ 37% of all Canadians were eligible. Participants were recruited using randomly generated telephone lists from the region surrounding nine urban centres in Canada. A detailed description of the study design and population sampling has been published previously [32]. CaMos was approved by the Ethics Committee of McGill University and at each participating centre.

Of the 9423 participants recruited, 7689 aged 50+ were screened for medication uptake. CaMOS is an observational study, thus all the medication was initiated by each participant's physician without any intervention from the CaMOS investigators. Etidronate and alendronate received Canadian regulatory approval for osteoporosis treatment within a year of each other, and prior to the start of CaMOS. In most Canadian provincial drug plans, access to alendronate (and risedronate) was restricted to patients who had already suffered an

osteoporotic fracture; or had either failed to respond to etidronate (had lost bone density or suffered a new fracture) or were not able to tolerate etidronate. This is reflected in this observational study by the large number of participants (~40%) who switched between bisphosphonate types during the follow-up (Fig. 1). To account for any potential immortal time bias induced by this switch, the primary aim was investigated in the groups not treated versus those treated with only one type of bisphosphonate for the entire follow-up.

Inclusion criteria Individuals who used bisphosphonates during the study follow-up (etidronate, alendronate, and risedronate), and those who did not use any osteoporosis-related medication (NoRx) were included.

Exclusion criteria A number of osteoporosis-related medications were excluded due to small number of users (clodronate, $n = 22$, pamidronate, $n = 54$, zoledronic acid, $n = 44$, calcitonin, $n = 14$, denosumab, $n = 2$, raloxifene, $n = 50$), tamoxifen ($n = 100$), and testosterone ($n = 39$) (Fig. 1). A relatively large number of women reported hormone therapy ($N = 1268$) at baseline or throughout the study (Fig. 1). This group of women had more favourable characteristics than women who did not take any medication. They were younger, had higher BMD, a higher proportion of distal compared to proximal fractures, and also had better lifestyle habits (less smoking, more exercise, and more were taking vitamin D). Given the unknown duration of prior exposure and the potential effect on cardiovascular risk, this group was excluded from further analyses; however,

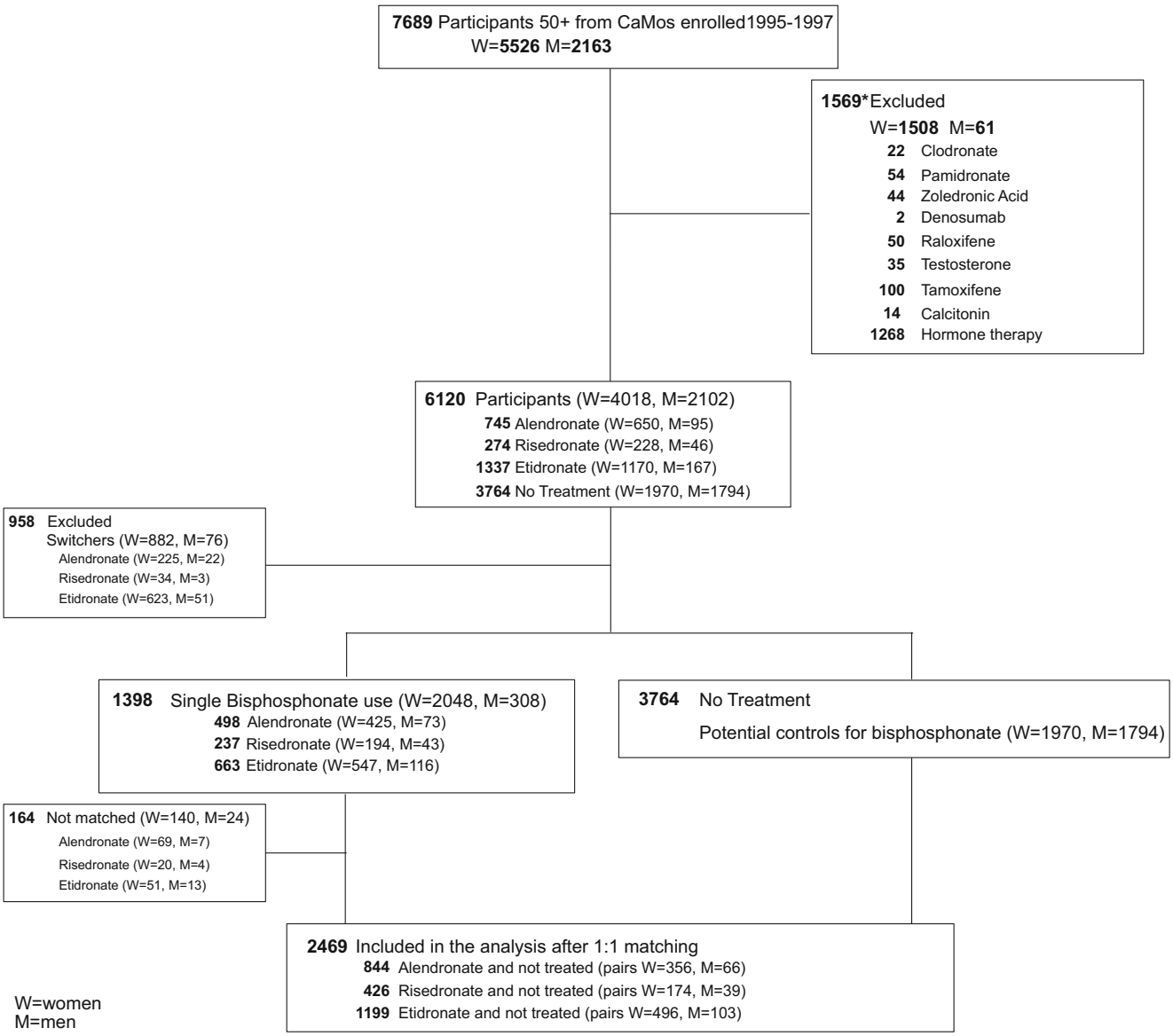


Fig. 1 Flow chart of participants aged 50+ from Canadian Multicentre Osteoporosis Study

after adjustment for baseline characteristics, their survival was not significantly better than those on no treatment.

Outcomes and risk factors

A standardised interviewer-administered questionnaire was obtained at baseline (1995–1997). Information was obtained on lifestyle factors (i.e. smoking, physical activity), demographics, education, co-morbidities, and medication use. In addition to this structured questionnaire, each participant had a clinical visit that included anthropometric measurements (i.e. height, weight) and femoral neck areal bone mineral density (BMD). This information was subsequently obtained in years 3 (40–60 years of age only), 5 and 10. Yearly postal self-administered questionnaires for incident fractures and medications were obtained between clinical visits.

Bisphosphonate exposure

Bisphosphonate uptake was determined from yearly questionnaires and the inventory of medications brought to each interview (baseline and years 3, 5 and 10). Participants were classified as bisphosphonate users based on yearly report of medication. Of the 2356 eligible bisphosphonate users, 985 participants used more than one type of bisphosphonate (Fig. 1). Thus, 50% participants initiated on etidronate, 33% on alendronate and 14% on risedronate switched during the study follow-up to another class of bisphosphonate. These participants were included in a sensitivity analysis, classified according to the first bisphosphonate used. The treatment initiation date was taken as the year of the first reported use of bisphosphonate.

The uptake of bisphosphonate during follow-up was much lower in men (~ 14%) then women (~ 40%). Therefore, we have performed two analyses: "any user" including both genders, and women only.

Adherence to bisphosphonates was not recorded. Participants who reported bisphosphonates only once during the follow-up ($n = 251$) were used as surrogate for non-adherence in a sensitivity analysis.

Participants did not receive any formal fracture risk assessment or management suggestions from the CaMOS investigators. They, and/or their primary care physician received a copy of the BMD report performed at baseline and all subsequent visits.

Fracture ascertainment

Self-reported incident clinical fractures were obtained yearly and at clinical visits. Information on the date, site, circumstance of the fracture, and an x-ray report was obtained by interview. Medical records were obtained and verified for 78% of fractures.

This study included only incident fragility fractures. Skull, sternum, finger and toe fractures were excluded.

Mortality ascertainment

Mortality ascertainment was conducted annually throughout the study follow-up. All participants provided contact detail for next of kin. If a participant did not respond to the yearly questionnaire, the study co-ordinator contacted the next of kin. If this failed, obituaries were screened for death records. Although mortality data were not formally validated using national figures or other external data sources, it was highly unlikely that these deaths were misclassified.

Statistical analysis

Baseline characteristics were examined for BP (alendronate, risedronate and etidronate) in comparison to NoRx (*t* tests for continuous and chi^2-square tests for categorical variables).

Whole cohort

For the primary analysis, participants who used only one type of bisphosphonate during the follow-up ($n = 1371$), classified as n-BP (alendronate and risedronate) and non-n-BP etidronate were matched 1:1 to non-treated participants. Matching was by a propensity score, including age, gender, fracture type, co-morbidities and life-style factors that predicted the likelihood of being treated [33], and time to starting medication. Follow-up was calculated from the time of medication start for both treated and non-treated. For non-treated, this starting point was obtained by the addition to baseline date his/her "pair's" time of medication commencement. This procedure ensured that all participants had similar baseline characteristics, avoiding selection bias, and that a participant who started treatment later during the follow-up was matched to a control still alive at that time point, avoiding immortal time bias. Mortality risk was analysed using a paired Cox proportional hazards model. Proportionality hazards assumption was tested by the inspection of Schoenfeld residuals over time. Kaplan Meier survival curves for each bisphosphonate were also created.

Subgroup and sensitivity analysis

To determine the role of individual bisphosphonate type on mortality risk, alendronate and risedronate users were separately compared to no treatment using a paired Cox proportional hazards model adjusted for any variable which became unbalanced after stratification.

To test the hypothesis that n-BPs have, a stronger association with mortality reduction than the non-n-BPs, a head-to-head comparison between the 2 classes of bisphosphonates

was performed in a set of n-BP matched 1:1 to etidronate by propensity score, using a paired Cox Proportional Hazards Model.

A sensitivity analysis including all bisphosphonate users ($n = 2356$), with switchers classified according to initial type of bisphosphonate was performed using inverse probability weighting with treatment as a time-dependent variable. The period of time prior to treatment initiation contributed to no treatment, while the interval following the first bisphosphonate uptake contributed to treatment, in an intention to treat analysis. Thus, all bisphosphonate users were classified according to the initial type of bisphosphonate, regardless if they continued on the same bisphosphonate, or switched to another type during the follow-up.

Individuals who reported bisphosphonate only at one visit during the follow-up ($n = 241$), were used as surrogate for non-adherence and excluded in a sensitivity analysis.

Fracture cohort

A subset analysis of the relationship between the bisphosphonate initiated at or following the time of fracture and mortality was performed for individuals with incident fractures. n-BP and etidronate users were matched 1:2 by age, gender and fracture type to individuals who did not use any treatment after the incident fracture. Fracture risk was assessed for all individuals using the Garvan fracture risk calculator [34]. The relationship between BP and survival was assessed using a paired Cox Proportional Hazard Model.

Subgroup analysis

Given the high mortality occurring immediately after the fracture event, this analysis was also performed according to the time of BP initiation post-fracture (0–2, 2–5) and 5+ years in n-BP group only, due to small number of etidronate users 2+ years post-fracture.

In order to examine whether the mortality reduction could be mediated by a reduction in subsequent fracture events, an additional Cox proportional hazards model with subsequent fracture as the outcome was conducted.

All statistical analyses were performed using SAS 9.4 and R statistical environment on a Windows platform. There were no missing values for the main outcome measurement (i.e. deaths). Missing variables were inputted using the R-Package Mice [35]. The plausible values of missing data for the covariates were imputed using multivariate imputation by chained equations algorithm (MICE) which created five completed imputed datasets. Each variable has its own imputation equation. The MICE method uses all variables in the dataset, including the outcome of interest for imputation of missing data via chained regression equations algorithm.

Results

Cohort characteristics

This study included 4018 women and 2102 men aged 50+ followed for a median of 13.5 (IQR: 6.5–15.0) and 12.5 years (IQR: 5.4–15.0) for women and men, respectively.

During the follow-up, 1081 (27%) women and 284 men (14%) experienced an incident fracture, 308 women and 53 in men experienced a further fracture and 899 women and 578 men died. The length of follow-up post-fracture was 5.5 (IQR: 2.6–9.5) and 5.1 years (IQR: 2.3–9.9) for women and men, respectively.

Approximately, 65% of women and 23% of men had osteoporosis at baseline (femoral neck T-score ≤ -2.5 SD). Of those with baseline osteoporosis, 60% of women and 29% of men received bisphosphonate medication during follow-up. Male gender, baseline diabetes and cardio-vascular disease, smoking, physical inactivity and lower level of education were associated with a higher likelihood of not receiving bisphosphonate therapy. A greater number of medications at baseline did not represent a barrier to receiving bisphosphonate therapy.

Treatment groups

Reflecting Canadian practice at baseline, etidronate was the most frequently prescribed bisphosphonate [1170 (57%) for women and 167 (54%) for men] followed by alendronate [650 (32%) for women and 95 (31%) for men], and risedronate [228 (11%) for women and 46(15%) for men] (Table 1). Risedronate only became available in 1999 and was started on average ~ 9 (± 3) years after baseline resulting in both the smaller number of risedronate users and shorter follow-up: 5 (± 3) years compared to 8 (± 4) years for alendronate and 9 (± 4) years for etidronate.

Bisphosphonate users had significantly lower femoral neck BMD, weight, and more incident fractures than NoRx. They also had several factors associated with "healthy users" such as better education lifestyle habits (less smoking, more exercise and more vitamin D use) and less cardiovascular disease and diabetes. There were no substantive differences in bisphosphonate uptake and year of initiation for the nine study centres across Canada (see supplemental table (Table S1).

Bisphosphonate type and mortality for individuals with and without fracture n-BP (alendronate and risedronate) vs NoRx

Of the 735 n-BP users, 635 (83% women) were matched to NoRx (Table 2). After propensity score matching, there were no statistically significant differences in baseline characteristics between treated and not treated. Mortality risk was

Table 1 Characteristics of participants according to medication-groups

	Bisphosphonate type			No treatment
	Alendronate	Risedronate	Etidronate	
	Women			
Number	650	228	1170	1970
Age[a], yrs.	**66 (8)**	**65 (8)**	68 (8)	70 (10)
Death[b]	**92 (14)**	**22 (10)**	**242 (21)**	543 (28)
Weight[a], kg	**64 (12)**	**65 (11)**	**65(12)**	71 (15)
Higher education[b]	**174 (27)**	50 (22)	236 (20)	335 (17)
Year of initiation	1996	1999	1995	
Years on medication[a]	7 (4)	5 (3)	7 (4)	**N/A**
Fractures[1,b]	**243 (37)**	**72 (32)**	**414 (35)**	352 (18)
Hip	25 (10)	6 (8)	52 (13)	50 (14)
Vertebral	47 (19)	9 (13)	50 (12)	25 (7)
Proximal[2]	81 (33)	19 (26)	131 (32)	102 (29)
Distal[3]	90 (37)	38 (53)	181 (44)	175 (50)
BMD[4,a], g/cm^2	**0.63 (0.10)**	**0.67 (0.09)**	**0.63 (0.09)**	0.71 (0.12)
Co-morbidities[b]				
Heart disease	**40 (6)**	**34 (15)**	199 (17)	233 (12)
Diabetes	**46 (7)**	**23 (10)**	**85 (7)**	320 (16)
Hypertension	**251 (39)**	104 (46)	537 (46)	993 (51)
Neurological	21 (3)	9 (4)	53 (5)	64 (3)
Respiratory	98 (15)	28 (13)	**186 (16)**	264 (14)
Cancer	**115 (18)**	34 (15)	213 (18)	297 (15)
Life style factors[b]				
Exercise	**409 (63)**	**139 (69)**	**679 (58)**	972 (49)
Smoking	76 (12)	27 (12)	131 (11)	302 (15)
Vitamin D	**256 (39)**	75 (33)	**453 (39)**	546 (28)
	Men			
Number	95	46	167	1794
Age[a], yrs.	64 (9)	65 (8)	**69 (9)**	66 (10)
Death[b]	22 (23)	11 (24)	54 (32)	491 (27)
Weight[a], kg	79 (12)	79 (13)	**76 (12)**	82 (14)
Higher education[b]	39 (41)	17 (37)	49 (29)	595 (33)
Year of initiation	1997	1999	1996	
Years on medication[a]	5 (4)	4 (3)	6 (4)	N/A
Fractures[1,b]	**24 (25)**	**8 (17)**	**39 (22)**	213 (12)
Hip	6 (25)	0 (0)	10 (25)	32 (15)
Vertebral	1 (4)	0 (0)	4(10)	16 (8)
Proximal[2]	10 (42)	7 (88)	11 (28)	88 (41)
Distal[3]	7 (29)	1 (12)	14 (36)	77 (36)
BMD[4,a], g/cm^2	**0.71 (0.11)**	**0.72 (0.11)**	**0.69 (0.11)**	0.81 (0.12)
Co-morbidities[b]				
Heart disease	14 (15)	5 (11)	18 (11)	293 (16)
Diabetes	10 (11)	6 (13)	18 (11)	297 (17)
Hypertension	35 (36)	22 (48)	67 (40)	728 (41)
Neurological	1 (1)	1 (2)	4 (2)	48 (3)
Respiratory	13 (14)	9 (20)	21 (13)	201 (11)
Cancer	17 (18)	8 (17)	**39 (23)**	265 (15)
Life style factors[b]				
Exercise	52 (55)	23 (50)	87 (52)	1002 (56)
Smoking	12 (13)	9 (20)	23 (14)	336 (19)
Vitamin D	**27 (28)**	9 (20)	**52 (31)**	358 (20)

Boldface corresponds to a global p value < 0.05 for the comparison between treated (alendronate, risedronate, etidronate) and not treated)

[a] Mean (sd)

[b] Number (%)

[1] Incident fragility fractures

[2] Proximal fractures: humerus, elbow, pelvis, femur

[3] Distal fractures: forearm, carpal, metacarpal, tibia/fibula, ankle, tarsal, metatarsal

[4] Femoral neck BMD missing values: weight 3%, BMD (13%), heart disease 0.001%, diabetes (0.001%), hypertension (4%), respiratory (13%)

Table 2 Characteristics of the treated and not-treated matched pairs of women by use of a single specific bisphosphonate

	n-BP vs not treated pairs		Etidronate vs not treated pairs		n-BP vs etidronate pairs	
	Women					
	Treated	Not treated	Treated	Not treated	n-BP	Etidronate
Number	530	530	496	496	340	340
Age[a], yrs.	66 (8)	66 (8)	68.9 (8.2)	68.9 (8.2)	68 (7)	68 (7)
Death[b]	**64 (12)**	**87 (16)**	103 (21)	110 (22)	**39 (11)**	**62 (18)**
Weight[a], kg	**64 (11)**	**70 (14)**	66.0 (12.9)	67.5 (13.5)	65 (11)	65 (11)
Higher education[b]	126 (24)	122 (23)	93 (19)	93 (19)	61 (18)	55 (16)
Years on medication	6 (4)	–	5 (4)	–	**4.9 (3.4)**	**5.5 (3.4)**
Fractures[1,b]	140 (26)	140 (26)	105 (21)	105 (21)	113 (33)	95 (28)
Hip	10 (7)	10 (7)	11 (10)	11 (10)	13 (4)	11 (3)
Vertebral	6 (4)	6 (4)	5 (5)	5 (5)	17 (5)	5 (1)
Proximal[2]	45 (38)	45 (38)	37 (35)	37 (35)	31 (9)	33 (10)
Distal[3]	79 (51)	79 (51)	52 (50)	52 (50)	52 (15)	46 (14)
BMD[4a], g/cm^2	0.66 (0.10)	0.68 (0.10)	0.64 (0.09)	0.65 (0.09)	**0.65 (0.10)**	**0.64 (0.09)**
Co-morbidities[b]						
Heart disease	27 (5)	32 (6)	51 (10)	44 (9)	32 (9)	29 (9)
Diabetes	18 (3)	27 (5)	41 (8)	49 (10)	28 (8)	26 (8)
Neurological	13 (2)	20 (4)	14 (3)	17 (3)	12 (4)	14 (4)
Respiratory	38 (8)	52 (11)	79 (16)	72 (15)	44 (13)	46 (14)
Cancer[a]	92 (17)	112 (21)	88 (17)	93 (19)	58 (17)	62 (18)
Life style factors[b]						
Exercise	319 (60)	326 (62)	280 (56)	291 (59)	211 (62)	201 (59)
Smoking	67 (13)	83 (16)	65 (13)	60 (12)	40 (12)	45 (13)
Vitamin D[a]	**188 (35)**	**156 (29)**	**174 (35)**	**137 (28)**	123 (36)	124 (36)

Bold face corresponds to a global p value < 0.05 for comparison between treated and not treated within each pair

[a] Mean (sd)

[b] Number (%)

[1] Incident fragility fractures

[2] Proximal fractures: humerus, elbow, pelvis, femur

[3] Distal fractures: forearm, carpal, metacarpal, tibia/fibula, ankle, tarsal, metatarsal

[4] Femoral neck BMD

reduced for the treated group [HR, 0.66 (95% CI, 0.48–0.91)], in particular for women [HR, 0.58 (95% CI, 0.39–0.84)].

Subgroup analysis according to n-BP type

In order to determine whether the relationship between treatment and survival was similar for the two nitrogen bisphosphonates, a secondary analysis was performed separately for alendronate and risedronate. In these models, mortality risk was adjusted for the baseline characteristics unbalanced after stratification (i.e. cancer for alendronate group; weight and smoking for risedronate group).

Alendronate users were associated with mortality risk reduction [HR 0.62 (95% CI, 0.42–0.92) for any user and 0.60 (95% CI, 0.38–0.93) for women only] (Table 3 and Fig. 2).

Risedronate was not associated with an overall mortality risk reduction [HR 0.97 (95% CI, 0.50–1.88)]; however, women who used risedronate appeared to have a mortality risk reduction compared to NoRx [HR, 0.52 (0.25–1.09)] (Table 3 and Fig. 2), albeit not statistically significant due to low numbers.

Etidronate vs NoRx

Of the 663 etidronate users, 599 (83% women) were matched to NoRx. By contrast with n-BP users, mortality rates of etidronate users were similar to the matched NoRx [103 deaths/3535 person-years equating to 2.91 deaths/100 person-years (95% CI, 2.40–3.53) vs 110 deaths/3355 person-years equating to 3.28 deaths/100 person-years (95% CI, 2.72–3.95) for

Table 3 Mortality rates and hazard ratio for pairs of participants treated with different bisphosphonates propensity matched 1:1 to those who were not treated

	N	Treated		Not treated		Paired HR[a] (95% CI) (treated vs not treated)
	Pairs	Deaths	Mortality rates (/100 person-year) (95% CI)	Deaths	Mortality rates (/100 person-year) (95% CI)	
n-BP	530	64 (12)	1.80 (1.41–2.30)	87 (16)	2.94 (2.39–3.63)	0.58 (0.39–0.84)
Alendronate	356	46 (13)	1.73 (1.29–2.31)	61 (17)	2.78 (2.16–3.57)	0.60 (0.38–0.94)
Risedronate	174	18 (10)	2.03 (1.28–3.22)	26 (15)	3.42 (2.32–5.01)	0.67 (0.30–1.49)
Etidronate	496	103 (21)	2.91 (2.40–3.53)	110 (22)	3.28 (2.72–3.95)	0.88 (0.63–1.25)

[a] HRs were adjusted for all the baseline variables still unbalanced after matching (cancer for alendronate group, weight and smoking for risedronate group)

etidronate and matched NoRx, respectively; $p = 0.33$)] (Table 3 and Fig. 2). Etidronate use was not associated with survival benefit in whole group [HR, 0.89 (95% CI, 0.66–1.20)] or in women only [HR 0.88 (95% CI, 0.63–1.25)] (Table 3).

The exclusion of participants who reported bisphosphonates (n-BP or etidronate) only once during the follow-up, did not change the findings.

Importantly, close inspection of the 2-year KM plots for both n-BP and etidronate matched sets revealed that there was no difference in survival during the first 6 months, suggesting that the groups were well matched for mortality risk prior to treatment initiation.

n-BP (alendronate and risedronate) vs etidronate

Given the differences in the baseline characteristics between bisphosphonate types, reflecting different indication criteria, only a third of n-BP users ($n = 340$) were successfully matched 1:1 to etidronate ($n = 340$) by propensity score (Table 2). After matching, all characteristics were balanced; however, n-BP users had a borderline higher bone mineral density [0.65 g/cm^2 (0.10) and 0.64 g/cm^2 (0.09); $p = 0.07$ for n-BP and etidronate, respectively] and a shorter duration on medication [average 4.9 (± 3.4) years and 5.5 (± 3.4) years; $p = 0.03$ for n-BP and etidronate, respectively]. Mortality risk was significantly lower for n-BP users compared to etidronate [paired HR, 0.47 (95% CI, (95% CI, 031–0.70)] (Fig. 3).

Sensitivity analysis

In the analysis of all the bisphosphonate users, including those who switched to a different type of bisphosphonate, the results were comparable to the single user analysis. n-BP use was associated with 30–50% mortality risk reduction in the unadjusted [HR, 0.58 (95% CI, 0.48–0.72)], and BMD-adjusted

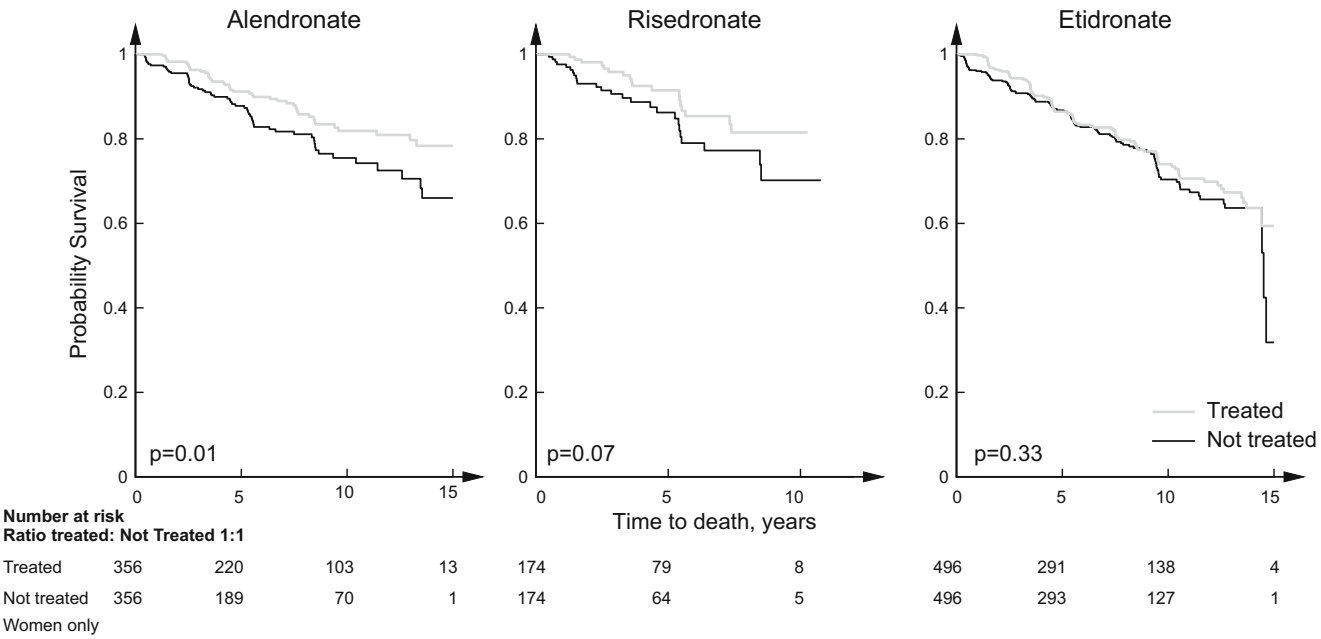
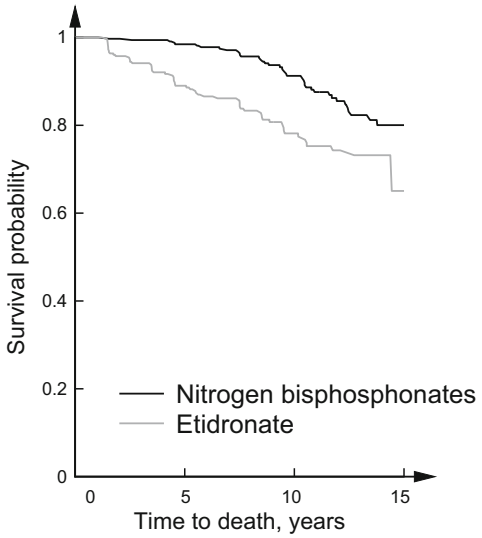


Fig. 2 Kaplan-Meier survival curves for alendronate, risedronate and etidronate and matched not treated



Number at risk

Ratio Nitrogen bisphosphonate: Etidronate 1:1

Nitrogen Bisphosphonate	340	304	178	7
Etidronate	340	228	114	2

Women only

Fig. 3 Kaplan Meier survival curves for nitrogen bisphosphonate (n-BP: alendronate or risedronate) and etidronate versus matched not treated in individuals with incident fracture

[HR, 0.66 (95% CI, 0.52–0.83)] analyses. Etidronate use was not associated with mortality risk reduction in unadjusted [HR, 0.99 (95% CI, 0.84–1.14)] or BMD-adjusted [HR, 1.18, 95% CI, 0.99–1.40)] analyses. Low BMD was a significant confounder in the model of etidronate and survival. A stratified analysis according to BMD level, demonstrated that etidronate was associated with increased mortality risk for osteoporosis group [HR, 1.28 (95% CI, 1.06–1.54)], and a non-significant survival benefit for normal/osteopenia group [HR, 0.72 (95% CI, 0.46–1.15)].

However, when the models where adjusted for inverse treatment probability scores, both n-BP and etidronate users were associated with survival benefit [HRs, 0.50 (95% CI, 0.39–0.63) and 0.69 (95% CI, 0.59–0.82), for n-BP and etidronate, respectively].

Bisphosphonate type and mortality for women with incident fracture

Of the 1081 women with incident fracture, 659 received bisphosphonates at the time or after the fracture and 412 used only one type of bisphosphonate. n-BP ($n = 260$ alendronate or risedronate) and etidronate users ($n = 114$) were matched 1:2 to women who never used osteoporosis treatment following fracture. Treated and not treated participants had similar baseline characteristics; however, individuals on treatment had a higher estimated 5-year fracture risk than those not treated (p value < 0.0001 for both n-BP and etidronate pairs).

In women with incident fracture, use of n-BP was associated with better survival [HR, 0.49 (0.29–0.80)] while etidronate was not associated with survival benefit [HR, 0.82 (95% CI, 0.46–1.49)] (Fig. 4).

The relationship between n-BP and mortality was similar regardless of the time of its initiation: HR, 0.48 (95% CI, 0.27–0.85), 0.41 (95% CI, 0.11–1.57) and 0.53 (95% CI, 0.10–2.76) for 0–2, 2–5 and 5+ years post-fracture, respectively).

The risk of a further fragility fracture was similar for BP and matched NoRx [HR, 1.20 (95% CI, 0.74–1.94)] and etidronate [HR, 1.55 (95% CI, 0.78–3.11)].

Discussion

Individuals with osteoporotic fracture are at increased risk of death. Emerging evidence suggests that bisphosphonate treatment of those with an osteoporotic fracture is associated with a reduction of all-cause mortality; however, the mechanism for this association is unknown. In this observational study, we found that participants on the nitrogen bisphosphonates, alendronate and risedronate, experienced a 40% survival benefit, particularly in women. Participants on non-n-BP, etidronate had no overall survival benefit. These findings were further supported by a head to head comparison which demonstrated that nitrogen bisphosphonate users had ~ 50% better survival compared to etidronate users.

These findings suggest that the benefit seen with the nitrogen bisphosphonates either lies in their greater anti-resorptive effect or via a non-bone effect that may be related to their disruption of the mevalonate kinase pathway [36]; however, most importantly, this analysis in a population-based cohort of two different bisphosphonate biochemistries meant that user bias played a less significant role in the different outcomes observed, thus increasing the likelihood that there is a true decrease in mortality associated with use of nitrogen bisphosphonates.

The magnitude of mortality reduction associated with nitrogen bisphosphonates [HR 0.66 (95% CI, 0.48–0.9 [1]] in this study, is comparable to previous studies on all-cause mortality risk [15, 16, 18, 37]. In the Dubbo Osteoporosis Epidemiology Study, bisphosphonate use in women was associated with a 69% reduction in mortality risk compared to no treatment [16]. Another study reported 27% lower mortality in institutionalised older people [38], and two other studies reported a survival benefit of bisphosphonates in critically ill people [18, 37]. In a Danish database study, the association between bisphosphonates and mortality following hip fracture was similar to this study [15], while two other previous prospective cohort studies reported a stronger relationship (~ 63–66%) with mortality risk reduction [13, 17]. The differences between these results are most likely related to differences in

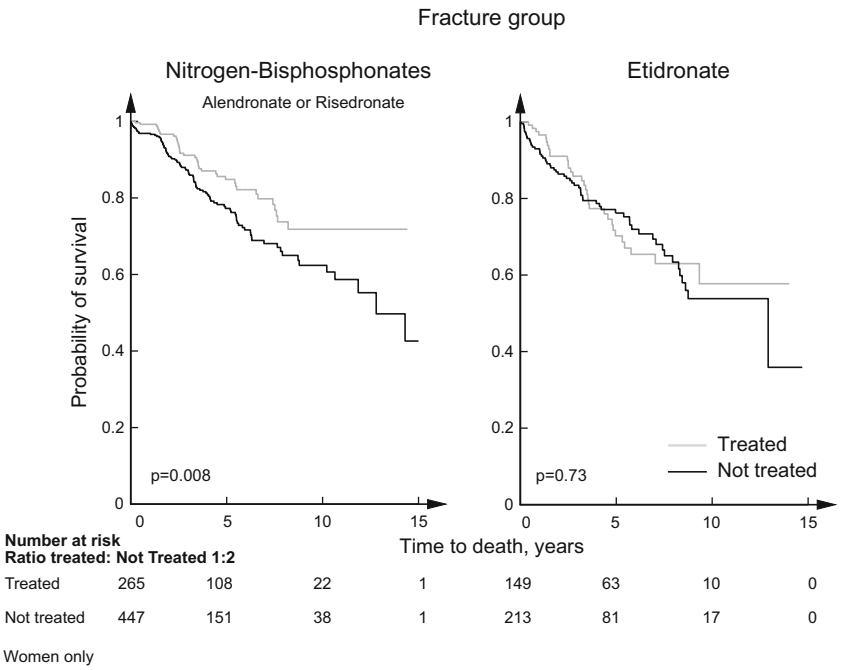


Fig. 4 Kaplan Meier survival curves for nitrogen bisphosphonate and etidronate and matched not treated for individuals with incident fractures. This includes only bisphosphonate initiated at the time of or after the initial incident fragility fracture

baseline characteristics between the treated and non-treated populations. Importantly, these findings are also consistent with the 28% mortality risk reduction observed in the zoledronic acid RCT [11].

The role of etidronate on mortality risk reduction was less clear. Our primary analysis, with participants who only used etidronate during the follow-up, showed no survival benefit over the follow-up period. By contrast, in a sensitivity analysis, including a large number of participants who switched during follow-up to either alendronate or risedronate, etidronate was associated with ~ 31% mortality risk reduction; however, this finding has to be interpreted in the light of the immortal time bias inherently induced by longer follow-up with participants being alive to switch treatments. In addition, based on the previous analyses, the benefit in etidronate 'switchers' could also be attributed to the n-BP to which they were switched.

The uptake of bisphosphonate by men in this study was very low in comparison to women. The association in men between bisphosphonate use and mortality risk was in a similar direction to women, particularly for alendronate and etidronate. The effect of risedronate in men is most likely unreliable, due to the joint effects of a very small sample size ($n < 50$) and a shorter follow-up time. The gender discrepancy in both use of bisphosphonates as well as survival benefit has been reported previously [14, 16]. In an Austrian study, only 12% of men compared to 30% of women reported initiation of bisphosphonate therapy following hip fracture. The association between bisphosphonates and survival was lower than that for women, perhaps driven by the smaller number of men [14].

The mechanism through which bisphosphonates may reduce mortality risk is likely to be multifactorial. The most obvious mechanism would be through a reduction in subsequent fracture risk; however, the RCT of zoledronic acid in women with hip fracture showed that only 8% of the mortality risk reduction in the treatment group was attributable to a reduction in the subsequent fracture rate [39]. Similarly, reduction in subsequent fracture risk in the current study did not account for the observed mortality risk reduction. The lack of a significantly lower subsequent fracture risk reduction in the treated groups is probably due to their higher baseline fracture risk and possibly the survival advantage providing more time to sustain a fracture.

It is also possible, that the relationship between bisphosphonates and mortality risk could be mediated through a reduction in the rate of bone loss, a marker of poor health and increased mortality [40] in both individuals with [41] and without fractures [42, 43]. This would also be consistent with the current finding that mortality reduction was greater with n-BP than with etidronate; parallel with their greater antiresorptive effects. On the other hand, there is emerging evidence that nitrogen bisphosphonates may have anti-inflammatory [30] and anti-cancer effects [31].

This study has several strengths. The large number of bisphosphonates users permitted a detailed analysis of bisphosphonates by biochemistry and mortality as well as adjusting for a large set of risk factors not available in registry-based studies; however, there are some limitations. Treatment was a decision made in clinical care and not randomly allocated, thus part of the observed association could be related to confounding. In order to counteract this potential

confounding bias, this study employed propensity score matching which is currently recognised as a valid method to account for bias in observational studies [44]. Although this procedure cannot account for unmeasured confounding, the resultant treatment groups had equal baseline risks for all measured variables. Furthermore, matching by the time of medication commencement ensured that the treatment groups started follow-up around the same calendar time. Furthermore, Kaplan Meier survival for matched treated versus non-treated did not diverge until after 6 months, suggesting that pairs were well matched and had similar mortality risk at initiation of treatment.

It is possible that there was residual unmeasured confounding such as number of medications, severity of co-morbidities and socio-economic status that could not be accounted for in this observational study. The cost of the different included bisphosphonates was not directly addressed in this study; however, in the main analysis, adjustment was made for education as a surrogate of socio-economic status. Furthermore, medication number did not predict likelihood of receiving bisphosphonate treatment.

Etidronate was not approved worldwide for the treatment of osteoporosis. It is a weaker anti-resorptive than nitrogen-bisphosphonates and is given in a cyclical regime for 2 weeks every 3 months. Didrocal was a formulation of etidronate (Didronel) for ease of managing the 2 weeks on each 3 months with calcium provided for the other days. Etidronate was available before the nBPs and could have been prescribed to sicker patients; however, this is unlikely to have been the case as in many jurisdictions, etidronate had to have 'failed' or not been tolerated before n-BPs could be prescribed. Thus n-BPs were often prescribed to sicker patients. Any such differences could not be identified or excluded.

Given the yearly collection of data, this study could not address the issue of misclassification of exposure due to differences in treatment adherence. It is possible that some participants may have been prescribed bisphosphonates between yearly questionnaires but did not adhere to treatment for the full year. In this situation, participants would have been classified as non-treatment despite a 'window' of treatment exposure. These participants would have only under-estimated the true effect; however, the exclusion of participants who reported bisphosphonates only once during the study follow-up (~ 10%) and thus more likely to be non-adherent did not impact the findings.

In summary, compared to no treatment, nitrogen bisphosphonate use, particularly in women, was associated with better survival in this long-term prospective population-based cohort study irrespective of incident fracture status while etidronate either lacked or had a minor mortality benefit. This observation is important as it points toward mechanistic hypotheses that need to be confirmed in further studies. Importantly, this study suggests that nitrogen bisphosphonate treatment for osteoporosis, whether or not a fragility fracture has occurred, improves survival irrespective of fracture risk prevention.

Contributors DB, TT, TvG, JAE and JRC designed the study. DB, TT, JAE and JRC analysed the data. DB, TT and JRC drafted the manuscript. All authors contributed to the interpretation of the data and revision of the manuscript. JRC had primary responsibility for final content and acts as guarantor. All authors read and approved the final manuscript. The funding sources had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; nor did they have a role in preparation, review, or approval of the manuscript and the decision to submit for publication.

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Compliance with ethical standards

Conflicts of interest DB, TT, TvG, CB, DG, RGJ, LL, CSK, SMK and JCP have no competing interests to declare. JDA has received research grants and/or personal fees from Amgen, Eli Lilly, Merck, Actavis and AgNovos. JvdB has received grants and/or personal fees from Amgen, MSD and Eli Lilly. JAE has consulted for and/or received research funding from Amgen, deCode, Merck Sharp and Dohme and Sanofi-Aventis. PG was advisory member for Amgen, has received speaker fee and/or research grants from Amgen, Pfizer, MSD, UCB, Abbott, Lilly, BMS, Novartis, Roche and Will Pharma. DAH has consulted for and/or received speaker fee and/or research funding from Amgen, Merck and Eli Lilly. TVN has received honoraria for consulting and symposia from Merck Sharp and Dohme, Roche, Servier, Sanofi-Aventis and Novartis. JRC has consulted for and/or given educational talks for Merck Sharp and Dohme, Amgen, Actavis and Sanofi-Aventis.

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