Osteoporosis Medication and Reduced Mortality Risk in Elderly Women and Men

Jacqueline R. Center, Dana Bliuc, Nguyen D. Nguyen, Tuan V. Nguyen, and John A. Eisman

Osteoporosis and Bone Biology Program (J.R.C., D.B., N.D.N., T.V.N., J.A.E.), Garvan Institute of Medical Research, and St. Vincent's Hospital (J.R.C., J.A.E.), Darlinghurst, Sydney, New South Wales, 2010 Australia; and Faculty of Medicine (J.R.C., T.V.N., J.A.E.), and School of Public Health and Community Medicine (T.V.N.), University of New South Wales, Sydney, New South Wales 2052, Australia

Context: Osteoporotic fractures are associated with premature mortality. Antiresorptive treatment reduces refracture but mortality reduction is unclear.

Objective: The objective of the study was to examine the effect of osteoporosis treatment [bisphosphonates (BP), hormone therapy (HT), and calcium ± vitamin D only (CaD)] on mortality risk.

Design: This was a prospective cohort study (April 1989 to May 2007).

Setting: The study was conducted with community-dwelling elderly (aged 60+ yr) subjects in Dubbo, a semiurban city, Australia.

Subjects: Subjects included 1223 and 819 women and men in the Dubbo Osteoporosis Epidemiology Study.

Main Outcome Measure: Mortality according to treatment group was recorded.

Results: There were 325 (BP, n = 106; HT, n = 77; CaD, n = 142) women and 37 men (BP, n = 15; CaD, n = 22) on treatment. In women, mortality rates were lower with BP 0.8/100 person-years (0.4, 1.4) and HT 1.2/100 person-years (0.7, 2.1) but not CaD 3.2/100 person-years (2.5, 4.1) *vs.* no treatment 3.5/100 person-years (3.1, 3.8). Accounting for age, fracture occurrence, comorbidities, quadriceps strength, and bone mineral density, mortality risk remained lower for women on BP [hazard ratio (HR) 0.3 (0.2, 0.6)] but not HT [HR 0.8 (0.4, 1.8)]. For 429 women with fractures, mortality risk was still reduced in the BP group [adjusted HR 0.3 (0.2, 0.7)], not accounted for by a reduction in subsequent fractures. In men, lower mortality rates were observed with BP but not CaD [BP 1.0/100 person-years (0.3, 3.9) and CaD 3.1/100 person-years (1.5, 6.6) *vs.* no treatment 4.3/100 person-years (3.9, 4.8)]. After adjustment, mortality was similar, although not significant [HR 0.5 (0.1, 2.0)].

Conclusions: Osteoporosis therapy appears to reduce mortality risk in women and possibly men. **(*J Clin Endocrinol Metab* 96: 1006–1014, 2011)**

Osteoporotic fractures represent an important health problem, resulting in increased disability, future fracture risk, and premature mortality (1–5). Although premature mortality is well recognized after hip and vertebral fractures (6–10), there is now comparable evidence from us and others that premature mortality is also associated with other major (2, 3, 11, 12) and even minor fractures in the elderly (13, 14) and that this increased risk is relatively worse for men than women. Despite the clear evidence for this major health impact, most people with osteoporotic fractures remain untreated (15–18).

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Abbreviations: BMD, Bone mineral density; BP, bisphosphonate; CaD, vitamin D with or without calcium; CI, confidence interval; CrI, credible interval; HR, hazard ratio; HT, hormone therapy; IQR, interquartile range; OR, odds ratio; RCT, randomized controlled trial; SMR, standardized mortality ratio.

Although many studies have tried to identify factors that generate the excess postfracture mortality, the basis for this association remains unclear. Some studies conclude that increased mortality risk is due to prefracture health status, including comorbidities, physical and mental function, low bone density, and rapid bone loss (2, 7, 19–21). However, others have found little association between mortality and underlying health status, suggesting that the fracture event may explain much of the excess mortality (6).

Recently there has been some evidence that osteoporosis treatment may reduce mortality risk. In a randomized controlled trial, zoledronic acid, a potent iv bisphosphonate, was associated with a 28% reduction in mortality after hip fractures in women and men (22). This was supported by a metaanalysis of randomized studies suggesting an 11% decrease in mortality with treatment (23). There have also been some observational studies consistent with these findings. An early study reported a reduction in postfracture mortality for antiosteoporotic drugs including oral bisphosphonates, but individual drug classes were not separately reported (24). More recently there have been two studies examining oral bisphosphonate therapy on mortality. Both of these studies, the first in a relatively young, healthy population after hip fracture followed up for 3 yr and the second in a frail nursing home population followed up for 5 yr demonstrated a mortality benefit with bisphosphonate therapy (25, 26).

Other therapies may also have potential benefits. Despite the potential negative cardiac effects of hormone therapy, it does decrease fractures (27, 28), and a recent metaanalysis suggested that it may be associated with reduced mortality in younger women (29, 30). Vitamin D with or without calcium (CaD) may have a weak effect on fracture prevention (31, 32), and supplementation may have a small beneficial effect on mortality (33).

The aims of our study therefore, were to investigate the association between oral bisphosphonates (BPs), hormone therapy (HT), and CaD with mortality in older women and men (60+ yr), with and without fracture, over 18 yr of follow-up.

Subjects and Methods

Study population

The study cohort consisted of women and men aged 60+ yr participating in the Dubbo Osteoporosis Epidemiology Study. The study is an ongoing prospective observational population-based study that started in 1989 in Dubbo, a semiurban city with a population of 32,000. Approximately 60% of the eligible population was recruited into the study. The population is stable, with the same age and gender distribution as the Australian population. These characteristics, together with its relative isolation and centralized health services, make the site optimal for epidemiological research (34).

This study was approved by the St. Vincent's Hospital Human Research Ethics Committee.

Assessment of outcomes and risk factors

Data ascertainment

Bone mineral density (BMD) at the femoral neck, quadriceps strength, sway, and anthropometric measurements as well as questionnaire information on lifestyle factors, comorbidities, and medication were collected at baseline and twice yearly. Medication data included type, dose, and start and stop date.

Treatment was divided into three categories: BP, HT, and CaD. CaD was chosen to represent a group of people taking a more active interest in their health to address self-selection bias.

Participants were classified according to their medication in three nonoverlapping groups. BP users were those on BP ± other osteoporosis medication. HT participants were women on HT alone or with calcium ± vitamin D. CaD users were not present or past users of other osteoporosis treatments. At each visit, participants were asked about their medication use.

Comorbidities were categorized into five major groups: cardiovascular, respiratory, neurological, diabetes, and cancer. Participants were also classified according to number of illnesses: none, one, two, and three or more.

Bone mineral density

BMD was measured at the femoral neck by dual-energy x-ray absorptiometry using a GE Lunar densitometer (Madison, WI). The coefficient of reliability at our institution was 0.96 for normal subjects.

Fractures

All fractures occurring in Dubbo from April 1989 to May 2007 were identified through the two (and at one time three) radiological services in Dubbo, as previously reported (1). There were 85 (n = 62 women and n = 23 men) subjects with fractures occurring within 3 months before the study (11 on BPs). Their behavior was similar to the rest of the group, and so these subjects were included in all analyses except for the postfracture Kaplan-Meier survival curves due to potential survivor bias.

Circumstances of the fracture were obtained through direct interview. Only minimal trauma fractures (after a fall from standing height or less) were included. High trauma and pathological fractures (*e.g.* cancer or Paget's disease) and fractures of the head, fingers, or toes were excluded. However, given the recent evidence suggesting that high and low trauma fractures may be part of a continuum, a separate analysis was conducted with inclusion of the high trauma fractures.

Population and mortality data

Population and mortality data for the entire Dubbo population were obtained from the Australian Bureau of Statistics for each study year. Age-specific mortality rates for the Australian population in 1993 were also obtained as the year corresponding to the median time to death. Dubbo population mortality rates were used as reference in Kaplan-Meier survival curves when analysis was limited to the fracture group. However, for analysis of the whole cohort (>60% of Dubbo population aged 60+ yr), Australian population mortality rates were used as reference.

Mortality status for all study participants was continuously ascertained through systematic searches of funeral directors lists,

local newspapers, and Dubbo media reports. Death certificates were obtained from the New South Wales Registry of Births, Deaths, and Marriages.

Statistical analysis

Age-specific mortality rates were calculated separately for each treatment group and mortality risk estimated relative to the nontreated group. Age-adjusted standardized mortality ratios (SMRs) were calculated.

The hazard ratio of survival using Cox proportional hazards models was adjusted by baseline variables. In a separate Cox proportional hazards model, propensity scores were used, derived from logistic regression models using all baseline characteristics. Propensity score is a technique to account for unbalanced variables when comparing two or more groups that have a range of common characteristics. Logistic regression equations were used to assign a value between 0 and 1 for each participant based on all the variables. This value represents the predicted probability of being in the treatment (or nontreatment) group. An additional propensity score-matched set was created by matching each BP participant with a nontreated participant with a similar propensity score and analyzed using conditional logistic regression (35).

Treatment status was classified as a time-dependent variable. Thus, subjects were classified as treated only from the date treatment was started. Fracture was analyzed both as a categorical variable and as a time-dependent variable in the models.

Given the smaller numbers of men, a Bayesian approach was used. This statistical method makes use of information that is already known, *i.e.* prior knowledge. Information from the current study is added to prior knowledge and the posterior distribution or posterior hazard ratio (HR) calculated, *i.e.* the estimate of the association using the joint information. In essence, given the observed value, this indicates the likelihood that the observed value is actually true. For this study two Bayesian models were constructed. In the first model, the posterior HR [and 95% credible interval (CrI)] of the association between BP therapy and mortality in men was estimated using the observed association in women as prior information. Additionally, a Bayesian approach was used to calculate the posterior distribution of the association between BP therapy and mortality in both women and men, using the data on zoledronic acid and mortality (22) as the prior probability.

Statistical analyses were performed using SAS version 9 (SAS Institute, Cary, NC) and the R platform for Bayesian analyses. *P* values were two tailed.

Results

Cohort characteristics

Data were available on 1223 women and 819 men. Median follow-up was 15.2 [interquartile range (IQR) 8.8–16.6] and 13.8 yr (IQR 7.1–16.2), women and men, respectively. The mean (SD) age for women was 71 (7) yr and for men was 70 (6) yr. There were 429 fractures in women (35%) and 153 in men (19%) over the follow-up period. Sixty-one percent reported one or more comorbidities with cardio-vascular being the most common (Table 1).

Treatment groups

A total of 325 women (26.6%) (BP, n = 106; HT, n = 77; and CaD, n = 142) and 37 men (4.5%) (BP, n = 15; CaD, n = 22) received osteoporosis medication. (Table 1 and Fig. 1). The majority of BPs prescribed were alendronate (83 in women and 11 in men) followed by risedronate (21 in women and three in men). There was one woman and one man on etidronate and one woman on zoledronic acid.

Women who received BPs were slightly younger but weighed less and had more fractures and lower femoral neck BMD (Table 1). The number of comorbidities was similar between treatment groups and genders (Table 1). The duration of BP treatment was a median of 2.99 (IQR 1.75–4.64) yr in women and 2.57 (IQR 1.65–3.09) yr in men.

Women who received HT were younger, and those on CaD had more fractures, but there were no other baseline differences between them and the no-treatment group (Table 1).

The subjects in the treated group were cared for by a broad range of primary care physicians in the Dubbo area, representing more than 95% of practicing physicians. There were two physicians who were overrepresented, presumably reflecting practice size. However, even when analyses were repeated excluding subjects from these physicians, the results were not altered.

Mortality

There were 466 deaths in women and 400 in men over 15,453 and 9,522 person-years yielding crude mortality rates of 3.02/100 person-years [95% confidence interval (CI) 2.76–3.31] for women and 4.20/100 person-years (95% CI 3.74–4.54) for men. Mortality rates in this cohort were higher than for the Australian population [age adjusted SMR, women 1.48 (95% CI 1.32–1.65) and men 1.28 (95% CI 1.14–1.43)], which may relate to the high numbers of fracture participants. Mortality rates of women and men without fracture on no treatment were similar to Australian population rates [age adjusted SMR, women 1.00 (95% CI 0.76–1.34) and men 1.02 (95% CI 0.80–1.31)].

Bisphosphonates

Women on BPs had significantly lower mortality rates [0.76/100 person-years (95% CI 0.42, 1.37)] than women on no treatment [3.46/100 person-years (95% CI 3.13–3.83)] with correspondingly lower SMRs. Similarly in men, mortality rates were lower for those on BPs compared with those on no treatment [0.99/100 person-years (95% CI 0.25, 3.94) *vs.* 4.30/100 person-years (95% CI 3.89, 4.75)] (Table 2).

In women, after adjusting for propensity score [HR 0.27 (95% CI 0.15, 0.50)] or in a multivariable analysis

TABLE 1. Participant characteristics according to medication use

	Total	BP	HT	CaD	No therapy
Women					
Number[a]	1223	106 (9)	77 (6)[b]	142 (12)	898 (73)
Fractures[a]	429 (35)	71 (67)[c]	19 (25)	55 (39)[c]	284 (32)
Age (yr)[d]	71 (7)	69 (6)[c]	67 (5)[c]	70 (7)	71 (7)
Height (cm)[d]	160 (6)	161 (6)	160 (6)	160 (7)	160 (6)
Weight (kg)[d]	65 (12)	63 (12)[c]	62 (9)	64 (12)	66 (13)
FNBMD (g/cm^2)[d]	0.79 (0.13)	0.75 (0.11)[c]	0.82 (0.12)	0.78 (0.13)	0.79 (0.13)
Quad strength (kg)[d]	19 (8)	20 (7)	21 (8)	19 (8)	19 (8)
Sway (cm^2)[d]	35 (61)	38 (69)	32 (61)	34 (56)	35 (61)
Disease[a]					
None	475 (39)	44 (42)	34 (44)	52 (37)	345 (38)
One	521 (43)	40 (38)	30 (39)	65 (46)	386 (43)
Two	190 (16)	17 (16)	12 (16)	20 (14)	141 (16)
Three or more	37 (3)	5 (4)	1 (1)	5 (4)	26 (3)
Cardiovascular[a]	493 (40)	27 (25)[c]	28 (36)	64 (45)	374 (42)
Respiratory[a]	106 (9)	20 (19)[c]	4 (5)	11 (8)	74 (8)
Neurological[a]	162 (13)	24 (23)[c]	15 (19)	16 (11)	107 (12)
Diabetes[a]	119 (10)	5 (5)[c]	4 (5)	12 (8)	98 (11)
Cancer[a]	135 (11)	14 (13)	6 (8)	17 (12)	98 (11)
Smoking[a]	376 (31)	38 (36)	22 (29)	37 (26)	279 (31)
Men					
Number[a]	819	15 (2)		22 (3)	782 (95)
Fractures[a]	153 (19)	8 (53)[c]		4 (18)	141 (18)
Age (yr)[d]	70 (6)	69 (7)		71 (7)	70 (6)
Height (cm)[d]	173 (7)	173 (9)		171 (7)[a]	174 (7)
Weight (kg)[d]	79 (12)	73 (8)[c]		71 (13)[a]	79 (12)
FNBMD (g/cm^2)[d]	0.91 (0.15)	0.88 (0.17)		0.85 (0.15)[a]	0.92 (0.15)
Quad strength (kg)[d]	34 (11)	36 (12)		31 (10)	34 (11)
Sway (cm^2)[d]	29 (55)	36 (64)		46 (77)	29 (54)
Disease[a]					
None	279 (34)	3 (20)[c]		12 (55)	264 (34)
One	356 (44)	5 (33)		6 (27)	345 (44)
Two	158 (19)	6 (40)		4 (18)	148 (19)
Three or more	26 (3)	1 (7)		0 (0)	25 (3)
Cardiovascular[a]	326 (40)	6 (40)		6 (27)	314 (40)
Respiratory[a]	104 (13)	5 (33)[c]		3 (14)	96 (12)
Neurological[a]	125 (15)	3 (20)		2 (9)	120 (15)
Diabetes[a]	88 (11)	1 (7)		2 (9)	85 (11)
Cancer[a]	108 (13)	5 (36)[c]		1 (5)	102 (13)
Smoking[a]	524 (64)	8 (53)		12 (55)	505 (64)

FNBMD, Femoral neck BMD.

[a] Number (percent); [b] 60 of 77 were current users; [c] $P \leq 0.05$ for comparison with no therapy; [d] mean (SD).

with BP use entered as a time-dependent variable, adjusted for age, femoral neck BMD, height, weight, postural sway, quadriceps strength, comorbidities, and the occurrence of fracture, a similar benefit of BP on mortality was observed (Table 3). In men, there was a similar magnitude of effect of BP treatment on mortality risk [HR 0.27 (95% CI 0.07, 1.00)]. After adjustment, this was similar but not significant (Table 3).

Given the differences in baseline characteristics between untreated women and those on BPs, a subset matched by propensity score was constructed. There were 102 of 106 treated women matched with 102 nontreated women. In this sample, 10 (9.8%) in the BP group died, compared with 44 (43.1%) in the nontreated group ($P < 0.0001$). Using conditional logistic regression and after adjusting for any unbalanced variables, BP therapy was still associated with benefit [adjusted odds ratio (OR) 0.20 (95% CI 0.10–0.43)].

Mortality in those on BP without fracture was examined to see whether the effect was driven by the fracture participants. For nonfractured women, mortality risk was still reduced by 76% (95% CI 3–97%) in a Cox proportional hazard model after adjustment. For men, mortality risk was reduced, but this was of smaller effect size and not significant after multivariate adjustment [HR 0.96 (95% CI 0.24–3.93)].

To further address the potential for treatment selection bias, we specifically examined risk factors predictive of receiving BP treatment. Models were constructed for women alone and for both sexes together adjusting for

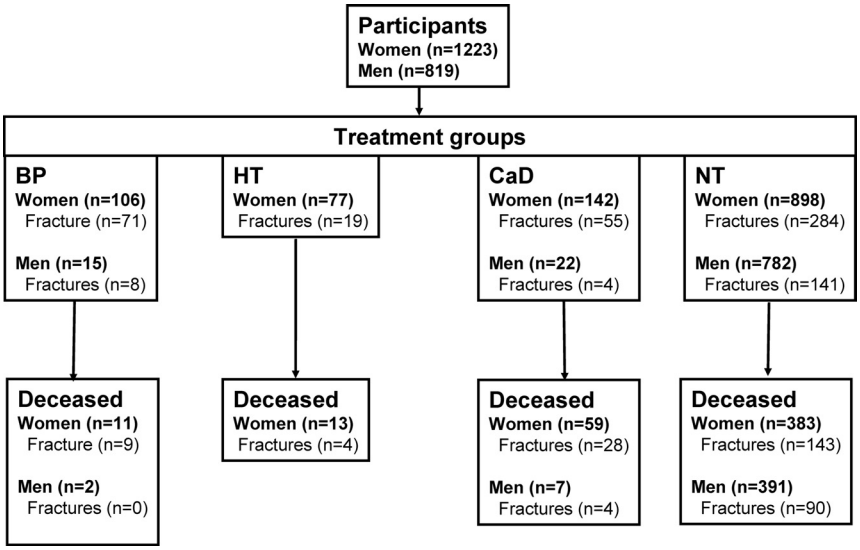

FIG. 1. Flow diagram for the participants of the Dubbo Osteoporosis Epidemiology Study. NT, No treatment.

gender. Independent risk factors for BP treatment were younger age [OR of 5 yr decrease, 1.45 (95% CI 1.22–1.76)], lower weight [OR of 5 kg decrease, 1.12 (95% CI 1.00–1.25)], lower BMD [OR of 0.12 g/cm^2, 1.5 (95% CI 1.15–1.97)], fracture in the presence of low BMD [OR 9.93 (95% CI 5.36–18.41)], and greater height [OR 5 cm increase 1.21 (95% CI 1.00–1.47)], and in the combined group, a greater number of comorbidities [OR each additional comorbidity 1.23 (95% CI 1.02–1.64)]. Apart from age (which was adjusted for in the age standardized mortality ratios) and height (neutral), all other factors would actually be expected to predict increased mortality risk.

There were 88 subjects who sustained high trauma fractures and survived beyond a few weeks after the trauma. Five of the subjects who sustained these fractures were on BPs (three women and two men). Including the 88 fractures in the cohort did not significantly change the results [age and fracture adjusted HR of 0.27 (0.15–0.50) for women and 0.25 (0.06–1.02)] for men.

Hormone therapy

Women on HT also had lower mortality rates than women on no treatment [HR 0.54 (95% CI 0.31–0.94)] (Table 3), but it was no longer significant in an adjusted model with HT as a time-dependent variable [HR 0.78 (95% CI 0.35–1.76)].

Calcium with or without vitamin D

The CaD-alone group had mortality rates similar to the nontreated group for both genders (Table 2).

Postfracture mortality

Results were similar in those 429 women with osteoporotic fractures for all treatment groups (Table 3). Kaplan-Meier curves were consistent with these analyses (Fig. 2). From these curves, the survival benefit appeared to start very early and persist for at least 5 yr after which the slope started to approximate that of the general population.

Subsequent fracture risk

Subsequent fractures were analyzed to determine whether the mortality effect of treatment was related to fracture reduction. Eight women who started treatment after refracture were excluded. Women on BPs had a similar number of subsequent fractures [21 of 63 (33%)] as women on no treatment [96 of 284 (34%); $P = 0.94$]. However, there was a significant interaction between BP use and femoral neck BMD, suggesting that women with osteoporosis ($T \leq -2.5$ SD) had a lower refracture risk with BP use. Restricting the analysis to these women (n = 186), BP use was associated with a refracture risk reduction, albeit not significant [HR 0.78 (95% CI 0.37–1.63)]. Thus, the beneficial effect of BPs on mortality could not be explained by a decrease in subsequent fracture risk.

TABLE 2. Mortality rates for osteoporosis medication *vs.* no medication

Medication	Deaths (n)	Person-years	Rates (95% CI)	SMR[a]
Women				
No therapy	383	11,066	3.46 (3.13–3.83)	1.56 (1.41–1.73)
BP	11	1,451	0.76 (0.42–1.37)	0.49 (0.32–0.74)
HT	13	1,082	1.20 (0.70–2.07)	0.98 (0.57–1.69)
CaD	59	1,854	3.18 (2.47–4.11)	1.63 (1.07–2.49)
Men				
No therapy	391	9,095	4.30 (3.89–4.75)	1.29 (1.17–1.43)
BP	2	203	0.99 (0.25–3.94)	0.38 (0.16–0.88)
CaD	7	224	3.13 (1.49–6.56)	1.03 (0.36–2.95)

[a] SMR compared with Australian population.

TABLE 3. Crude and adjusted HRs of mortality according to osteoporosis treatment

Osteoporosis medication	Women HR (95% CI) Whole cohort (n = 1229)	Women HR (95% CI) Fractures (n = 429)	Men HR (95% CI) Whole cohort (n = 819)
BP			
Age adjusted	**0.28** (0.15–0.50)	**0.35** (0.17–0.72)	**0.27** (0.07–1.00)
Propensity score adjusted[a]	**0.27** (0.15–0.50)	**0.36** (0.17–0.75)	0.31 (0.08–1.25)
Multivariate[b]	**0.31** (0.17–0.59)	**0.33** (0.16–0.66)	0.48 (0.11–1.98)
HT			
Age adjusted	**0.54** (0.31–0.94)	0.55 (0.20–1.50)	
Multivariate[b]	0.78 (0.35–1.76)	0.56 (0.20–1.56)	
CaD			
Age adjusted	0.99 (0.76–1.31)	0.95 (0.63–1.43)	0.86 (0.41–1.83)
Multivariate	0.91 (0.68–1.21)	0.92 (0.61–1.41)	0.82 (0.39–1.74)

[a] Propensity scores were based on a logistic regression model with the participant characteristics of the treated group as independent variables and the not-treated group as the dependent variable. Each participant's propensity score reflects the conditional probability of being treated, given baseline characteristics (femoral neck BMD, comorbidities, fracture occurrence, height, weight, postural stability, and quadriceps strength).

[b] Model adjusted for the above confounders with treatment entered as time-dependent variable.

Bolded values are significant.

Bayesian analysis

Using data for women as prior information, a likely true association between BP therapy and mortality in men was observed with an all confounder-adjusted posterior distribution HR of 0.35 (95% credible interval CrI, 0.19, 0.63)].

In addition, a Bayesian approach was used to estimate the posterior distribution of BP therapy and mortality observed in this study using previously published data on zoledronic acid and mortality (relative risk reduction of 0.72) as prior information. The all confounder-adjusted posterior HR for BP treatment and mortality was 0.65 (95% CrI 0.51–0.82) for women and 0.71 (95% CrI 0.56–0.92) for men.

Causes of death

In those who fractured who were not on BPs, the main causes of death were 30% cardiovascular, 22% respiratory (77% of these being due to pneumonia), 16% cerebrovascular, and 5% malignancy. If the individuals who were on BPs after fracture had the same frequency of and causes of death as those who were not treated, there would have been seven cardiovascular deaths (*vs.* three observed); five respiratory deaths, four of these being due to pneumonia (*vs.* five all due to pneumonia); four deaths from cerebrovascular disease (*vs.* none observed); and one from cancer (*vs.* two observed). Although these numbers are too small to make definitive conclusions, it would appear that there was unlikely to have been any major change in deaths from infection or malignancy and a possible reduction in cardiovascular and cerebrovascular deaths.

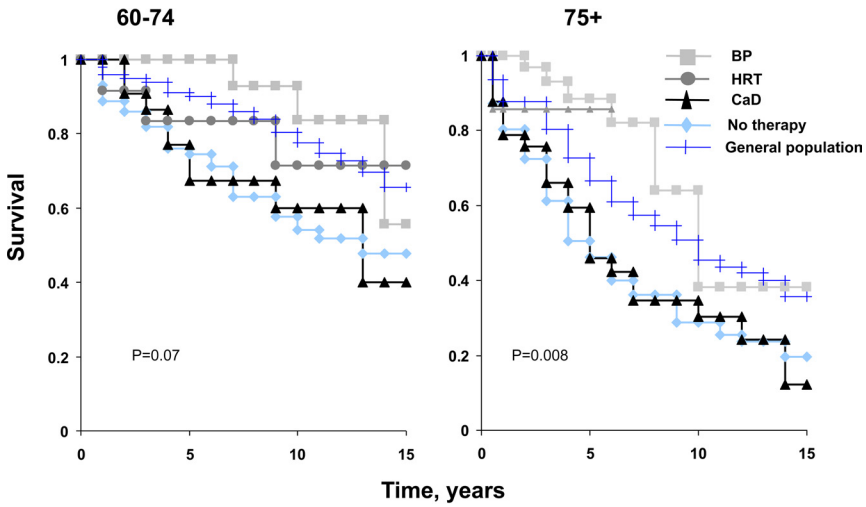

FIG. 2. Kaplan-Meier survival curves according to osteoporosis medication for women with osteoporotic fractures aged 60–74 yr (A), aged 75+ yr (B). The *P* value refers to differences between treatment groups.

Discussion

This longitudinal study in older women with and without fractures has demonstrated a 69% reduction in mortality [adjusted HR 0.31 (95% CI 0.17–0.59)] in those on BPs. This remained after accounting for age and frailty markers including lower BMD, postural instability, quadriceps weakness, smoking, and comorbidities. A similar but nonsignificant mortality risk reduction with BP therapy was observed in the smaller number of men. However, a likely true benefit of BP ther-

apy on mortality risk in men was obtained using prior information from published data on zoledronic acid. Current HT use was associated with a reduction in mortality in some analyses, and CaD had a small, although not significant, effect size similar to a recent metaanalysis (33).

To our knowledge, this is the first long-term study specifically designed to examine the association between antiresorptive therapy, particularly BP, and mortality risk after all fracture types. Five previous studies [four observational and one randomized controlled trial (RCT)] have described BP therapy and mortality risk. Of these, the first four were restricted to individuals after hip fracture and the last to a frail nursing home cohort. Two of the four observational studies reported similar magnitudes of mortality risk reduction as the current study: 0.34 (95% CI 0.17–0.70) in an early study aimed at identifying the level of osteoporosis treatment after hip fracture (24) and 0.37 (95% CI 0.28–0.51) per year of BP use in a 3-yr study of 209 relatively healthy hip fracture subjects taking part in a study of case manager intervention *vs.* usual care (25). A third small observational study reported an additive effect of calcium and vitamin D supplements together with BPs resulting in a 43% mortality reduction. However, in that study calcium and vitamin D supplements alone resulted in a 36% mortality reduction, whereas the results of the BP group alone was not reported, probably due to small numbers (36). The final observational study of frail nursing home subjects followed up for 5 yr reported a lower risk reduction of 27% (95% CI 0.56–0.94) (26). This latter finding was similar to the one randomized, double-blind, placebo-control study of iv zoledronic acid after hip fractures in elderly women and men in which a 28% decreased mortality risk was reported (22).

The differences in the risk reduction between the latter two studies and the current study may be explained by different fractures studied, *i.e.* hip *vs.* all osteoporotic fractures, different populations with hip fracture subjects generally being older, and/or the shorter exposure period (3–5 yr) *vs.* the mean 10 yr in the present observational study. Finally, despite all the adjustment, there may be confounders for which the results have not been able to be accounted. In the present study, a healthy user effect was specifically examined in the design with CaD users only being represented as a separate group.

However, most importantly, a Bayesian analysis, using the RCT data as prior information, supported a 35% mortality risk reduction in women and a 29% risk reduction in men associated with BPs, suggesting that this is a true relationship. That there appears to be an effect on mortality with BPs, albeit with varying effect size, is supported by a recent metaanalysis of osteoporosis treatments that reported an 11% mortality reduction (23).

The mechanisms by which antiresorptive therapy could reduce mortality risk are multifactorial. One possibility may be by preventing new fractures. However, this appears unlikely to be the major mechanism. In the current study, there was a 20% reduction in subsequent fracture risk with BP therapy but only in women with osteoporosis, at most only partially explaining the observed reduction in mortality risk. The lack of a greater effect may be obscured by the high mortality after fracture (35% had died within 2 yr in the current study). Consistent with the current study, the reduction in mortality in the zoledronic acid RCT could also only be partially explained by a reduction in fracture risk amounting to 8% of the overall 28% mortality risk reduction (37).

Although BPs are primarily used for their effects on bone resorption, extraskeletal effects have also been described (38, 39). Recent studies suggest they may modulate the immune processes by influencing the production of pro- and antiinflammatory cytokines ($\gamma\delta$ T cells, TNF-α, and interferon-γ) influencing infection-related deaths. Supporting this hypothesis was a reduction in pneumonia-related deaths in the zoledronic acid study (37). In that study, there was also a reduction in arrhythmia-related deaths, believed to be biologically plausible through the BP effects on the ion channels. In the current study, there was a suggestion of a possible reduction in cardiovascular and cerebrovascular deaths, but the numbers were small.

However, another possible mechanism, for which there is indirect evidence, could be the potent suppression of bone turnover and bone loss observed with BPs. Bone loss is an independent predictor of mortality (21), as is high bone turnover (40). High turnover or loss may result in the release of potentially toxic compounds, including lead, which are stored in the skeleton (41). Lead and other toxic heavy metals can be stored in bone for decades; however, during conditions of increased bone resorption, these toxic heavy metals are released into the bloodstream with potentially deleterious effects. Increased levels of lead have been associated with cognitive decline, renal disease, hypertension, and increased mortality (42, 43). Lead could also be a marker of other toxic materials sequestered in the skeleton being released on bone dissolution. In this study, bone loss was less in those taking BPs with CaD, and this group also had fewer deaths.

There are many studies examining HT and mortality risk, with conflicting results. However, a recent Bayesian metaanalysis reported a mortality benefit associated with HT in younger postmenopausal women (relative risk 0.72; CrI 0.62–0.82) (30).

In the present study, those treated with CaD had higher mortality rates than expected for their age and gender in the general population, possibly related to the higher prev-

alence of osteoporotic fracture (40%) in this group. After adjustment there was a minimal nonsignificant beneficial effect, similar to the weak effect reported from a meta-analysis of studies with supplemental vitamin D (33).

The strength of our study is a large cohort followed up prospectively over 18 yr. The data collection, including the ascertainment of fracture and mortality, is highly reliable. The use of personal treatment cards minimizes recall bias for treatment groupings. Both multivariable and propensity score matching was used to adjust for a large number of confounders.

However, there are some limitations. As an observational study, treatment was not randomly allocated. The group that received treatment was possibly self-selected and health oriented. However, women treated with BPs, although younger by 1 yr, had more fractures, were lighter, and had lower BMD, each difference of which is actually associated with higher mortality. To overcome any potential bias, a separate analysis in a large subgroup matched for propensity score was carried out to correct for all these factors. It yielded a similar result. Additionally, we specifically chose a group of people treated with CaD only, consistent with individuals also concerned about their bone health. A comparable benefit was not observed in this group. We also specifically constructed models in the whole group to examine factors predictive of receiving BP treatment to uncover any additional bias. In addition to the above mentioned variables of younger age, lower BMD, and lower weight, fracture in the presence of low BMD greater height and increased number of comorbidities were independent factors. Apart from age (adjusted for in the age standardized mortality) and a probable neutral contribution of height, all other factors are associated with increased mortality risk, again increasing the robustness of our findings. We also sourced the primary care physician of each of the treated subjects to ensure that the effect was not due to better overall health care by a single or several providers. Finally, this cohort is almost entirely Caucasian; therefore, the results may not be generalizable to other ethnic groups.

In summary, these data suggest that oral BPs reduce mortality risk, irrespective of prior fracture history. These benefits remain, even after the adjustment for a large number of frailty factors including low BMD. These findings support and extend the results from the RCT data and other observational studies of hip fracture and elderly subjects. Although the degree of magnitude of mortality reduction may not be as great as that found in the current study, all the data point toward a benefit. These findings have potentially extremely important consequences, which should have a major impact on the way osteoporosis treatment is viewed and used. The apathy that currently surrounds osteoporosis treatment, whereby even in those with fractures, less than 20% of women and less than 10% of men are treated, should no longer be tolerated.

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Address all correspondence and requests for reprints to: J. R. Center, Garvan Institute of Medical Research, 384 Victoria Avenue, Darlinghurst, New South Wales 2010, Australia. E-mail: j.center@garvan.org.au.

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