Effect of alendronate on the age-specific incidence of symptomatic osteoporotic fractures

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The Effect of Alendronate on the Age-Specific Incidence of Symptomatic Osteoporotic Fractures

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MICROABSTRACT

Analyses of data from 3658 postmenopausal women with osteoporosis enrolled in the Fracture Intervention Trial demonstrate that alendronate is effective in reducing the risk of symptomatic osteoporotic fractures across a spectrum of age.

ABSTRACT

Introduction: Most osteoporosis studies examine the relative risk of fracture based upon the entire duration of treatment. Since older patients tend to be at higher risk for osteoporosis-related fractures, the present analysis examined the effect of alendronate treatment on the relative risk of fracture in terms of the age that patients attained during the study.

Methods: We studied 3658 postmenopausal women with osteoporosis aged 55 to 80 years at baseline enrolled in the Fracture Intervention Trial, a large randomized, double-blind, placebo-controlled study. Patients were treated with placebo or with alendronate at a daily dose of 5 mg for 2 years followed by 10 mg for an additional 1 to 2.5 years, and monitored for clinical fractures. Age, rather than study time, was the dynamic variable in our analysis.

Results: The relative risk reductions for hip, clinical spine, and wrist fractures were constant across age groups, without evidence of a decline at older ages. Specifically, alendronate reduced the risk of clinical fracture by 53% at the hip (RR=0.47; 95% CI=0.27 to 0.81; P<0.01), 45% at the spine (RR=0.55; 95% CI=0.37 to 0.83; P<0.01), and 31% at the wrist (RR=0.69; 95% CI=0.50 to 0.98; P=0.038). In addition, alendronate produced a significant risk reduction of 40% (RR=0.60; 95% CI=0.47 to 0.77; P<0.01) for the composite event of clinical hip, spine, and wrist fractures. As a consequence of the constant relative risk model, the absolute risk reduction with alendronate treatment increased with age because of the age-related increase in fracture risk in

the placebo group. The absolute risk reduction for the composite event (hip, spine, and wrist fractures together) for alendronate treatment versus placebo was 65, 80, 111, and 161 women with fractures per 10,000 PYR for the 55 to <65, 65 to <70, 70 to <75, and 75 to 85 year old age groups, respectively.

Conclusions: These data demonstrate that alendronate is effective in reducing the risk of symptomatic osteoporotic fractures across a spectrum of age. The effectiveness is somewhat greater in patients with femoral neck T-score $\leq$ -2.5 than in those with a T-score $\leq$ -2.0.

KEY WORDS

alendronate, osteoporosis, age, fracture, clinical trial

INTRODUCTION

Fractures related to osteoporosis remain a significant cause of morbidity in older people. Several antiresorptive agents have been approved by the Food and Drug Administration for the treatment of osteoporosis in postmenopausal women, including alendronate.[1] In the Fracture Intervention Trial (FIT), alendronate reduced the incidence of morphometric vertebral and clinical fractures in postmenopausal women with a previous vertebral fracture, and in postmenopausal women without a vertebral fracture, but with osteoporosis, defined as a femoral neck bone mineral density T-score of –2.5 or below.[1-4]

In all studies of osteoporosis therapies to date, the key variable of interest was the relative risk reduction (RRR) for fracture over the entire study time (i.e., duration of treatment). However, when there is a wide range of ages among the study patients, modeling the relative risk as a function of study time may not be fully informative, since older patients are at higher absolute risk for fracture than are younger patients. Furthermore, physicians may have more interest in the effect of the treatment on specific age groups, particularly women aged 75 and above, who often have the highest risk. Thus, whether older patients are protected with alendronate to the same extent from fracture occurrence as younger patients is a relevant clinical question. In the present analysis, we used data from FIT[4] to determine if the effect of alendronate was consistent among the different age groups, based upon the ages of individuals in each year of the study.

METHODS

Study Design

The FIT was a randomized, double-blind, placebo-controlled study conducted at 11 centers in the United States with a coordinating center at the University of California, San Francisco.[5] The Vertebral Fracture Arm (FIT I) enrolled women who had morphometric vertebral fractures identified on radiographs at baseline.[2] The Clinical Fracture Arm (FIT II) enrolled women without morphometric vertebral fractures.[3] Both arms of FIT enrolled women with low bone mineral density (BMD) defined as described below. The data analysis plan in the FIT protocol prespecified an analysis of study end points in the two arms combined and in BMD subgroups (using T-score cutoffs of -2.0 and -2.5), with the intent of obtaining more precise estimates of treatment and subgroup effects and to provide greater power to explore associations among study variables. The present analyses were not pre-specified in the data analysis plan.

Study Patients

Study participants were women aged 55 to 80 years who had been postmenopausal for at least 2 years and had a femoral neck BMD of ≤0.68 g/cm^2, measured using Hologic densitometers (see below). At the start of the study, this BMD value was believed to correspond to at least 2 standard deviations (SD) below the mean BMD of normal, young adult Caucasian women (femoral neck T-score of -2.0 or less), based on the manufacturer's reference values. However, subsequent results from the third National Health and Nutritional Examination Survey (NHANES III; a survey of a representative sample of the US civilian non-institutionalized population conducted by the Centers for Disease Control and Prevention) indicated that this femoral neck BMD value corresponded to about 1.6 SD below the mean for young white

women.[6] All women provided written informed consent, and the study protocol was approved by the appropriate institutional review boards. Further details of the FIT design, recruitment procedures, and results have been described in detail.[2-6]

A total of 6459 women were enrolled and randomly assigned to treatment with either alendronate or placebo: 2027 in FIT I and 4432 in FIT II. Among the women in FIT II, 1631 had an entry femoral neck BMD T-score of less than -2.5 (using the revised NHANES reference data). Combining this latter group of women with the 2027 in FIT I yielded 3658 women with osteoporosis who are included in the present analysis. The rationale for studying this group has been presented elsewhere.[4]

Treatment

During the first 2 years of the FIT, the dose of alendronate was 5 mg/day. However, the alendronate dose was increased to 10 mg/day at the second annual visit, while maintaining the double-blind, because another trial suggested that a daily dose of 10 mg had greater effects on bone density and bone markers[7] than did a 5-mg dose. Women in FIT I received alendronate (or matching placebo) for up to 3 years, whereas those in FIT II received alendronate (or placebo) for 4 to 4.5 years. Eighty-two percent of participants in each treatment group had dietary calcium intakes at baseline of less than 1000 mg/day; they were given a daily supplement containing 500 mg elemental calcium (as the carbonate salt) and 250 IU of vitamin D.

The average duration of treatment and follow-up according to the FIT protocol was 2.9 years in FIT I and 4.25 years in FIT II.[2,3]

Assessment of Outcomes

Clinical fractures: All fractures were adjudicated by a blinded Endpoints Adjudication Committee.[2] A clinical fracture was defined as a fracture diagnosed by a community physician and confirmed by written reports of radiographs or other tests.[5] Fracture reporting and confirmation procedures were identical in the Clinical Fracture and Vertebral Fracture arms. Pathologic fractures (e.g. those caused by malignancies) and fractures caused by trauma sufficient to fracture normal bones in most young adults were excluded. Facial and skull fractures were excluded because they are not associated with osteoporosis or low BMD.[8]

Clinical vertebral fractures were defined as those diagnosed by a participant's physician during the study. For each reported clinical vertebral fracture, a copy of the radiograph used by the participant's physician was obtained and compared with the baseline study radiograph by the study radiologist using semiquantitative criteria.[2,9] Only those in which an incident fracture could be confirmed were included in the analyses.

Before study unbinding, subgroups of clinical fractures were classified into the following endpoint categories as defined in the FIT protocol: clinical vertebral fractures, wrist fractures, and hip fractures. Participants could have more than one type of fracture and, therefore, could appear in more than one category.

BMD: BMD was measured at the hip and posterior-anterior spine of all participants using a Hologic QDR-2000 densitometer (Hologic, Inc., Waltham, MA). Measurements were taken at baseline and were repeated annually. Quality control measures have been described previously.[5]

Statistical Analysis

The fracture endpoints were analyzed with respect to attained age during the study. The primary analysis was conducted in the 3658 study patients who were 55 to 80 years of age at

baseline, and were 60 to 85 years old at the close of the study. For ease of presentation only, the data were categorized within the following four age groups: 55 to < 65, 65 to < 70, 70 to < 75, and 75-85 years. The analysis was conducted using age as a continuous variable. For each fracture endpoint, the number of patient-years at risk (PYR) was calculated for each of the age categories. Patients could contribute time at risk to more than one age category. This approach to the analysis of time to event data is described elsewhere.[10,11] For example, if a patient entered the study at age 67 and left at age 72, she would have contributed 3 person years of risk to the 65 to < 70 category and 2 person years of risk to the 70 to < 75 category. We used a stratified Cox proportional hazards model to compute relative hazards and 95% confidence intervals.[12] The analysis was controlled for various baseline risk factors (baseline femoral neck BMD, number of prevalent vertebral fractures, history of non-vertebral fracture and history of falls) and study time. We generated incidence curves for each fracture endpoint using the Cox proportional hazards regression analysis model. Person-year calculations were done using DATAB and the Cox model was fitted in AMFIT.[13] All estimates and confidence intervals were based on the profile likelihood.

We performed a true intent-to-treat analysis[14] in which all events after randomization were analyzed. In FIT, all women continued follow-up, regardless of whether or not they continued on study medication. We were, therefore, able to include all fractures, regardless of whether or not the participant was taking study medication at the time of the fracture. About 15% of women discontinued study drug before the close of the study; however, follow-up continued for about 98% of randomized survivors.

A secondary analysis was conducted in the group of women from FIT I and those from FIT II who had a baseline femoral neck BMD T-score of –2.0 or below. Parallel analyses were conducted using definitions of osteoporosis based on BMD at the total hip and at the lumbar spine to confirm the general findings with respect to femoral neck BMD.

RESULTS

The baseline characteristics of the 3658 women included in the primary analysis are and the 5093 women included in the secondary analysis are both shown in Table 1. The patients randomized to treatment with alendronate and those randomized to the placebo group were similar with respect to baseline age, years since menopause, spine BMD, hip BMD, number of prevalent vertebral fracture, history of falls, and prior clinical fractures.

The number and crude rate of fracture cases per 10,000 PYR within each of the four age groups for the 3658 women is presented in Table 2. The overall clinical fracture rate increased steadily as the ages attained by the patients increased during the study. Compared to placebo, alendronate treatment resulted in fewer clinical fracture cases and a lower fracture rate at the hip, spine, wrist or composite, regardless of patient age. The number of PYR depends on the fracture site being evaluated. For the composite endpoint, the PYRs were 6042 (887, 1538, 1794 and 1823 for age groups 55-65, 65-70, 70-75 and 75-85 respectively) and 6254 (1045, 1488, 1829, 1892 for age groups 55-65, 65-70, 70-75 and 75-85 respectively) for the placebo and alendronate groups, respectively. Patients over age 80 during the study contributed slightly under 8% of the PYR: 468 and 485 in the placebo and alendronate groups, respectively. The number of fractures (composite endpoint) for those over 80 was 22 and 9 in the placebo and alendronate groups, respectively.

The Cox proportional hazards models confirmed and quantified the patterns seen in Table 2. The effect of alendronate (vs placebo) on the risk of hip, spine or wrist fractures did not depend on age: $p=0.43$ for the hip, 0.47 for the spine, 0.36 for the wrist. The same was true for the composite endpoint (hip, wrist or spine), $p = 0.53$. The incidence curves for each fracture type as a function of patient age were generated using Cox proportional hazards models of the

age-specific fracture data (per 10,000 PYR) (Figure 1: A to C). The reductions in risk among alendronate-treated patients were significant relative to the placebo group for each of the individual fracture types analyzed. Alendronate reduced the risk of clinical fracture by 53% at the hip (RR = 0.47; 95% CI = 0.27 to 0.81; P <0.01), 45% at the spine (RR = 0.55; 95% CI = 0.37 to 0.83; P <0.01), and 31% at the wrist (RR = 0.69; 95% CI = 0.50 to 0.98; P = 0.038). In addition, alendronate produced a significant risk reduction of 40% (RR = 0.60; 95% CI = 0.47 to 0.77; P <0.01) for the composite event of clinical hip, spine, and wrist fractures (Figure 1: D). The magnitude of the difference in clinical fracture rate (absolute risk reduction) between the alendronate and placebo treatment groups increased with patient age for each of the three fracture sites (Figure 2). For the hip, the absolute risk reduction (ARR) increased from 11 women with fractures per 10,000 PYR for the 55 to < 65 year old women to 53 women per 10,000 PYR for the women aged 75 to 85 years. The corresponding ARR for the youngest and oldest age groups were 15 women per 10,000 PYR and 75 women per 10,000 PYR for the spine, and 32 women per 10,000 PYR and 44 women per 10,000 PYR for the wrist. For the composite endpoint, the ARR was 65, 80, 111, and 161 women with fractures per 10,000 PYR for the 55 to < 65, 65 to < 70, 70 to < 75, and 75 to 85 year old age groups, respectively. Figure 3 shows the actual number of excess fractures that can be prevented with alendronate therapy, relative to placebo.

When a secondary analysis was performed that included patients with a femoral neck T-score of -2.0 or below or with a vertebral fracture at baseline, 1435 additional women were added to the analysis (Table 1). These additional 1435 patients were slightly younger (mean age 67), and had fewer falls in the year prior to randomization (26%) and fewer (33%) previous fractures. The mean T-score at the femoral neck and lumbar spine was -2.3 and -1.7, respectively. The relative

risk reductions for fractures for those with T < -2.0 or with a vertebral fracture at baseline were also independent of age, p> .40 for all sites. The overall reductions were 39% at the hip (RR = 0.61, CI = 0.38 to 0.98), 49% at the spine (RR = 0.51, CI = 0.34 to 0.75), 18% at the wrist (RR = 0.82, CI = 0.62 to 1.10) and 32% (RR = 0.68, CI = 0.55 to 0.84) at the composite endpoint (hip, wrist, and spine). The patterns for the ARR were similar to those seen in the cohort defined by -2.5 cutpoint (data not shown). For the hip, the ARR ranged from 6 in the lowest age group (55 to 65) to 33 per 10,000 PYR in the oldest age group (75 to 85). The corresponding ARRs for the composite endpoint were 40 and 116 per 10,000 PYR.

DISCUSSION

Previous analyses from the FIT have clearly demonstrated that alendronate is effective in reducing the risk of clinical osteoporotic fractures in postmenopausal women with or without existing vertebral fracture, and reducing the risk of morphometric vertebral fracture in all women with low bone mass ($T < -1.6$ at the femoral neck).[2-4] The unique aspect of the current analysis is the focus on the patient's age attained during the trial as opposed to the age of patient at randomization. A previous subgroup analysis reported that among patients with existing vertebral fracture, the effect of alendronate was not dependent on the age at randomization.[15] In the present analysis, age is a dynamic variable and the analysis can be viewed as demonstrating the effect of age attained during study, while controlling for study time. As a consequence, we have now demonstrated that the protection conferred upon postmenopausal women by alendronate occurs, regardless of the age the patient attained during the trial. Specifically, this is the first analysis to show that alendronate is equally effective in reducing the risk of symptomatic osteoporotic fractures in women between ages 75 and 85 years compared to women under age 65 years. Furthermore, it demonstrates that while the relative risk reduction for alendronate is constant across the age span of women in FIT, the reduction in the number of women who sustain fractures is greatest in the older women because their absolute risk of fracture is the highest.

Our analysis focused on modeling the relative risk as a function of age attained during the trial. This constant relative risk model fits the data very well from a statistical viewpoint. Although we reported the results using four age groups, the overall findings remain unchanged if finer partitions for age were used, or if age was used as a continuous variable (data not shown). A consequence of accepting the findings from a constant relative risk model is that the absolute

risk reduction (the excess risk) becomes dependent on age. The excess risk can be viewed as the number of women with fractures (per 10,000 PYR) that would occur in the placebo group because they were not treated with alendronate. The gradient, or the shape, of the excess risk curve as a function of age was also related to the type of fracture. Clinical spine fractures and hip fractures had a steeper gradient with age than did wrist fractures. The study does not have the power to determine if the differences in the gradients, however, are significant. Thus, we cannot rule out this being an artifact of the data. However, it is interesting that the findings are consistent with results of epidemiological studies.[16]

It is clear from the increase in incidence with age (in this and epidemiologic studies[16]) that the burden of illness for those not being treated is greatest in the elderly. The excess risk for clinical spine or hip fracture among the oldest (ages 75-85) patients not treated with alendronate is more than 7 times higher than among women aged 55-65, whereas the corresponding figure for wrist is only 2- to 3-fold. Since treatment is never fracture specific, it is instructive to focus on the composite event: hip, clinical spine, and wrist fracture. Although the relative risk reduction observed with alendronate was consistent across the groups by attained age, the absolute risk reduction increased across the groups, consistent with the higher rate of fracture in the placebo group. The increase in risk in the placebo group is also dependent on factors such as age, BMD, and fracture status, to mention a few. This finding is of potential importance for health care planners and economists.

It is of clinical utility, for example, to know whether older patients, who are at the highest risk for fracture, are protected to the same degree as the larger group. This question is of particular relevance in light of data from other studies, which suggested that relative risk reductions for alendronate and risedronate did not vary by age group below age 80[17-18,20], but that

risedronate did not appear to reduce the risk of hip fractures in women ages 80 years and older selected primarily on the basis of nonskeletal risk factors.[19] In our present study, which included about 10,000 person years at risk for women over age 80, the fracture-reducing effect of alendronate was constant with age. More importantly, we did not see any evidence of a decline in treatment effect around age 80. In fact, for patients over 80, the raw data suggested reductions of approximately 60% for hip fractures and 63% for the composite endpoint (hip, wrist, and spine).

The consistency of the relative risk reduction with age attained during the follow-up period was independent of the BMD cutpoint used. The lower relative risk reduction for the hip and the wrist in the cohort defined by the presence of a vertebral fracture and/or femoral neck BMD T-score of –2.0 or below are consistent with findings from previous reports.[3] For clinical spine fracture, the RRR was somewhat larger in the -2.0 cohort than in the -2.5 cohort. For clinical spine fractures, the effect of alendronate is independent of age and BMD.

Our study has a number of strengths. The loss to follow-up was very low (<3%). Although approximately 15% of patients discontinued treatment prior to the end of the study, follow-up continued for nearly 98% of surviving participants. In addition, the reporting and confirmation of fractures was overseen by an independent adjudication committee. Despite the large number of person years available for the analysis, there are limitations to the inferences that can be made from this paper. First, this study was limited to patients between the ages of 55 and 85. Second, we did not study patients with femoral neck T-score above -2.0 who did not have a vertebral fracture. Third, almost all of the women included in the study were Caucasian. Hence, further study is required in women of other ethnic groups and men

In summary, the results demonstrate that alendronate is effective in reducing the risk of symptomatic osteoporotic fractures across a spectrum of age. The effectiveness is somewhat

greater in patients with femoral neck BMD T-score $\leq$ -2.5 than in patients with femoral neck BMD T-score $\leq$ -2.0. The use of attained age, as opposed to age at randomization, provides for an accurate assessment of age-specific incidence. Indeed, the burden of illness is highest in the oldest age group. Preventing these fractures may reduce the associated morbidity and mortality.

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Table 1. Baseline Characteristics of Study Patients

	Vertebral Fracture and/or T < = -2.5		Vertebral Fracture and/or T < = -2.0	
	Alendronate n = 1841	Placebo n = 1817	Alendronate n = 2567	Placebo n = 2526
Mean age (years)	69.8 (6.0)	70 (5.9)	69.1 (6.1)	69.3 (6.0)
Mean years since menopause	23.7 (8.3)	23.9 (8.2)	23.1 (8.4)	23.1 (8.4)
Mean femoral neck T-score	-2.7 (0.6)	-2.8 (0.6)	-2.6 (0.5)	-2.6 (0.5)
Mean lumbar spine T-score	-2.3 (1.2)	-2.4 (1.2)	-2.2 (1.2)	-2.2 (1.2)
Number of prevalent vertebral fractures				
0	44.5%	44.7%	60.2%	60.2%
1	39.0%	37.5%	28.0%	27.0%
2	9.3%	9.4%	6.7%	6.8%
3 or more	7.2%	8.4%	5.1%	6.0%
History of falls in year prior to randomization	27.8%	28.4%	28.1%	26.9%
Prior clinical fracture (since age 45)	50.8%	49.9%	46.2%	44.9%

Table 2. Fracture Rates Per 10,000 PYR, and (Number of Cases) by Fracture Type and Age Group

	Hip		Spine*		Wrist		Hip, Wrist, or Spine*	
Age group	ALN	PBO	ALN	PBO	ALN	PBO	ALN	PBO
55 – <65	9(1)	22(2)	19(2)	33(3)	76(8)	101(9)	105(11)	158(14)
65 – <70	26(4)	44(7)	40(6)	64(10)	67(10)	122(19)	112(18)	202(31)
70 – <75	16(3)	70(13)	59(11)	97(18)	97(18)	130(24)	164(30)	284(51)
75 – 85	56(11)	93(18)	87(17)	173(33)	104(20)	141(27)	248(47)	406(74)

Number of cases are in parentheses

*Clinical vertebral fractures

PYR: person-years at risk.

Figure 1A: Hip

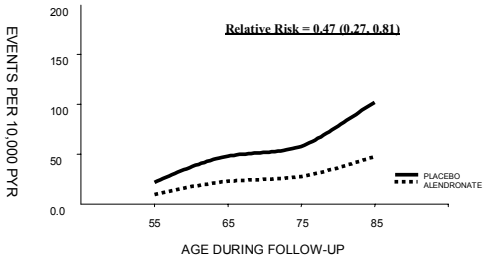


Figure 1B: Spine

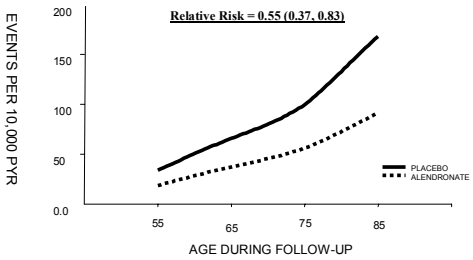


Figure 1C: Wrist

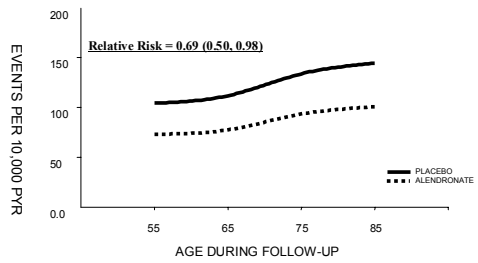


Figure 1D: Composite (Hip, Spine, Wrist)

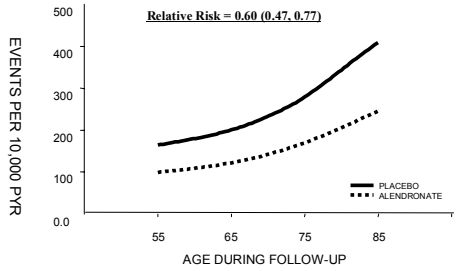


Figure 2

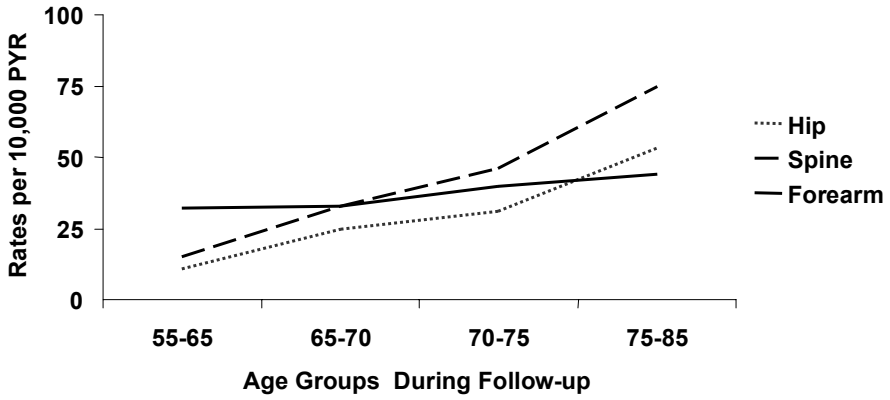

100
75
50
25
0
Rates per 10,000 PYR
55-65
65-70
70-75
75-85
Age Groups During Follow-up
Hip
Spine
Forearm

Figure 3

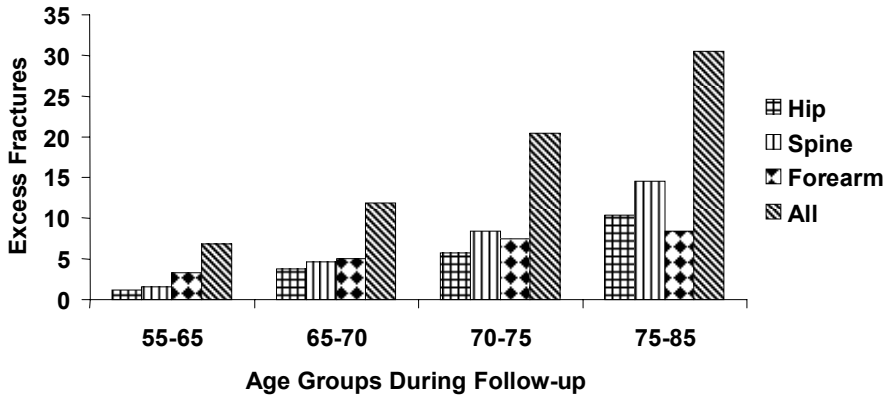

35
30
25
20
15
10
5
0
Excess Fractures
55-65
65-70
70-75
75-85
Age Groups During Follow-up
Hip
Spine
Forearm
All

Figure Legends

Figure 1. Rates of fracture per 10,000 person-years by attained age. Incidence curves were generated using a Cox proportional hazards model of the age-specific fracture data.

A. Hip fracture incidence by attained age.

B. Clinical spine fracture incidence by attained age.

C. Wrist fracture incidence by attained age.

D. Incidence of the composite event (hip, spine, and wrist fractures) by attained age.

Figure 2: Comparison of excess fracture rates in untreated patients. The magnitude of the difference in clinical fracture rate (absolute risk reduction) between the alendronate and placebo treatment groups increases with patient age for each of the three fracture sites.

Figure 3: The number of excess clinical fractures that can be prevented with alendronate therapy, relative to placebo.

Figure 1A: Hip

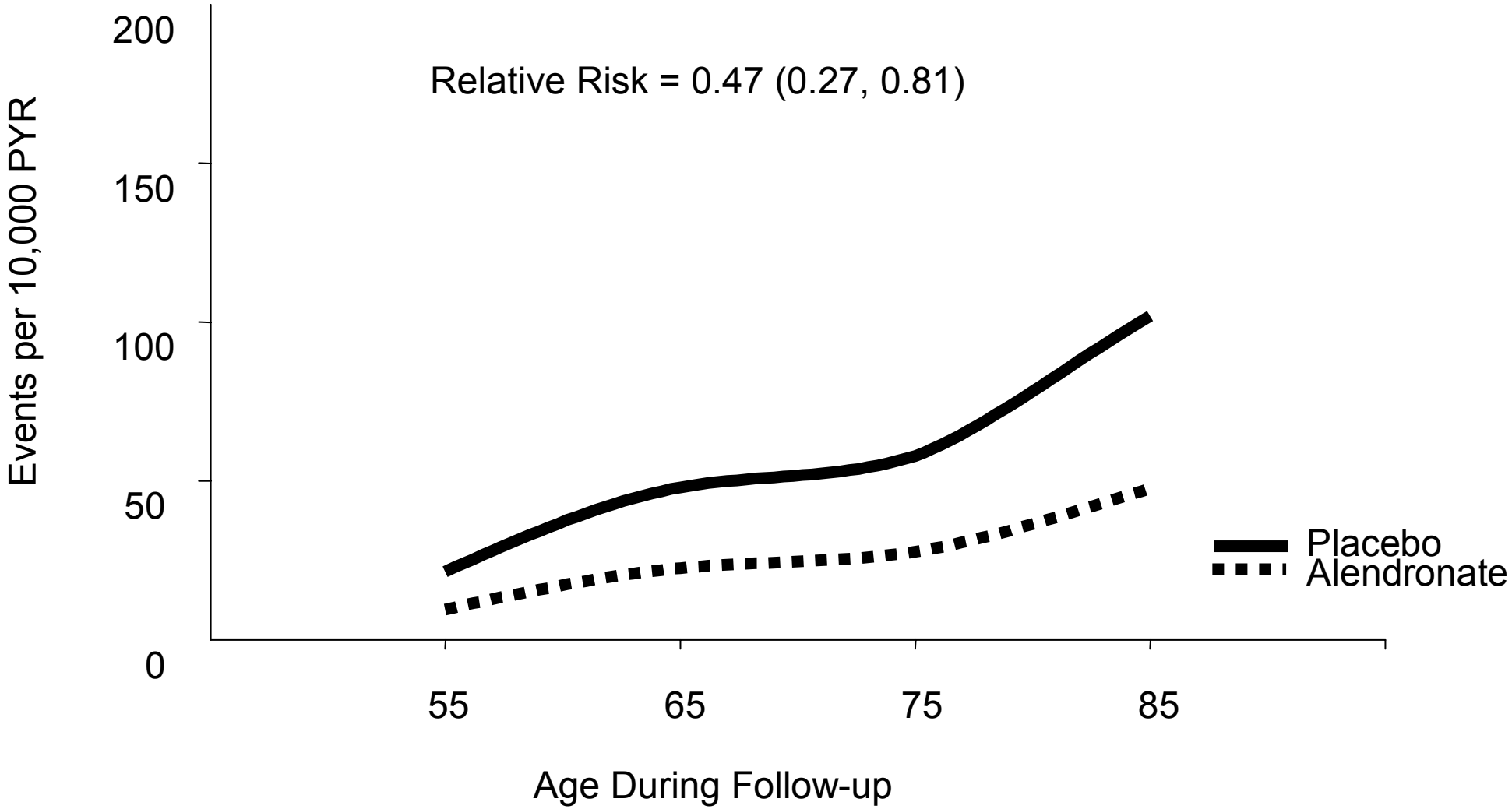


Figure 1B: Spine

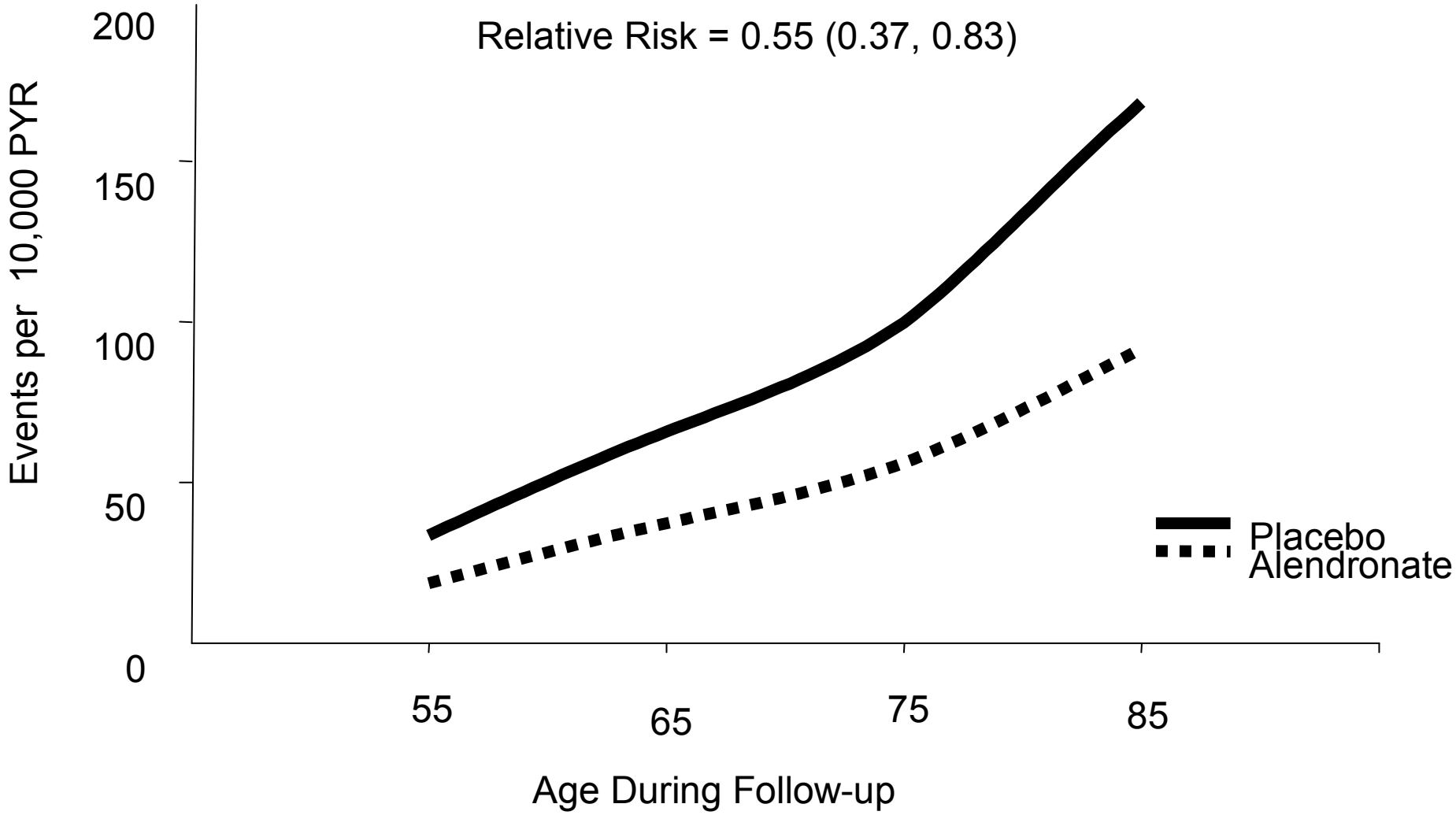


Figure 1C: Wrist

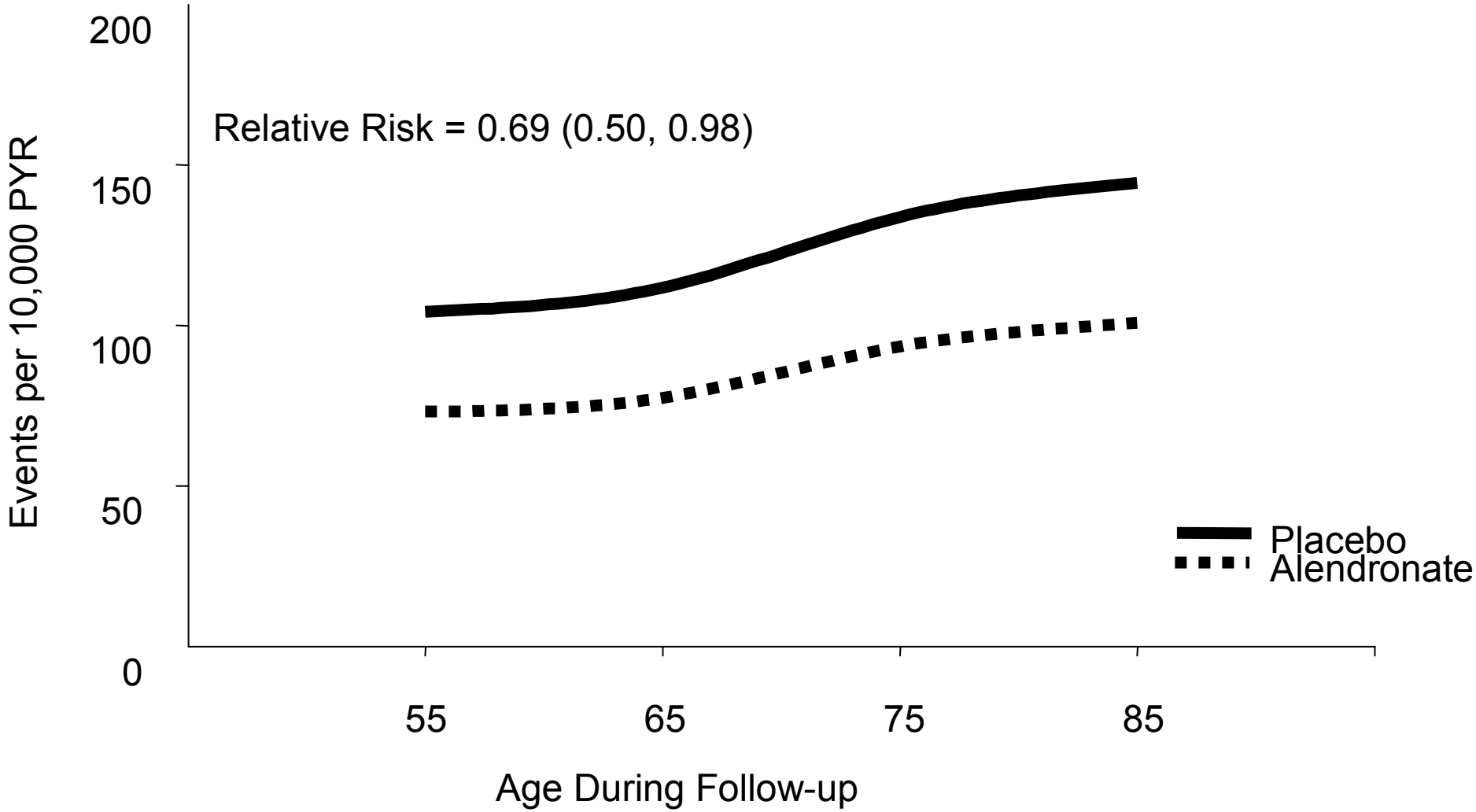


Figure 1D: Composite (Hip, Spine, Wrist)

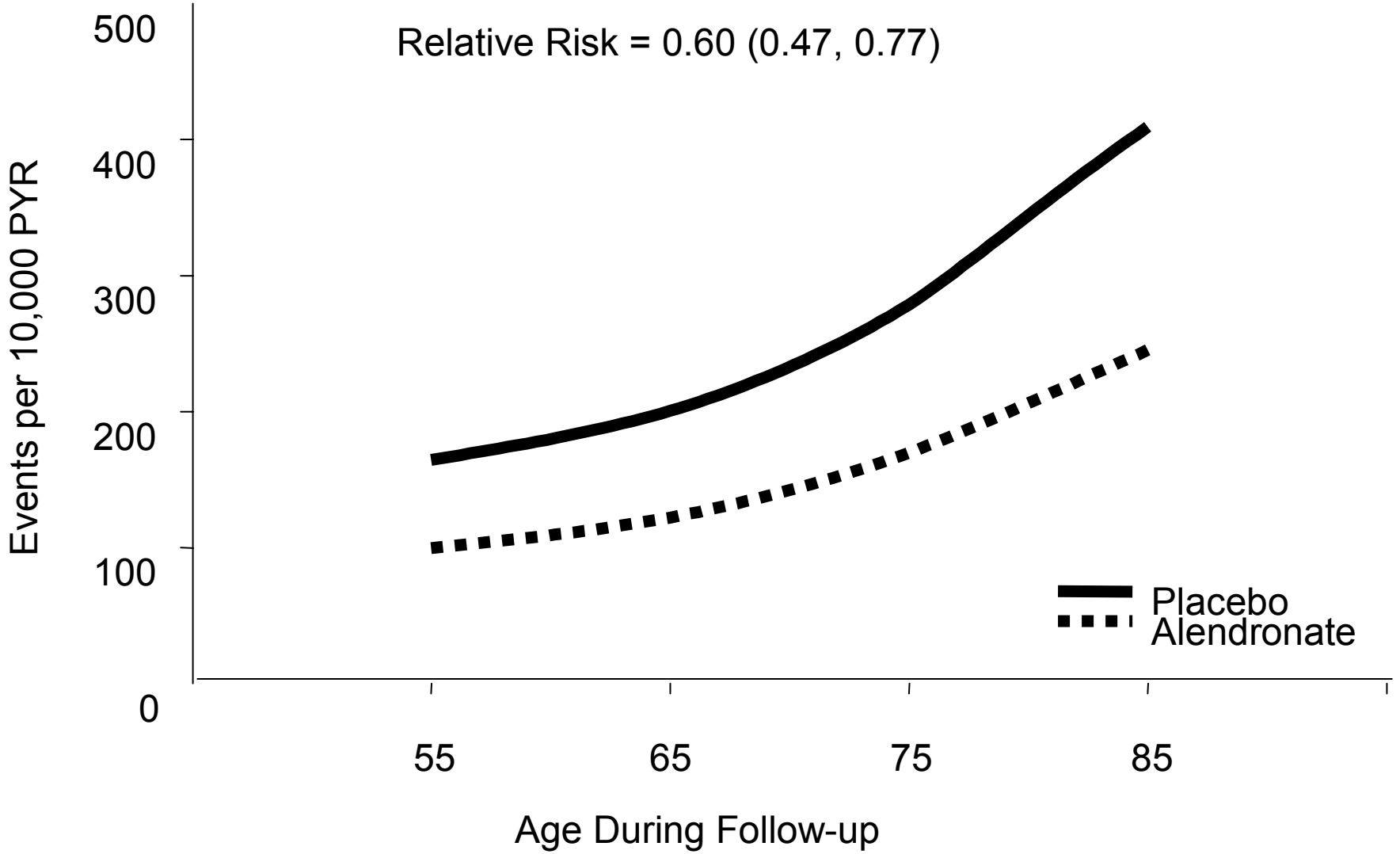


Figure 2

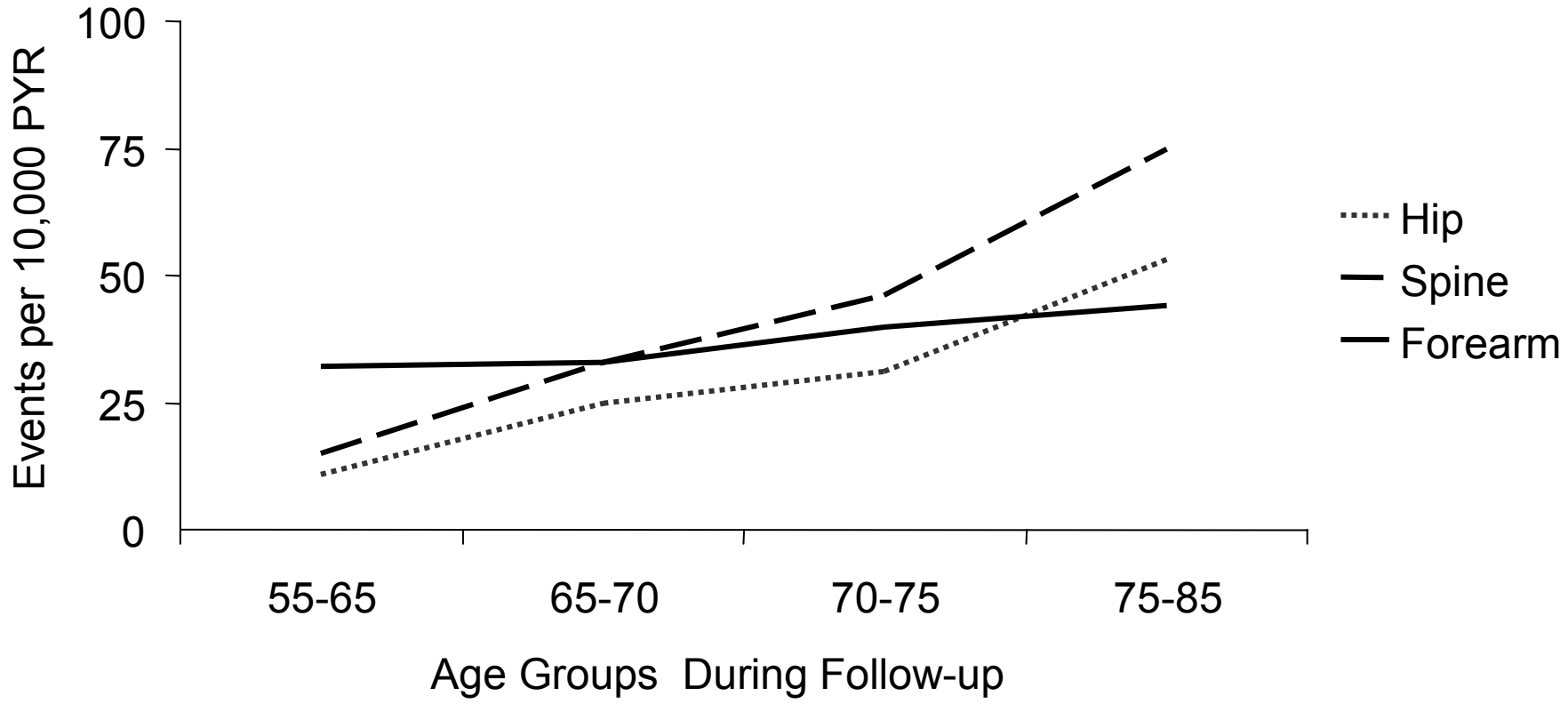
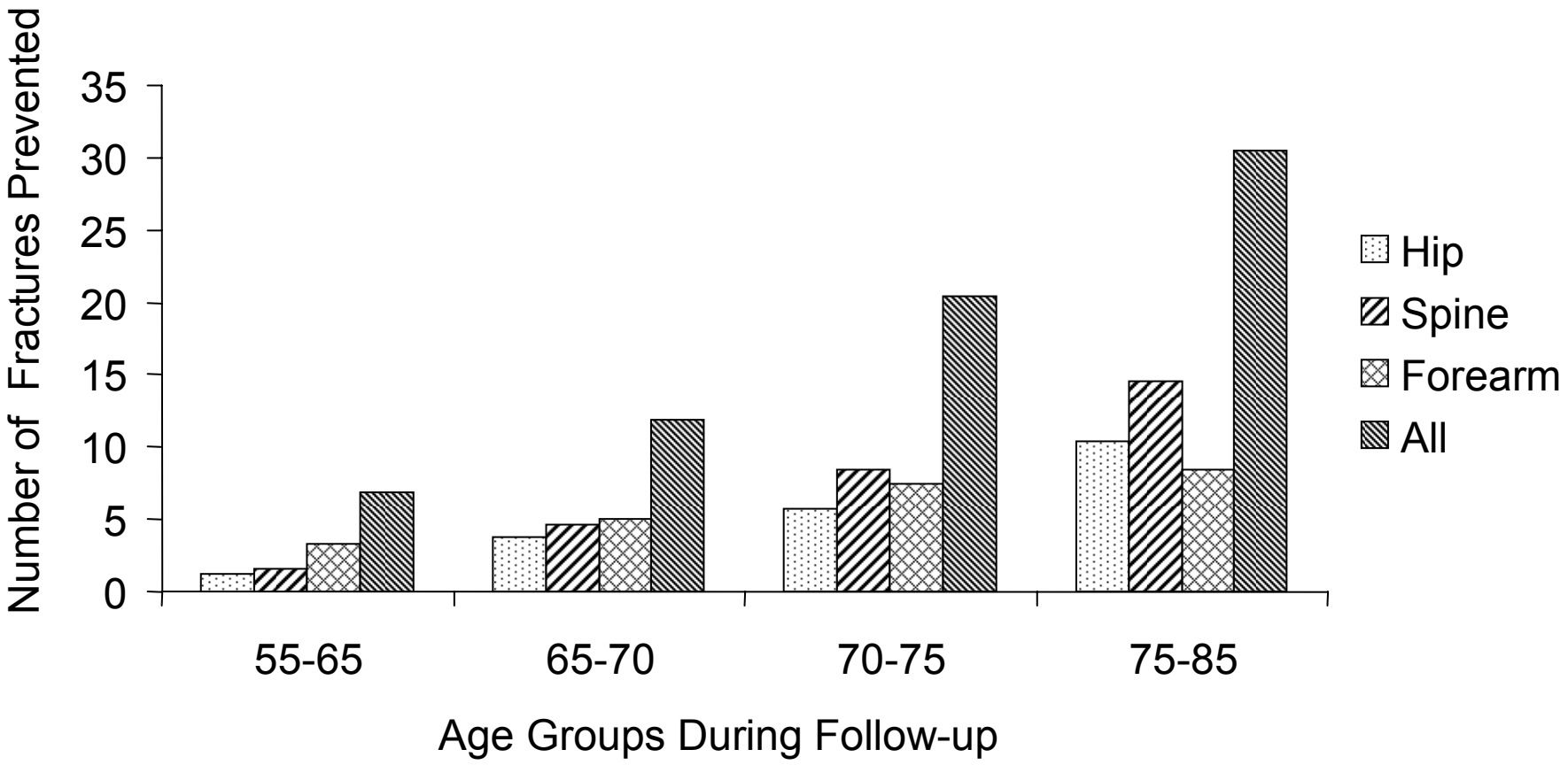

100
75
50
25
0
Events per 10,000 PYR
55-65
65-70
70-75
75-85
Age Groups During Follow-up
Hip
Spine
Forearm

Figure 3


Number of Fractures Prevented
0
5
10
15
20
25
30
35
55-65
65-70
70-75
75-85
Age Groups During Follow-up
Hip
Spine
Forearm
All