

# UCSF

## UC San Francisco Previously Published Works

### Title

Influence of age on the efficacy of pharmacologic treatments on fracture risk reduction and increases in BMD: RCT results from the FNIH-ASBMR-SABRE project.

### Permalink

<https://escholarship.org/uc/item/2bf1k1jv>

### Journal

Journal of Bone and Mineral Research, 39(5)

### Authors

Schini, Marian

Vilaca, Tatiane

Vittinghoff, Eric

et al.

### Publication Date

2024-05-24

### DOI



10.1093/jbmr/zjae040

### Copyright Information

This work is made available under the terms of a Creative Commons Attribution-NonCommercial License, available at <https://creativecommons.org/licenses/by-nc/4.0/>

Peer reviewed

# Influence of age on the efficacy of pharmacologic treatments on fracture risk reduction and increases in BMD: RCT results from the FNIH-ASBMR-SABRE project

Marian Schini<sup>1,\*</sup>, Tatiane Vilaca<sup>1</sup> , Eric Vittinghoff<sup>2</sup>, Li-Yung Lui<sup>3</sup>, Susan K. Ewing<sup>2</sup>, Austin R. Thompson<sup>2</sup>, Douglas C. Bauer<sup>2,4</sup>, Mary L. Bouxsein<sup>5</sup>, Dennis M. Black<sup>2</sup>, Richard Eastell<sup>1</sup> 

<sup>1</sup>Division of Clinical Medicine, School of Medicine and Population Health, University of Sheffield, Sheffield, S10 2TN, United Kingdom

<sup>2</sup>Department of Epidemiology & Biostatistics, University of California, San Francisco, CA 94158, United States

<sup>3</sup>California Pacific Medical Center Research Institute, San Francisco, CA 94158, United States

<sup>4</sup>Department of Medicine, University of California, San Francisco, CA 94158, United States

<sup>5</sup>Department of Orthopedic Surgery, Harvard Medical School, Center for Advanced Orthopedic Studies, Beth Israel Deaconess Medical Center, Boston, MA 02215330, United States

\*Corresponding author: Marian Schini, Metabolic Bone Centre, Northern General Hospital, Herries Road, Sheffield S5 7AU, United Kingdom (m.schini@sheffield.ac.uk).

## Abstract

There is a common belief that antiosteoporosis medications are less effective in older adults. This study used data from randomized controlled trials (RCTs) to determine whether the anti-fracture efficacy of treatments and their effects on BMD differ in people  $\geq 70$  compared to those  $< 70$  yr. We used individual patient data from 23 RCTs of osteoporosis medications collected as part of the FNIH-ASBMR SABRE project. We assessed the following fractures: radiographic vertebral, non-vertebral, hip, all clinical, and all fractures. We used Cox proportional hazard regression to estimate treatment effect for clinical fracture outcomes, logistic regression for the radiographic vertebral fracture outcome, and linear regression to estimate treatment effect on 24-mo change in hip and spine BMD in each age subgroup. The analysis included 123 164 (99% female) participants; 43% being  $\geq 70$  yr. Treatment with anti-osteoporosis drugs significantly and similarly reduced fractures in both subgroups (eg, odds ratio [OR] = 0.47 and 0.51 for vertebral fractures in those below and above 70 yr, interaction  $P = .19$ ; hazard ratio [HR] for all fractures: 0.72 vs 0.70, interaction  $P = .20$ ). Results were similar when limited to bisphosphonate trials with the exception of hip fracture risk reduction which was somewhat greater in those  $< 70$  (HR = 0.44) vs  $\geq 70$  (HR = 0.79) yr (interaction  $P = .02$ ). Allocation to anti-osteoporotic drugs resulted in significantly greater increases in hip and spine BMD at 24 mo in those  $\geq 70$  compared to those  $< 70$  yr. In summary, anti-osteoporotic medications similarly reduced the risk of fractures regardless of age, and the few small differences in fracture risk reduction by age were of uncertain clinical significance.

**Keywords:** age, BMD, SABRE, osteoporosis, treatment, bisphosphonates

## Lay Summary

Medications used for osteoporosis maybe are less effective in older adults. This study used data from clinical trials to determine whether these medications work equally well in reducing the risk of fractures in people  $\geq 70$  compared to those  $< 70$  yr. The analysis included 123 164 participants with data from 23 trials. Treatment with anti-osteoporosis drugs significantly reduced fractures in both groups in a similar way. The BMD increased more in the older group.

## Introduction

Increasing age is a known risk factor for fragility fractures.<sup>1</sup> As a result, a higher proportion of older people are treated for osteoporosis, therefore, understanding whether age influences the treatment benefit is important. Medications currently used include antiresorptive (bisphosphonates [oral and parenteral], selective estrogen receptor modulators [SERMs], denosumab, hormone replacement treatment [HRT]), anabolic (PTH and PTH-Related Protein analogs [teriparatide and abaloparatide]) and the sclerostin inhibiting antibody, romosozumab, that increases bone formation and

decreases resorption. A study evaluating data from the Swedish national health registry showed that osteoporosis treatments work equally well for women above and below age 80.<sup>2</sup> On the contrary, some studies have shown a better effect in older adults.<sup>3</sup> A recent systematic review, network meta-analysis, and meta-regression analysis of 69 randomized clinical trials found that antiresorptive medications are likely to be more effective in reducing the risk of clinical fractures with increasing mean age. The researchers suggested that these results are vulnerable to aggregation bias and study-level confounding and require confirmation using individual patient data (IPD).<sup>4</sup>

Received: December 13, 2023. Revised: February 20, 2024. Accepted: March 15, 2024

© The Author(s) 2024. Published by Oxford University Press on behalf of the American Society for Bone and Mineral Research.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<https://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact [journals.permissions@oup.com](mailto:journals.permissions@oup.com)

This analysis used IPD from a large set of RCTs to address whether the anti-fracture efficacy of antiosteoporotic drugs differs with age. These data were compiled as part of the FNIH-ASBMR-SABRE project, which is using these data to apply for Food and Drug Administration (FDA) qualification of BMD change as a surrogate endpoint for fracture in trials of new anti-osteoporosis medications.<sup>5</sup>

## Materials and methods

### IPD and fracture outcomes

As previously described,<sup>6,7</sup> a systematic review was undertaken to identify eligible studies, from which IPD were collected and standardized across all studies. Our analysis utilized 5 fracture endpoints: radiographic vertebral, non-vertebral, hip, all clinical (combination of non-vertebral and clinical vertebral fractures), and all fractures (combination of non-vertebral, clinical vertebral, and radiographic vertebral fractures). We were able to create standardized definitions of non-vertebral fractures across all studies using IPD. All non-vertebral fracture locations were included with the exception of fractures of the skull, face, fingers, toes, and cervical spine. Pathological fractures and traumatic fractures (ie, trauma sufficient to cause a fracture in a young, normal individual) were excluded when possible. When trauma information was not available, the fractures were included. We excluded studies that had too few or no participants in either the older or younger subgroup.

For radiographic vertebral fractures, the individual study definitions were used based on comparisons of the baseline lateral spine radiographs with one or more of follow-up radiographs. The definitions of an incident vertebral fracture differed across the studies, as some used quantitative morphometry, semiquantitative assessment, or a combination of these criteria. Some studies evaluated radiographic vertebral fractures on more than one occasion; in these cases, the data from the final study evaluation were used.

### BMD data

BMD was measured using various devices across studies (Hologic, GE Lunar, and Norland Corporation). Unstandardized hip BMD values for Lunar and Norland participants were converted to Hologic BMD values using equations provided in Lu et al.,<sup>8</sup> while spine BMD values were converted to Hologic values using equations provided in Hui et al.<sup>9</sup> This created Hologic-standardized BMD values comparable across DXA devices. When available, the LS vertebrae L1–4 were used, otherwise L2–4 were used. The non-Hispanic white female NHANES III database was used to calculate the TH and FN BMD T-scores,<sup>10</sup> and Hologic reference values for young non-Hispanic white females were used to calculate the LS BMD T-score.

### Statistical analysis

Participants were stratified into 2 subgroups: those aged <70 and ≥70 yr. This dichotomous threshold was chosen because it gave a similar number of subjects with incident all-fractures. We also present an analysis with a 75-year-old threshold. Baseline characteristics of the 2 subgroups were compared using *t*-tests for continuous characteristics and chi-square tests for categorical characteristics.

For each age subgroup, we estimated the treatment effect on fracture reduction using data pooled across all trials. All results were adjusted for trial. We used Cox proportional hazard models to estimate the treatment effect in each age subgroup on time to first fracture for non-vertebral, hip, all clinical and all fractures, with results reported as hazard ratios (HR) and 95% confidence intervals (CIs). We used logistic regression models for the incident radiographic vertebral fracture outcome, where exact time to event was unknown, to estimate the treatment effect in each age subgroup, with results reported as odds ratios (ORs) and 95% CIs. All analyses were by intention-to-treat.

To determine if anti-fracture treatment efficacy differed in the younger and older subgroups, we tested for interaction between treatment and age subgroup. The interaction models included indicators for trial, treatment, age subgroup, and the interaction between treatment and age subgroup. We also checked the interaction with continuous age. We first estimated the anti-fracture treatment effect using data from all trials and in secondary analyses, limited to bisphosphonate trials only.

We also analyzed the effect of treatment on 24-mo change in TH, FN, and LS BMD for each age subgroup across all trials. The active-placebo difference in mean absolute change in BMD at 24 mo was estimated using linear regression and presented as mean (95% CI); all results were adjusted for trial. We first estimated the effect using data from all studies, then limited to bisphosphonate trials only. We tested the interaction between treatment assignment and age subgroup to determine if treatment-related BMD increases differed in the younger and older subgroups.

We used SAS software (version 9.4, SAS Institute Inc.) for the analyses and RStudio (2022.07.1) for creating the forest plots.

## Results

The studies included in the fracture analyses are shown in Table 1. The analysis included 23 RCTs (11 of bisphosphonates [5 alendronate, 2 ibandronate of which one was intravenous, 2 risedronate, and 2 zoledronate], 1 of odanacatib, 3 of anabolic medications [1 PTH (1-84), 1 abaloparatide, 1 teriparatide], 1 of denosumab, 1 of romosozumab, 2 of HRT, and 4 of SERMs).

Baseline characteristics by age subgroup are shown in Table 2. The analysis included a total of 123 164 (99% female), with 43% being ≥70 yr. On average, participants ≥70 yr of age had lower BMI, and were more likely to have suffered vertebral and non-vertebral fractures. On average, TH and FN BMD were lower in those ≥70 yr, while their LS BMD was slightly higher.

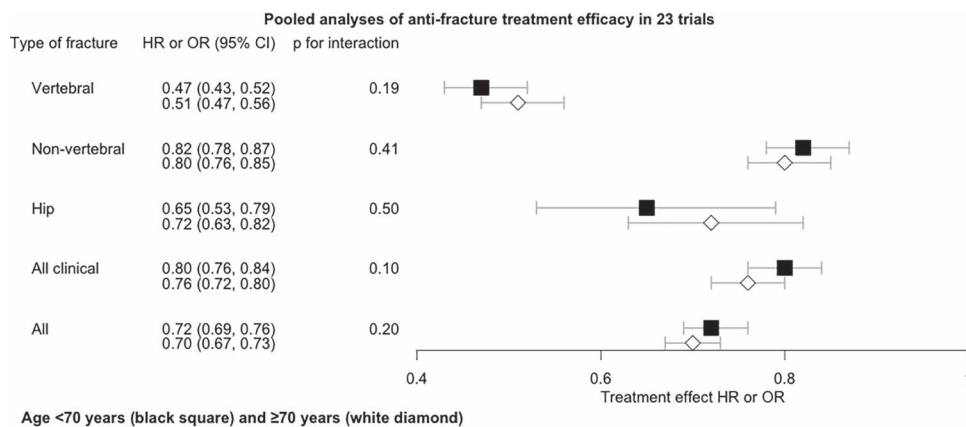
Figure 1 and Appendix Table S1 provide the anti-fracture treatment efficacy within each age subgroup across the combined set of 23 trials. Although a higher proportion of older participants had incident fractures compared to the younger ones, treatment efficacy was similar in the 2 subgroups with no statistically significant interactions of age subgroup with anti-fracture treatment efficacy.

We also analysed age as a continuous variable and did not find any statistically significant interactions with anti-fracture efficacy (interaction *P* values: .16 for vertebral, .64 for non-vertebral, .10 for hip, .29 for all clinical, and .15 for all).

**Table 1.** Description of studies included in the analysis.

Trial	Drug Class	Study Drug	Inclusion criteria (sex and age)	N in Age < 70	N in Age ≥ 70
ALN Phase 3 <sup>16</sup>	Bisphosphonate	Alendronate	PMW 45–80 yr	780	214
FIT I <sup>17</sup>	Bisphosphonate	Alendronate	PMW 55–81 yr	876	1151
FIT II <sup>18</sup>	Bisphosphonate	Alendronate	PMW 55–81 yr	2798	1634
FOSIT <sup>19</sup>	Bisphosphonate	Alendronate	PMW ≤ 85 yr	1546	352
MENs <sup>20</sup>	Bisphosphonate	Alendronate	Men 31–87 yr	160	81
BONE <sup>21</sup>	Bisphosphonate	Ibandronate	PMW 55–80 yr	1522	1407
IBAN IV <sup>22</sup>	Bisphosphonate	Ibandronate (intravenous)	PMW 55– 76 yr	1828	1032
VERT-MN <sup>23</sup>	Bisphosphonate	Risedronate	PMW < 85 yr	341	473
VERT-NA <sup>24</sup>	Bisphosphonate	Risedronate	PMW < 85 yr	929	699
HORIZON PFT <sup>25</sup>	Bisphosphonate	Zoledronate (intravenous)	PMW 65–89 yr	2314	5422
HORIZON RFT <sup>26</sup>	Bisphosphonate	Zoledronate (intravenous)	Men and women ≥50 yr	621	1506
LOFT <sup>27</sup>	Odanacatib	Odanacatib	PMW ≥ 65 yr	5067	11 004
ACTIVE <sup>28</sup>	Anabolic	Abaloparatide	PMW 49–86 yr	940	705
TOP <sup>29</sup>	Anabolic	PTH (1-84)	PMW ≥ 45 yr	1870	662
FPT <sup>30</sup>	Anabolic	Teriparatide	PMW	829	808
FRAME <sup>31</sup>	Romosozumab	Romosozumab (subcutaneous)	PMW 55–90 yr	3279	3901
WHI-E <sup>32</sup>	Hormone therapy	Estrogen	PMW 50–79 yr	8164	2575
WHI-EP <sup>33</sup>	Hormone therapy	Estrogen and progestin	PMW 50–79 yr	13 029	3579
FREEDOM <sup>34</sup>	Denosumab	Denosumab (subcutaneous)	PMW 60–90 yr	2058	5750
GENERATIONS <sup>35</sup>	SERMs	Arzoxifene	PMW 60–85 yr	6268	3086
BZA <sup>36</sup>	SERMs	Bazedoxifene	PMW 55–85 yr	3810	1833
PEARL <sup>37</sup>	SERMs	Lasofosifene	PMW 59–80 yr	5561	2995
MORE <sup>38</sup>	SERMs	Raloxifene	PMW	5079	2626

Abbreviations: ACTIVE, Abaloparatide Comparator Trial in Vertebral Endpoints; ALN, alendronate; BONE, Oral Ibandronate Osteoporosis Vertebral Fracture Trial in North America and Europe; BZA, bazedoxifene; FIT, Fracture Intervention Trial; FPT, Fracture Prevention Trial; FRAME, Fracture Study in Postmenopausal Women with Osteoporosis; FREEDOM, Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 mo; FOSIT, Fosamax International Trial; HIP, Hip Intervention Program Study Group; HORIZON PFT, Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly Pivotal Fracture Trial; HORIZON RFT, Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly Recurrent Fracture Trial; IBAN, ibandronate; LOFT , Long-term Odanacatib Fracture Trial; MORE , Multiple Outcomes of Raloxifene Evaluation; PEARL , Postmenopausal Evaluation and Risk-Reduction with Lasofosifene Study; PMW, postmenopausal women; SERM , selective estrogen receptor modulator; VERT-MN , Vertebral Efficacy with Risedronate Therapy, Multinational Trial; TOP, Treatment of Osteoporosis with Parathyroid Hormone; VERT-NA , Vertebral Efficacy with Risedronate Therapy, North American Trial; WHI-E , Women’s Health Initiative, Estrogen Arm; WHI-EP , Women’s Health Initiative, Estrogen-Progestin Arm

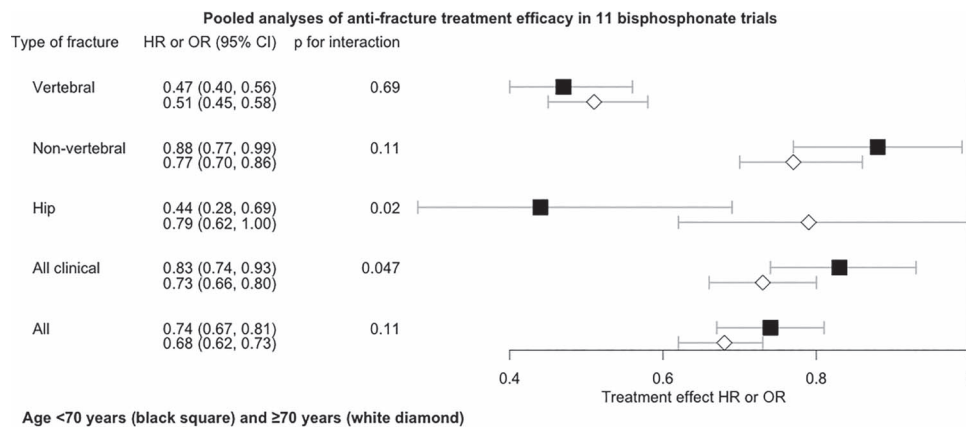


**Figure 1.** Pooled analyses of anti-fracture treatment efficacy by age subgroup across all studies. All results are adjusted for trial. \*2-way interaction: Treatment × age subgroup; HR = hazard ratio; OR = odds ratio.

**Table 2.** Baseline characteristics by age subgroup.

	Age < 70 (N = 69 669)	Age ≥ 70 (N = 53 495)	P-value
Age (yr) (mean ± SD)	62.9 ± 4.9	74.7 ± 4.0	<.0001
Female (%)	99.5	99.3	<.0001
BMI (kg/m <sup>2</sup> ) (mean ± SD)	26.7 ± 5.3 (n = 69 352)	25.9 ± 4.4 (n = 53 271)	<.0001
Prevalent vertebral fracture (%)	36.7 (n = 46 095)	45.7 (n = 45 044)	<.0001
History of non-vertebral fracture (%)	19.0 (n = 33 035)	34.1 (n = 21 235)	<.0001
TH BMD T-score (mean ± SD)	-1.79 ± 0.88 (n = 44 994)	-2.18 ± 0.82 (n = 44 345)	<.0001
FN BMD T-score (mean ± SD)	-2.12 ± 0.74 (n = 49 398)	-2.46 ± 0.65 (n = 46 797)	<.0001
LS BMD T-score (mean ± SD)	-2.64 ± 1.10 (n = 46 418)	-2.60 ± 1.17 (n = 40 008)	<.0001

n = number of participants with data. Abbreviations: TH = total hip; FN = femoral neck; LS = lumbar spine; BMD = bone mineral density



**Figure 2.** Pooled analyses of anti-fracture treatment efficacy by age subgroup across 11 bisphosphonate trials. All results are adjusted for trial. \*2-way interaction: Treatment × age subgroup; HR = hazard ratio; OR = odds ratio.

Figure 2 and Appendix Table S2 provide the anti-fracture treatment efficacy across the combined set of 11 trials evaluating bisphosphonate treatments. The only fracture outcomes that showed a statistically significant interaction with age were the hip fracture and the all clinical fracture outcomes when restricted to bisphosphonate trials. For hip fracture, younger participants had a greater benefit (interaction P value = .02). For all clinical, older participants had a greater benefit (interaction P value = .047).

A total of 17 trials were included in the BMD analysis. We did not include trials that did not have BMD at 24 mo, specifically FOSIT, ACTIVE, TOP, FRAME, and WHI. Across these trials, the ≥70 yr subgroup had significantly greater treatment-related increases in absolute BMD over 24 mo at all 3 BMD sites compared to the <70 yr subgroup (Table 3).

Across the combined set of bisphosphonate trials, the older subgroup had significantly greater treatment-related increase in BMD only at the TH (Table 4).

When we used the 75-year-old threshold, the 2 groups had similar reductions in fracture risk when taking into account all trials. When studying the only-bisphosphonate trials, results were similar. The only significant result was the effect on hip fractures; reductions were more pronounced in the younger group (P = .04) (Appendix Tables S3 and S4).

## Discussion

Our study used IPD from 23 randomized, placebo-controlled trials of anti-osteoporosis therapies to evaluate whether the effect of treatment on fracture risk differed based on age. We assessed the effect on vertebral, non-vertebral, hip, all clinical, and all fractures (combination of non-vertebral, clinical vertebral, and radiographic vertebral fractures). We stratified our groups using the age threshold of 70 yr, as this yielded similar numbers of incident fractures. In summary, the fracture reductions across all medications were not different between the 2 age subgroups suggesting that anti-fracture effects of antiosteoporosis medications are similar for both age subgroups (ie, below and above 70 yr). When we limited the analysis to bisphosphonate trials, we found similar results. The only fracture outcomes that showed a statistically significant interaction with age were the hip fracture and the all clinical fracture outcomes when restricted to bisphosphonate trials. For hip fracture, younger participants had a greater benefit (P value for interaction = .02). For all clinical, older participants had a greater benefit. These 2 findings are likely to be spurious as they are in opposite directions and only found when limited to bisphosphonate trials. Finally, the ≥70 yr subgroup had significantly greater treatment-related absolute increases in BMD over 24 mo compared to the <70 yr subgroup.

**Table 3.** Comparison of Effect of Treatment on Changes in BMD by age subgroup across all trials.

<i>Absolute Difference in BMD Change (Active – Placebo) at 24 mo, mg/cm<sup>2</sup></i>					
	Age < 70		Age ≥ 70		Interaction P-value*
	N	Mean (95% CI)	N	Mean (95% CI)	
TH	30 965	21.8 (21.2, 22.4)	30 449	25.1 (24.5, 25.8)	<.0001
FN	33 732	17.9 (17.3, 18.5)	31 919	19.1 (18.4, 19.7)	.003
LS	29 701	28.8 (28.0, 29.6)	22 691	32.6 (31.6, 33.6)	<.0001

All results are adjusted for trial. \*2-way interaction: treatment × age subgroup; N = number of participants. Abbreviations: TH = total hip; FN = femoral neck; LS = lumbar spine; BMD = bone mineral density

**Table 4.** Comparison of Effect of Treatment on Changes in BMD by age subgroup across 11 bisphosphonate trials.

<i>Absolute Difference in BMD Change (Active – Placebo) at 24 mo, mg/cm<sup>2</sup></i>					
	Age < 70		Age ≥ 70		Interaction P-value*
	N	Mean (95% CI)	N	Mean (95% CI)	
TH	9214	23.5 (22.5, 24.6)	9791	26.0 (24.8, 27.2)	.002
FN	10 092	16.4 (15.2, 17.5)	10 444	17.6 (16.4, 18.8)	.15
LS	7820	35.2 (33.7, 36.8)	5670	34.8 (33.0, 36.7)	.86

All results are adjusted for trial. \*2-way interaction: treatment × age subgroup. Abbreviations: TH = total hip; FN = femoral neck; LS = lumbar spine; BMD = bone mineral density

The HR for fracture is similar for people below and above 70 yr; for example, it is 0.72 and 0.70 for “all fractures.” However, this underestimates the true benefit of treating older women as they have a higher absolute risk of fracture. We can see that the risk of all fractures in those below 70 was 10.9% and for those at least 70 yr, it was 13.9%, so more people in the older group would benefit from treatment (ie, the number needed to treat to prevent one fracture would be lower).

This study addresses a similar issue to a recent meta-analysis that studied the effect of antiosteoporosis medications using data from 69 RCTs based on published results without IPD. They found that the effect of antiresorptive medications on clinical fractures seemed to increase with age. Age did not affect the vertebral, non-vertebral, and hip fractures: these interactions were only found for all clinical fractures.<sup>4</sup> Our study results differed in that we did not find any consistent difference in treatment-related anti-fracture efficacy by age. Our study included IPD, and this allowed us to have a consistent definition of fracture, which would be expected to be more reliable, which could account for the differences. Nonetheless, both studies agree that it is worthwhile treating the older people with antiosteoporosis medications.

Individual study results support our findings. In a post hoc study of alendronate, women were separated into those <75 and ≥ 75 yr of age. No interaction was found between treatment and age.<sup>11</sup> The Horizon study of Zoledronic Acid showed no interaction between age, fracture risk reduction, or BMD increase.<sup>12</sup> Denosumab decreased the risk of vertebral fractures equally in women younger and older than 75 yr.<sup>13</sup> Lastly, age does not affect the efficacy of teriparatide in these subgroups.<sup>14</sup>

The fact that individuals >70 yr of age had higher BMD increases, yet the fracture reduction for all treatments was similar between groups was surprising. Other factors might be affecting the anti-fracture effectiveness in this population. For example, the strength of the relationship between BMD and fracture risk decreases with age in men and women.<sup>15</sup> Moreover, the incidence of falls increases markedly with increased age and might explain why a higher BMD did not lead to greater fracture reductions in the older age group. Lastly, another explanation for the higher BMD increases in older people could be the higher baseline bone turnover, but we do not have enough data to examine this.

We did not include the percentage change in BMD as we saw lower baseline hip BMD in the older group and thus the analysis of percent BMD change would be biased since the baseline denominators vary by subgroup.

There are several strengths of our study. It is a large, comprehensive study that used IPD from all major osteoporosis trials to create a large database including many participants. Moreover, a variety of medications were evaluated. We also harmonized fracture definitions across the trials.

A few things should be considered as limitations when interpreting our results. We chose the 70-year age cut-off because it gave similar numbers of all incident fractures. We also analysed age as a continuous variable and did not find any evidence of interaction with anti-fracture efficacy. We found similar results when we did an analysis using a 75-year threshold. We could not use a higher threshold, that is, 80 yr, because the data mainly come from 3 studies, that is, HIP, clodronate, and LOFT and thus would be biased. Some medications only have one placebo-controlled trial, for



example, denosumab, odanacatib, teriparatide; results can be due to chance finding. Most of the studies included only women so results might be different in men. Lastly, there were other significant differences between our groups, that is, BMI and BMD which could have affected the outcome, but we did not explore those interactions.

In summary, these analyses demonstrate that antiosteoporotic medications, including bisphosphonates, reduce the risk of fractures similarly among those above and below 70 yr of age, and therefore, strongly support treatment in those over age 70. These are important findings with potential impact in patient treatment since it goes against a common misconception that medications are less effective in older people.

## Author contributions

Marian Schini (Conceptualization, Project administration, Software, Visualization, Writing—original draft, Writing—review & editing), Tatiane Vilaca (Project administration, Writing—original draft, Writing—review & editing), Eric Vittinghoff (Formal analysis, Methodology, Software, Writing—review & editing), Li-Yung Lui (Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Writing—review & editing), Susan K. Ewing (Data curation, Formal analysis, Investigation, Methodology, Software, Writing—review & editing), Austin Thompson (Project administration, Writing—review & editing), Douglas C. Bauer (Conceptualization, Funding acquisition, Supervision, Writing—original draft, Writing—review & editing), Mary L. Bouxsein (Conceptualization, Funding acquisition, Supervision, Writing—review & editing), Dennis M. Black (Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing—review & editing), and Richard Eastell (Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Writing—original draft, Writing—review & editing)

## Supplementary material

Supplementary material is available at *Journal of Bone and Mineral Research* online.

## Funding

FDA grant # 1U01FD007772-01.

Grant from the American Society for Bone Mineral Research.

## Conflicts of interest

M.S. received consultancy from Kyowa Kirin International.

T.V. received consultancy funding from Pharmacosmos.

E.V. None.

L.L. None.

S.K.E. None.

A.T. None.

D.C.B. None.

M.L.B. Advisory Board/Consulting: Angitia, Beryl Therapeutics. Lecture honoraria: Alexion.

D.M.B. Denosumab membership for Eli Lilly.

R.E. receives consultancy funding from Immunodiagnostic Systems, Sandoz, Samsung, CL Bio, CureTeQ, Biocon, Takeda, UCB, meeting presentations for Pharmacosmos, Alexion, UCB and Amgen, and grant funding from Alexion and Osteolabs.

## Data sharing

All study data were acquired by requesting IPD from study sponsors. An overarching data use agreement was created between all parties and individual data use agreements were created between individual study sponsors, FNIH, and University of California, San Francisco (UCSF). Per the data sharing agreements that we have with each sponsor, the data can be used for surrogate marker analyses, including any surrogate qualification processes with regulatory authorities. However, other uses of the data are restricted by this agreement, and UCSF is not allowed to share the data.

## References

1. Kanis JA, Johnell O, Oden A, Johansson H, McCloskey E. FRAX and the assessment of fracture probability in men and women from the UK. *Osteoporos Int.* 2008;19(4):385–397. <https://doi.org/10.1007/s00198-007-0543-5>
2. Ström O, Lauppe R, Ljunggren Ö, et al. Real-world effectiveness of osteoporosis treatment in the oldest old. *Osteoporos Int.* 2020;31(8):1525–1533. <https://doi.org/10.1007/s00198-020-05380-6>
3. Vandembroucke A-M, Luyten F, Flamaing J, Gielen E. Pharmacological treatment of osteoporosis in the oldest old. *Clin Interv Aging.* 2017;12:1065–1077. <https://doi.org/10.2147/cia.s131023>
4. Händel MN, Cardoso I, Von Bülow C, et al. Fracture risk reduction and safety by osteoporosis treatment compared with placebo or active comparator in postmenopausal women: systematic review, network meta-analysis, and meta-regression analysis of randomised clinical trials. *BMJ.* 2023;381:e068033. <https://doi.org/10.1136/bmj-2021-068033>
5. Black DM, Bauer DC, Vittinghoff E, et al. Treatment-related changes in bone mineral density as a surrogate biomarker for fracture risk reduction: meta-regression analyses of individual patient data from multiple randomised controlled trials. *Lancet Diabetes Endocrinol.* 2020;8(8):672–682. [https://doi.org/10.1016/S2213-8587\(20\)30159-5](https://doi.org/10.1016/S2213-8587(20)30159-5)
6. Bouxsein ML, Eastell R, Lui L-Y, et al. Change in bone density and reduction in fracture risk: a meta-regression of published trials. *J Bone Miner Res.* 2019;34(4):632–642. <https://doi.org/10.1002/jbmr.3641>
7. Bauer DC, Black DM, Bouxsein ML, et al. Treatment-related changes in bone turnover and fracture risk reduction in clinical trials of anti-resorptive drugs: a meta-regression. *J Bone Miner Res.* 2018;33(4):634–642. <https://doi.org/10.1002/jbmr.3355>
8. Lu Y, Fuerst T, Hui S, Genant HK. Standardization of bone mineral density at femoral neck, trochanter and Ward's triangle. *Osteoporos Int.* 2001;12(6):438–444. <https://doi.org/10.1007/s001980170087>
9. Hui SL, Gao S, Zhou XH, et al. Universal standardization of bone density measurements: a method with optimal properties for calibration among several instruments. *J Bone Miner Res.* 1997;12(9):1463–1470. <https://doi.org/10.1359/jbmr.1997.12.9.1463>
10. Looker AC, Wahner HW, Dunn WL, et al. Updated data on proximal femur bone mineral levels of US adults. *Osteoporos Int.* 1998;8(5):468–490. <https://doi.org/10.1007/s001980050093>
11. Ensrud KE. Treatment with alendronate prevents fractures in women at highest risk. *Arch Intern Med.* 1997;157(22):2617. <https://doi.org/10.1001/archinte.1997.00440430099012>
12. Eastell R, Black DM, Boonen S, et al. Effect of once-yearly zoledronic acid five milligrams on fracture risk and change in femoral

- neck bone mineral density. *J Clin Endocrinol Metab.* 2009;94(9):3215–3225. <https://doi.org/10.1210/jc.2008-2765>
13. Mcclung MR, Boonen S, Törring O, et al. Effect of denosumab treatment on the risk of fractures in subgroups of women with postmenopausal osteoporosis. *J Bone Miner Res.* 2012;27(1):211–218. <https://doi.org/10.1002/jbmr.536>
  14. Boonen S, Marin F, Mellstrom D, et al. Safety and efficacy of teriparatide in elderly women with established osteoporosis: bone anabolic therapy from a geriatric perspective. *J Am Geriatr Soc.* 2006;54(5):782–789. <https://doi.org/10.1111/j.1532-5415.2006.00695.x>
  15. De Laet CE, van Hout BA, Burger H, Hofman A, Pols HA. Bone density and risk of hip fracture in men and women: cross sectional analysis. *BMJ.* 1997;315(7102):221–225. <https://doi.org/10.1136/bmj.315.7102.221>
  16. Liberman UA, Weiss SR, Bröll J, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. *N Engl J Med.* 1995;333(22):1437–1444. <https://doi.org/10.1056/nejm199511303332201>
  17. Black DM, Cummings SR, Karpf DB, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. *Lancet.* 1996;348(9041):1535–1541. [https://doi.org/10.1016/s0140-6736\(96\)07088-2](https://doi.org/10.1016/s0140-6736(96)07088-2)
  18. Cummings SR, Black DM, Thompson DE, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures results from the fracture intervention trial. *JAMA.* 1998;280(24):2077–2082. <https://doi.org/10.1001/jama.280.24.2077>
  19. Pols HAP, Felsenberg D, Hanley DA, et al. Multinational, placebo-controlled, randomized trial of the effects of alendronate on bone density and fracture risk in postmenopausal women with low bone mass: results of the FOSIT study. *Osteoporos Int.* 1999;9(5):461–468. <https://doi.org/10.1007/pl00004171>
  20. Orwoll E, Ettinger M, Weiss S, et al. Alendronate for the treatment of osteoporosis in men. *N Engl J Med.* 2000;343(9):604–610. <https://doi.org/10.1056/nejm200008313430902>
  21. Chesnut CH, Skag A, Christiansen C, et al. Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. *J Bone Miner Res.* 2004;19(8):1241–1249. <https://doi.org/10.1359/jbmr.040325>
  22. Recker R, Stakkestad JA, Chesnut CH, et al. Insufficiently dosed intravenous ibandronate injections are associated with suboptimal antifracture efficacy in postmenopausal osteoporosis. *Bone.* 2004;34(5):890–899. <https://doi.org/10.1016/j.bone.2004.01.008>
  23. Reginster J-Y, Minne HW, Sorensen OH, et al. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. *Osteoporos Int.* 2000;11(1):83–91. <https://doi.org/10.1007/s001980050010>
  24. Harris ST, Watts NB, Genant HK, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. *JAMA.* 1999;282(14):1344–1352. <https://doi.org/10.1001/jama.282.14.1344>
  25. Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med.* 2007;356(18):1809–1822. <https://doi.org/10.1056/NEJMoa067312>
  26. Lyles KW, Colón-Emeric CS, Magaziner JS, et al. Zoledronic acid and clinical fractures and mortality after hip fracture. *N Engl J Med.* 2007;357(18):1799–1809. <https://doi.org/10.1056/NEJMoa074941>
  27. McClung MR, O'Donoghue ML, Papapoulos SE, et al. Odanacatib for the treatment of postmenopausal osteoporosis: results of the LOFT multicentre, randomised, double-blind, placebo-controlled trial and LOFT extension study. *Lancet Diabetes Endocrinol.* 2019;7(12):899–911. [https://doi.org/10.1016/S2213-8587\(19\)30346-8](https://doi.org/10.1016/S2213-8587(19)30346-8)
  28. Miller PD, Hattersley G, Riis BJ, et al. Effect of abaloparatide vs placebo on new vertebral fractures in postmenopausal women with osteoporosis. *JAMA.* 2016;316(7):722–733. <https://doi.org/10.1001/jama.2016.11136>
  29. Greenspan SL, Bone HG, Ettinger MP, et al. Effect of recombinant human parathyroid hormone (1-84) on vertebral fracture and bone mineral density in postmenopausal women with osteoporosis: a randomized trial. *Ann Intern Med.* 2007;146(5):326–339. Not in File. <https://doi.org/10.7326/0003-4819-146-5-200703060-00005>
  30. Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med.* 2001;344(19):1434–1441. <https://doi.org/10.1056/nejm200105103441904>
  31. Cosman F, Crittenden DB, Adachi JD, et al. Romosozumab treatment in postmenopausal women with osteoporosis. *N Engl J Med.* 2016;375(16):1532–1543. <https://doi.org/10.1056/NEJMoa1607948>
  32. Jackson RD, Wactawski-Wende J, Lacroix AZ, et al. Effects of conjugated equine estrogen on risk of fractures and BMD in postmenopausal women with hysterectomy: results from the Women's Health Initiative Randomized Trial. *J Bone Miner Res.* 2006;21(6):817–828. <https://doi.org/10.1359/jbmr.060312>
  33. Cauley JA, Robbins J, Chen Z, et al. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. *JAMA.* 2003;290(13):1729–1738. <https://doi.org/10.1001/jama.290.13.1729>
  34. Cummings SR, Martin JS, Mcclung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med.* 2009;361(8):756–765. <https://doi.org/10.1056/nejmoa0809493>
  35. Cummings SR, Mcclung M, Reginster J-Y, et al. Arzoxifene for prevention of fractures and invasive breast cancer in postmenopausal women. *J Bone Miner Res.* 2011;26(2):397–404. <https://doi.org/10.1002/jbmr.191>
  36. Silverman SL, Christiansen C, Genant HK, et al. Efficacy of bazedoxifene in reducing new vertebral fracture risk in postmenopausal women with osteoporosis: results from a 3-year, randomized, placebo-, and active-controlled clinical trial. *J Bone Miner Res.* 2008;23(12):1923–1934. Not in File. <https://doi.org/10.1359/jbmr.080710>
  37. Cummings SR, Ensrud K, Delmas PD, et al. Lasofoxifene in postmenopausal women with osteoporosis. *N Engl J Med.* 2010;362(8):686–696. <https://doi.org/10.1056/nejmoa0808692>
  38. Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. *JAMA.* 1999;282(7):637–645. <https://doi.org/10.1001/jama.282.7.637>