Health and Spending Consequences of Bisphosphonate Treatment for Prevention of Osteoporosis-Related Hip Fracture: A Markov Model Approach

Final Report

Prepared By:

Chaoling Feng, PhD
Lane Koenig, PhD
Fang He, PhD
Elizabeth Hamlett, BS
KNG Health Consulting, LLC

Prepared For:

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KNG HEALTH CONSULTING LLC

Contents

Abstract

Purpose/Introduction: Osteoporosis-related hip fractures are a major source of avoidable disability and costs. However, treatment with bisphosphonates, an effective therapy, is low. This study assesses the health and spending consequences of treatment with injectable and oral bisphosphonates by risk of hip fracture.

Methods: We ran two Markov models to assess the effects of bisphosphonate treatment on hip fractures, long-term-care (LTC) facility admissions, life years, and medical and custodial care spending for females aged 65 and 75 across three osteoporotic hip fracture risk levels. Medical spending was limited to spending to treat hip fractures and did not include drug or drug-related spending. Assumptions were developed using 2011-2013 Medicare claims, a mixed-effect meta-analysis of prior clinical studies, and literature review. We assumed patients were treated with injectable bisphosphonates if oral use was contra-indicated.

Results: For females age 75 with a high risk of osteoporotic hip fracture, bisphosphonate treatment would result in 4,965 fewer hip fractures per 100,000 people; and 2,982 avoided LTC admissions per 100,000 people. Over a 75 year old woman's lifetime, bisphosphonate treatment decreases expected medical services spending ($US 2012) for hip fracture between $640 (mild risk) and $2,006 (high risk) ($p<.05$) and LTC spending by $1,785 (mild risk) and $5,816 (high risk) ($p < .05$).

Conclusions: Despite the value of bisphosphonates to patients, their utilization remains low due, in part, to lack of patient education and insurance restrictions on injectable bisphosphonates. Increased utilization of bisphosphonate would reduce fractures and generate significant offsets to spending on bisphosphonates.

I. Introduction

Osteoporosis is one of the most prevalent musculoskeletal conditions in the United States. In 2012, 6.5 million (18.3%) Medicare beneficiaries were diagnosed with osteoporosis, 83.4% of whom were women (Appendix E). Osteoporosis is defined by a bone mineral density (BMD) of at least 2.5 standard deviations (T-score) below the mean BMD of the reference population[1], and is characterized by weakened bone strength and increased risk of hip, wrist, vertebrae and other fractures.[2] Every year, roughly two million fractures in the U.S. are attributable to osteoporosis, with hip fractures accounting for a significant share of the cost burden of the condition[3]. Osteoporosis-related hip fractures result in increased mortality and admissions to long-term care facilities due to post-surgical disability.[4]

For individuals with clinically defined osteoporosis, the National Osteoporosis Foundation recommends vitamin D, calcium, bisphosphonates and other FDA-approved pharmaceutical treatments.[5] Bisphosphonates, which can be taken orally or through an annual injection, have been shown to reduce the risks of hip fracture by as much as 50% compared to placebo or no treatment.[6, 7] Several studies have reported on the value of bisphosphonate treatment and its impact on the user's quality of life.[8-10]

Our work adds to the existing literature on the effects of bisphosphonates by incorporating the effects of oral and injectable bisphosphonates, generating estimates of LTC utilization, and stratifying our analysis by the risk of osteoporosis-related hip fractures. We hypothesized that bisphosphonate treatment would decrease spending for medical services, and custodial care by reducing the incidence of osteoporotic hip fracture fractures, as compared to usual care (adequate vitamin D and calcium). We used Markov microsimulation models to simulate the effects of bisphosphonate and test our hypothesis.

II. Methods

Model Structure and Parameters

We constructed a Markov model to understand the impact of bisphosphonates from the patient's perspective. We contrasted bisphosphonate treatment with usual care (adequate calcium and vitamin D intake) with only usual care for women of varying osteoporotic hip fracture risks. As mentioned above, osteoporosis is defined by a T-score of -2.5 or lower - the lower the T-score, the higher the relative risk of fracture.[11] Based on that principle, we generated results for three osteoporotic hip fracture risk levels based on T-scores: (1) mild risk (T-score of -2.5); (2) moderate risk (T-score of -3.25); and (3) high risk (T-score of -4.0). Research has also shown that fracture risk can be more accurately predicted by using both t-score and age[12]. As a result, we assessed all three risk levels for women aged 65 and 75.

In the model, we evaluated two bisphosphonate treatments: (1) alendronate, an oral bisphosphonate, and usual care (adequate vitamin D and calcium); and (2) zoledronic acid, an injectable bisphosphonate, and usual care (adequate vitamin D and calcium). Alendronate and zoledronic acid were both used in our model because patients may develop drug resistance or have comorbidities that may undermine the efficacy of one of the drugs. In this regard, we followed a large Medicare Part D plan's coverage policy[13],

and assumed patients were treated with zoledronic acid if they had a history of esophageal stricture, achalasia, or other severe esophageal dysmotility; or if they had evidence of failed use or intolerance to oral bisphosphate treatment (See Appendix E).

Consistent with clinical guidelines, we assumed that a patient who chooses to take bisphosphonate would take the treatment for three years. After completion of treatment, the drug's efficacy would linearly discount toward no effect over a five year period ("offset period").[14] We also assumed the patient was community-dwelling when entering the model. During the treatment, offset, and post-offset periods, the patient could stay asymptomatic, have a hip fracture, survive hip fracture surgical repair, or expire. Contingent upon their recovery after surgical hip repair, the patient may be discharged to a long-term care facility or discharged home. Finally, if the patient was initially discharged to the community, the patient may remain in the community or be transferred to a long-term care facility for fracture or other aging-related causes. Our model included seven health states for the bisphosphonate treatment arm: (1) bisphosphonate treatment state; (2) treatment offset state; (3) asymptomatic (i.e., no hip fracture) in post-offset period; (4) hip fracture and surgical repair; (5) post-surgical repair community residency; (6) post-surgical repair long-term care residency; and (7) death (Fig. 1). For the non-treatment arm, our model included five health states: (1) asymptomatic; (2) hip fracture and surgical repair; (3) post-surgical repair community residency; (4) post-surgical repair long-term care residency; and (5) death (Fig. 2).

Figure 1. Model Diagram: Bisphosphonate Treatment Pathway and Health State Transition

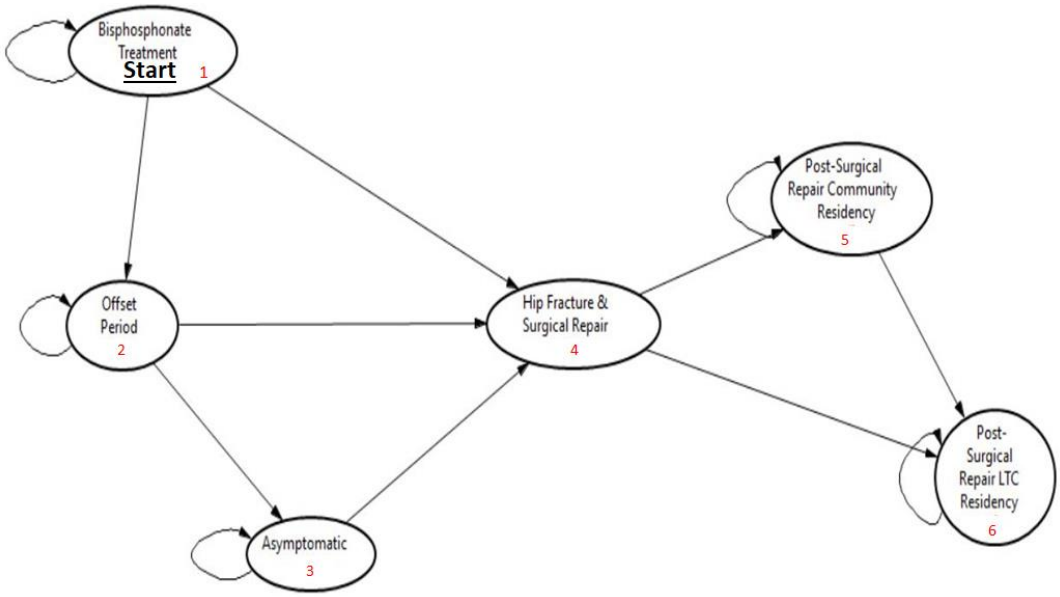
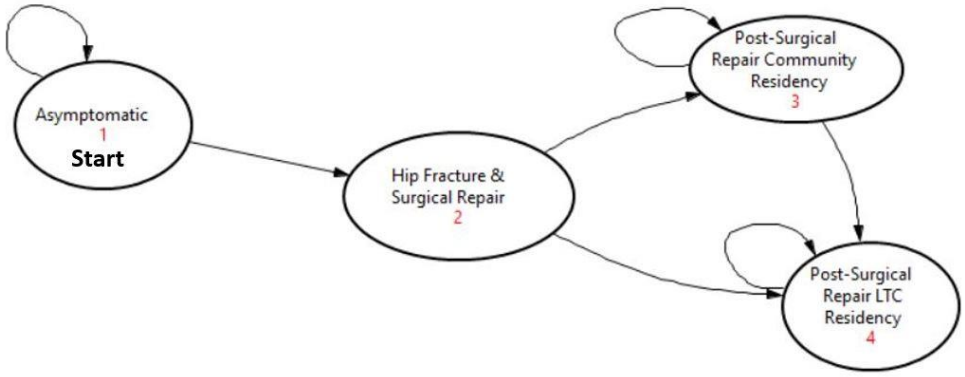


Figure 2. Model Diagram: Health State Transition for No Treatment



The patient enters the model in the treatment period. During the subsequent cycles, the patient could transit from any from current state to another state, as far as there is a transition arc between the two.

We report on the incidence and timing of hip fractures, long-term care admissions, hospitalizations and long-term care utilization and associated costs to payers, as well as life-years accumulated over the patient's lifetime. Our estimates of costs are always from the payer perspective and do not include spending for bisphosphonates or other drugs. We used a one-year cycle length, and the model simulation ended when the patient turned 99 years old or expired. Costs were discounted at a 3% annual rate. We implemented the model in TreeAge Pro 2016.[15]

Treatment Efficacy: Relative Risk of Hip Fracture

We assumed that an average American woman with osteoporosis was ambulatory, had no secondary osteoporosis diagnosis, did not have rheumatoid arthritis, did not smoke, had less than 3 drinks per day, and had no prior hip fracture. We applied this information to the World Health Organization's Fracture Risk Assessment (FRAX) tool to obtain the baseline risk of an osteoporotic hip fracture (See Appendix A). We also assumed that the patient was female, age 65 or 75, and of average American height and weight (65-year-old female: 63.6 inches, 170.5 lbs.; 75-year-old female: 62.6 inches, 164.9 lbs.).[16] The relative risks of hip fracture, associated with both bisphosphonate treatment regimens plus usual care (Vitamin D and calcium), were derived using a meta-analysis of studies included in a systematic literature review published by the Agency for Healthcare Research and Quality (AHRQ), and a collection of randomized control studies published after the publication of the AHRQ study (Appendix B).

Side Effects

Mild upper gastrointestinal symptoms, particularly esophagitis and esophageal ulcerations are the primary adverse effects of alendronate.[17] Therefore, for patients who were particularly susceptible to these types of side effects, we assumed zoledronic acid would be administered to the patient (See details in Appendix E). Osteonecrosis of the jaw, another reported side effect of bisphosphonate in prior studies, was not considered in this model given its low incidence rate (0.01% to 0.001%) [18]. Zoledronic acid's side effects are no more significant than a placebo's.[6,19] Because other side effects of oral and injectable bisphosphonates are generally mild and temporary[16], we did not incorporate those adverse events into the model.

Mortality

Baseline mortality rates were retrieved from the Center for Disease Control life tables.[20] The probability of death after hip fracture is significantly higher than for the general population.[21] To model the elevated mortality due to hip fracture, we estimated the incremental mortality of hip fractures at one year and at two years after surgical repair of hip fracture. We assumed that the mortality rate three or more years after the surgical repair would return to the natural death rate.

To estimate the probability of death in the first and second year following hip fracture, we calculated an incremental probability, using a difference-in-difference modeling approach. We analyzed 2011-2013 5% Medicare Inpatient, Outpatient, and Carrier Claims Data to select a hip fracture patient group and control group with no hip fracture diagnoses. For the control group, we randomly assigned pseudo index admission dates to each patient. Pseudo index admission dates assigned to the control group were randomly generated from the same distribution of hip surgical repair dates observed in the hip fracture group. We excluded patients with hip fracture diagnoses one year prior to the index admission date for the hip fracture and control groups. Hip fracture cases were matched to comparisons using propensity score matching. The risk adjustment measures used in the matching process included age, race, sex, and CMS hierarchical condition categories (HCC) for comorbid conditions (See Appendix C for cohort selection process). We then ran a difference-in-difference model (over time and between the hip fracture and control group) to estimate the excess mortality due to hip fractures. We also estimated cohort-specific incremental probabilities of death separately based on patient characteristics (age and sex) and living arrangements (community-dwelling versus long-term care facility dwelling) after surgical repair (Appendix Table D.2).

Medical and Healthcare Utilization

Surgical Care of Hip Fracture

Similar to our estimate of the effects of hip fractures on mortality, we used a difference-in-difference model to estimate the direct medical utilization and resultant Medicare spending associated with hip fractures. To develop the hip fracture and control groups, we followed the same approach used to develop these groups in the analysis of mortality. For the control group, we again randomly assigned

pseudo index admission dates generated from the same distribution of hip fracture repair dates observed in the hip fracture group. We used a propensity score matching approach to select the control group. The risk adjustment measures used in the matching process replicated those used in the mortality analysis. We then ran a difference-in-difference model (over time and between the hip fracture and control group) to estimate the direct treatment utilization and Medicare costs due to hip fractures (See detailed method description in Appendix C).

Long-term Custodial Care Utilization

To estimate long term care utilization, we estimated the frequency of nursing home stays for residents with and without hip fracture. We identified nursing home stays with an algorithm described in two previous studies[22,23], using the relevant Evaluation and Management procedure codes in the carrier claims (Current Procedure Terminology-4 codes 99304-99318 and with a place of service of "nursing facility").[24] We excluded patients with prior nursing home stays in the one-year period before index admission date for the hip fracture group and the pseudo index admission date for the control group. We identified patients with a nursing home stay during the one-year period after hip fracture. To estimate the effect of hip fracture on long term care utilization, we calculated the difference in the proportion of patients who were in a nursing home before and after hip fracture surgery. To control for confounding risk factors, we used propensity score matching to further restrict the control group to patients who were similar to the hip fracture group in terms of age, sex, race, and comorbidities. The difference between the hip fracture and comparison groups was our estimated effect of hip fracture on nursing home use. We obtained annual costs for long-term care from a national survey, which were adjusted to 2012 U.S. dollars (See detailed method description in Appendix D).

A summary of all parameter estimates and sources are described in Table 1.

Table 1. Model Parameter Values, Range, Distribution, and Sources

Parameter	Baseline	Range*	Distribution	Source(s)
Direct Medical Costs (2012 USD)				
Vitamin D with Calcium	$62	$22, $102	N.A.	Walgreen, 2016
Alendronate	$1,238	$692, $1,784 (95% C.I.)	N.A.	Consumer Report 2013; Saloner et al. 2015
Zoledronic Acid	$1,807	$964, $1,684 (95%C.I.)	N.A.	Consumer Report 2013; Saloner et al. 2015
Timing and Choice of Bisphosphonate Treatment				
Treatment period	3 years	N.A.		FDA, 2011
Offset period	5 years	N.A.		Diab et al. 2013
Percent of patients treated with zoledronic acid	31.39%	N.A.		Authors' analysis of 2011-2013 Medicare Claims See Appendix E
Relative Risks of Hip Fracture				
Probability of Hip Fracture w/o treatment	Vary by age and T-score			World Health Organization, 2011 See Appendix A
Usual care vs no treatment	0.83	(0.79, 0.87)	Lognormal	See Appendix B
Alendronate + usual care vs usual care	0.55	(0.45, 0.68)	Lognormal	See Appendix B
Zoledronic Acid+ usual care vs usual care	0.54	(0.41, 0.70)	Lognormal	See Appendix B
Probabilities				
Baseline Mortality Rate	Varies by patient cohort			CDC life tables
Incremental Mortality after Hip Fracture	Varies by age		Normal	Authors' calculation See Appendix C and Appendix D
Incremental Mortality after Hip Fracture in the Community	Varies by age		Normal	
Incremental Mortality after Hip Fracture in LTC	Varies by age		Normal	
Mortality Rate of LTC Patients	Varies by age		Normal	
LTC utilization rate after hip fracture	Varies by age		Normal	
Utilization Rates (2012 USD)				
Annual Rates of LTC use	$81,030	$81,030-$90,520	N.A.	MetLife (2012)

III. Results

Impact on hip fractures, life-expectancy and long-term care

Bisphosphonate treatment was associated with significant decreases in the incidence of hip fractures for all patients. Among 75 year old women with severe osteoporosis, the use of bisphosphonate prevents 4,965 hip fractures per 100,000 patients (Table 2). Through the avoided incidence of life-threatening hip fractures, bisphosphonate treatment increases life expectancy for patients of all ages and risk levels, ranging from 0.06 years for older patients (Age=75) with mild risk to 0.44 years for younger patients (Age=65) with high risk. Due to reduced incidence of hip fractures, patients were less likely to be admitted to long-term care facilities. Bisphosphonate treatment reduced lifetime long-term care admissions by 29 percent, for a 75 year old female with severe osteoporosis.

Among patients that experience a hip fracture, our model shows that bisphosphonate treatments could have delayed a hip fracture and thus delayed the need for custodial care for most patient groups. For patients who eventually fractured their hip, the mean hip fracture delay due to bisphosphonate treatment ranged from 0.36 years (Severe, Age = 65) to 6.54 years (Mild, Age=75).

Impact on Cost of Care Delivery

Prevented hip fractures and long-term care admissions are associated with significant reductions in hospitalizations and long-term care. Our analysis indicates that treatment with bisphosphonates could result in lower utilization of medical care and decrease the average per-person medical services spending from $350 (Mild, Age=65) to $2,006 (Severe, Age=75) over a lifetime (Table 2). In addition, bisphosphonate treatments could result in significantly reduced long-term custodial care use and save between $820 and $5,816 per person in terms of avoided lifetime, long-term custodial care costs for the same patients (Table 2).

Given that only half of non-fractured osteoporosis patients, with Medicare coverage, received treatments[25], full utilization and compliance with bisphosphonate treatment could result in a reduction of between $1.13 billion to $6.52 billion (2012 dollars) in Medicare payments due to avoided medical service costs and an additional reduction between $2.67 billion and $18.9 billion due to avoided custodial care of Medicare beneficiaries with osteoporosis in 2012 (Appendix Table E.1).

Table 2. Patient and Utilization Outcomes Estimates by Risk Group

		Bisphosphonate	No Treatment	Difference (%)
Hip Fractures per 100,000 Patients				
65 years	Mild Risk	7,313	8,254	941(11.4%)
	Moderate Risk	13,349	15,372	2,023(13.2%)
	High Risk	23,834	27,604	3,770(13.7%)
75 years	Mild Risk	5,139	6,717	1,578(23.5%)
	Moderate Risk	8,949	11,687	2,738(23.4%)
	High Risk	15,373	20,338	4,965(24.4%)
Long-term Care Facility Admissions per 100,000 Patients				
65 years	Mild Risk	3,583	4,071	488(12.0%)
	Moderate Risk	6,631	7,637	1,006(13.2%)
	High Risk	12,002	14,000	1,998(14.3%)
75 years	Mild Risk	2,340	3,305	965(29.2%)
	Moderate Risk	4,161	5,876	1,715(29.2%)
	High Risk	7,286	10,268	2,982(29.0%)
Mean Life Years				
65 years	Mild Risk	20.38	20.29	-0.09(-0.4%)
	Moderate Risk	20.07	19.85	-0.22(-1.1%)
	High Risk	19.47	19.03	-0.44%(-2.3%)
75 years	Mild Risk	13.08	13.02	-0.06(-0.5%)
	Moderate Risk	12.98	12.86	-0.12(-0.9%)
	High Risk	12.80	12.57	-0.23(-1.8%)
Mean Life Years in Long-Term Care Facility				
65 years	Mild Risk	0.11	0.12	0.01(10.7%)
	Moderate Risk	0.23	0.20	-0.03(-14.9)
	High Risk	0.37	0.43	0.06(14.6%)
75 years	Mild Risk	0.07	0.10	0.03(30.7%)
	Moderate Risk	0.13	0.18	0.05(29.8%)
	High Risk	0.22	0.31	0.09(29.7%)
Medical Cost of Hip Fracture (mean)				
65 years	Mild Risk	$1,999	$2,349	350(14.9%)
	Moderate Risk	$3,756	$4,506	750(16.6%)
	High Risk	$6,881	$8,322	1,441(17.3%)
75 years	Mild Risk	$1,661	$2,287	626(27.4%)
	Moderate Risk	$2,939	$4,035	1,096(27.2%)
	High Risk	$5,105	$7,111	2,006(28.2%)
Custodial Care cost in Long-Term Care Facility (mean)				
65 years	Mild Risk	$4,895	$5,715	820(14.3%)
	Moderate Risk	$9,350	$11,212	1,862(16.6%)
	High Risk	$17,406	$21,280	3,874(18.2%)
75 years	Mild Risk	$3,877	$5,743	1,866(32.5%)
	Moderate Risk	$6,945	$10,225	3,280(32.1%)
	High Risk	$12,274	$18,090	5,816(32.2%)

Probabilistic Sensitivity Analysis

To test the robustness of our baseline estimates, we also ran a probability sensitivity analysis (PSA) by sampling all parameters with distributions described in Table 1. Table 3 exhibits the point estimates and 95% C.I. of mean differences in all major model outcomes. Our results from the PSA indicate that the effects of bisphosphonate treatment are statistically significant and non-trivial. It is noteworthy that the effects under our baseline estimates are slightly lower than the mean estimates under the probability sensitivity analysis, mainly because the assumed relative risk distributions (log normal) are not symmetric around the baseline values.

Table 3. Probability Sensitivity Analysis of Patient and Cost Outcome Differences by Risk Group

		Mean	95% C.I.
Difference in Hip Fractures per 100,000 Patients			
65 years	Mild Risk	-959	(-987, -931)
	Moderate Risk	-1,974	(-2,011, -1,936)
	High Risk	-3,805	(-3,860, -3,750)
75 years	Mild Risk	-1,634	(-1,663, -1,605)
	Moderate Risk	-2,961	(-3,010, -2,913)
	High Risk	-5,050	(-5,126, -4,975)
Difference in Long-term Care Facility Admissions per 100,000 Patients			
65 years	Mild Risk	-486	(-505, -466)
	Moderate Risk	-1,005	(-1,035, -974)
	High Risk	-1,926	(-1,980, -1,871)
75 years	Mild Risk	-929	(-948, -909)
	Moderate Risk	-1,710	(-1,742, -1,678)
	High Risk	-2,971	(-3,019, -2,923)
Difference in Mean Life Years			
65 years	Mild Risk	0.10	(0.101, 0.107)
	Moderate Risk	0.23	(0.221, 0.229)
	High Risk	0.47	(0.461, 0.478)
75 years	Mild Risk	0.08	(0.075, 0.079)
	Moderate Risk	0.14	(0.140, 0.145)
	High Risk	0.25	(0.250, 0.258)
Difference in Mean Life Years in Long-Term Care Facility			
65 years	Mild Risk	-0.02	(-0.0158, -0.0145)
	Moderate Risk	-0.03	(-0.033, -0.031)
	High Risk	-0.06	(-0.0630, -0.0595)
75 years	Mild Risk	-0.03	(-0.0295, -0.0280)
	Moderate Risk	-0.05	(-0.054, -0.052)
	High Risk	-0.09	(-0.095, -0.092)
Difference in Medical Cost of Hip Fracture			
65 years	Mild Risk	$(350)	(-$359, -$342)
	Moderate Risk	$ (737)	(-$751, -$722)
	High Risk	$ (1,466)	(-$1490, -$1441)
75 years	Mild Risk	$ (645)	(-$655, -$634)
	Moderate Risk	$ (1,180)	(-$1199, -$1162)
	High Risk	$ (2,045)	(-$2076, -$2014)
Difference in Custodial Care cost in Long-Term Care Facility			
65 years	Mild Risk	$ (897)	(-$929, -$865)
	Moderate Risk	$(1,908)	(-$1961, -$1855)
	High Risk	$(3,785)	(-$3877, -$3693)
75 years	Mild Risk	$(1,785)	(-$1827, -$1742)
	Moderate Risk	$(3,321)	(-$3387, -$3255)
	High Risk	$ (5,848)	(-$5945, -$5750)

IV. Discussion

Our study found that bisphosphonate treatment yielded better health outcomes by reducing the incidence of hip fractures and long-term care facility admissions. Our results are comparable to a prior study[8], which estimated 19.1% and 22.2% reduction in hip fractures among bisphosphonate users 65- and 75-years old with no prior fractures, respectively.

Our study utilizes information about the clinical efficacy of bisphosphonate treatment on hip fracture-related health outcomes such as medical care and long-term care utilization. Similar studies that used Markov microsimulation models found that oral bisphosphonate therapy is cost-effective for preventing fractures and increasing life expectancy.[26, 27] Our work provides a unique contribution to the literature by capturing use of injectable and oral bisphosphonates in certain populations and estimates of hip fracture-induced LTC utilization and the risk of osteoporotic hip fracture into a Markov model approach.

In spite of treatment promotion initiatives, use of bisphosphonates remains low. According to one study, within one year of osteoporosis diagnosis, only 35% of women aged 55 and older receive some pharmacologic treatments.[28] Based on this finding, we estimate that in the US, of the approximately 8.6 million women who are 55-years or older with osteoporosis, 65% of them or 5.6 million do not use pharmaceuticals.[29] Even if we conservatively assume that these women all have only mild osteoporosis, our findings suggest that up to 52,543 lifetime hip fractures could be prevented by increasing pharmacological interventions in this population. U.S. Clinical guidelines[5] have highlighted the benefits of bisphosphonate treatments to prevent osteoporotic hip fractures, disability and mortality. The low rates of bisphosphonate treatments, despite their proven efficacy, have been attributable to several underlying causes: (1) asymptomatic and chronic nature of osteoporosis[19], (2) perceived risks of severe side effects of bisphosphonates[19, 30], and (3) lack of perception of long-term risks of hip fractures and loss of self-dependence.[31]

This study provides payers, providers, and patients with evidence that bisphosphonate treatment can prevent and delay hip fractures as well as long-term care admissions. These findings, in stark contrast to the poor outcomes of no treatment, inform patients of the measurable long-term consequences of not treating osteoporosis. Furthermore, our study demonstrates the benefits of having accessible bisphosphonate treatment. Although, a considerable portion (more than 30%) of osteoporosis patients have a history or diagnosis of upper gastrointestinal conditions, coverage criteria for injectable bisphosphonate remain restrictive under current Medicare Part B and Part D, which require evidences of prior non-traumatic bone fractures.[32,33] Patients with clinical risk factors for intolerance to oral bisphosphonate are discouraged from initiation and adherence to treatments. For these patients, early knowledge of and access to alternatives to oral bisphosphonates through, for example, Medicare beneficiary education programs, could improve use and adherence to treatment. Lastly, Medicare and Medicaid are responsible for a substantial amount of hip fracture care and nursing home costs, respectively. To increase treatment and adherence, Medicare could consider reducing Part D costs for bisphosphonates to encourage use, which could yield long-term benefits to both Medicare and Medicaid.

Our study has several limitations that need to be addressed in future research. First, concerns about side effects could easily affect patients' decisions to treat chronic and asymptomatic osteoporosis. Although we factored in major side effects of bisphosphonates, we did not account for patient concerns about mild but common side effects such as fever, myalgia or arthralgia.[17] Second, we did not present a voluntary drug termination mechanism in the model, which would otherwise better contrast the values of full compliance with different levels of treatment persistence. Third, our choice to use life-years as the efficacy measure likely understates the value of osteoporosis treatment by not factoring in significant loss of quality of life after the incidence of hip fracture. Last, we assumed that the mortality rate three or more years after hip fracture would return to the natural death rate, mainly due to the lack of long-term follow-up Medicare claims data. In practice, post hip fracture mortality rates might be higher than natural death rates even ten years after hip fractures.[34] In this regard, our analysis may underestimate the impact of the adverse effects of hip fractures and long-term care facility admission.

In conclusion, this study is one of the few to assess the value of oral and injectable bisphosphonate treatments for U.S. Medicare-aged patients by hip fracture risk and age in terms of major adverse events and associated economic consequences. We developed model assumptions based on U.S. Medicare claims data and a meta-analysis of systematic literature review and RCT studies. The financial benefits of bisphosphonate treatments are largely attributable to savings from avoided long-term care admissions. Increased utilization of these pharmaceuticals would benefit patients and reduce healthcare and long-term care costs to Medicare and Medicaid.

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Appendices Supplementary Data and Results

A. Baseline Annual Probability of Hip Fracture

We extracted baseline hip fracture probabilities from FRAX tool[1] by assuming: (1) female; (2) no prior hip fracture; (3) no hip fracture for parents; (4) non-smoker; (5) no exposure to glucocorticoids; (6) no diagnosis of rheumatoid arthritis; (7) secondary osteoporosis; (8) drinks less than 3 units per day; and (9) has the same weight as the average American at her age. Hip fracture risk level was based on T-scores: (1) mild risk (T-score of -2.5); (2) moderate risk (T-score of -3.25); and (3) high risk (T-score of -4.0). The following Appendix Table A.1 exhibits her annual probability of hip fracture extracted FRAX tool.

Appendix Table A.1 Baseline Probability Annual of Hip Fracture

	Age=65	Age=75
Mild Risk	0.27%	0.5%
Moderate Risk	0.6%	0.96%
High Risk	1.3%	1.8%

Source: FRAX Tool, 2011[1]

B. Probability Estimation of Treatment-Specific Hip Fracture

The probability of treatment-specific hip fracture was estimated using the methodology as described below.

Algorithm for Probability of hip fracture Estimation

$Prob\ (AL+\ UC) = RR_1 * Prob(UC) = RR_1 * RR_0 * Prob\ (NT)$ *Formula(I)*

$Prob\ (ZA+\ UC) = RR_2 * Prob(UC) = RR_2 * RR_0 * Prob\ (NT)$ *Formula(II)*

--Prob (x): Probability of hip fracture under treatment x.

--AL: Alendronate

--UC: Usual Care of vitamin D+ calcium

--ZA: Zoledronic Acid

--NT: No Treatment

--RR_0: Relative Risk of usual care vs no treatment

--RR_1: Relative Risk of Alendronate+ usual care vs. usual care

--RR_2 : Relative Risk of Zoledronic acid + usual care vs. usual care

Relative Risks of Hip Fracture

To estimate relative risk of hip fracture we conducted a mixed-effect meta-analysis of RCTs and systematic reviews study in the AHRQ report.[2] We also supplemented AHRQ studies with a structured literature review, to identify eligible RCT studies published after the AHRQ report. First, we identified AHRQ-cited systematic reviews which follow in the scope of our study: (1) patient samples must be community residents; (2) only focus on hip fracture; and (3) treatment comparisons should be either bisphosphonate treatment+ usual care versus usual care, or usual care versus no treatment. We did not exclude studies based on sex, prior osteoporotic hip fracture, or risk level (T-score / BMD score), because the patient population of interest in our study also presented heterogeneous clinical and demographic characteristics. Appendix Table B.1 lists all the systematic review studies or RCT studies used for the purpose of the meta-analysis.

Appendix Table B.1 Relative Risk of Hip Fracture: Eligible Systematic Reviews or RCT studies

Study ID	# of RCT trials	Sample Size	Relative Risk	95% C.I.
Alendronate + Usual Care vs. Usual Care				
Cranney (2002) [3]	-	11,808	0.63	(0.43, 0.92)
Karpf (1997) [4]	-	1,602	0.46	(0.15, 1.36)
Nguyen (2006) [5]	-	10,389	0.55	(0.27, 1.12)
Papapoulos (2005) [6]	-	6,804	0.45	(0.28, 0.71)
Stevenson (2005) [7]	-	3,021	0.46	(0.23, 0.91)
Wells (2008) [8]	-	9,807	0.61	(0.40, 0.92)
Pooled Relative Risk(1)	-	**43,431**	**0.55**	**(0.45, 0.68)**
Zoledronic Acid + Usual Care vs Usual Care				
Lyles (2007) [9]	-	1,065	0.70	(0.41, 1.18)
Black (2007) [10]	-	3,714	0.56	(0.40, 0.79)
Boonen (2012) [11]	-	242	0.31	(0.15, 0.65)
Pooled Relative Risk(2)	-	**5,367**	**0.54**	**(0.41, 0.70)**
Usual Care vs No treatment				
Avenell (2005) [12]	7	10,376	0.81	(0.68, 0.96)
Bischoff-Ferrari (2005)[13]	5	9,294	0.88	(0.69, 1.13)
Bischoff-Ferrari (2) (2005) [13]	3	5,572	0.74	(0.61, 0.88)
Bischoff-Ferrari (3) (2005) [13]	2	3,722	1.15	(0.88, 1.50)
Stevenson (2005) [7]	2	2,886	0.72	(0.59, 0.88)
Bergman (2010) [14]	5	7,473	0.70	(0.63, 0.90)
Avenell (1) (2009) [15]	4	6,988	0.83	(0.61, 1.12)
Avenell (2) (2009) [15]	4	40,524	0.81	(0.71, 0.93)
Avenell (3) (2009) [15]	8	46,658	0.84	(0.73, 0.96)
Avenell (4) (2009) [15]	6	42,805	0.91	(0.76, 1.08)
Bischoff-Ferrari (1) (2009) [16]	8	40,886	0.91	(0.78, 1.05)
Bischoff-Ferrari (2) (2009) [16]	5	31,872	0.82	(0.69, 0.97)
Boonen(1) (2007) [17]	6	N.A.	0.82	(0.71, 0.94)
Boonen(2) (2007) [17]	N.A.	N.A.	0.84	(0.70, 1.01)

Study ID	# of RCT trials	Sample Size	Relative Risk	95% C.I.
Izaks (2007) [18]	2	N.A.	1.04	(0.72, 1.50)
Pooled Relative Risk(3)	-	**>249,056**	**0.83**	**(0.79, 0.87)**

Note: (1) I^2=0.0%; (2) I^2=34.8%; (3) I^2=18.6 %;

C. Medical Care Cost of Hip Fracture

To estimate the effect of hip fractures on acute hospital care costs, we used Medicare 5% 2011-2013 Standard Analytical Files (including hospital inpatient, hospital outpatient, long-term acute care hospital, inpatient rehabilitation facility, skilled nursing facility, home health, and physicians/suppliers files) to construct two study groups: a hip fracture group and a comparison group.

Hip fracture group:

- We included patients with an inpatient stay for hip fracture in 2012; we identify hip fractures using the ICD-9 diagnosis codes listed under the Healthcare Cost and Utilization Project's Clinical Classifications Software 226 (fracture of neck of femur (hip)). We did not include ICD-9 codes 9053, V5413, and V5423 since those codes include the late effects and after-care of hip fracture.[19] The codes used include:
    - 820.0x and 820.1x (intracapsular fractures)
    - 820.2x and 820.3x (extracapsular fractures)
    - 820.8 (closed fracture of unspecified part of neck of femur)
    - 820.9 (open fracture of unspecified part of neck of femur);
- We included patients with at least a one year period before the hip fracture without another hip fracture (clean period).

Comparison group:

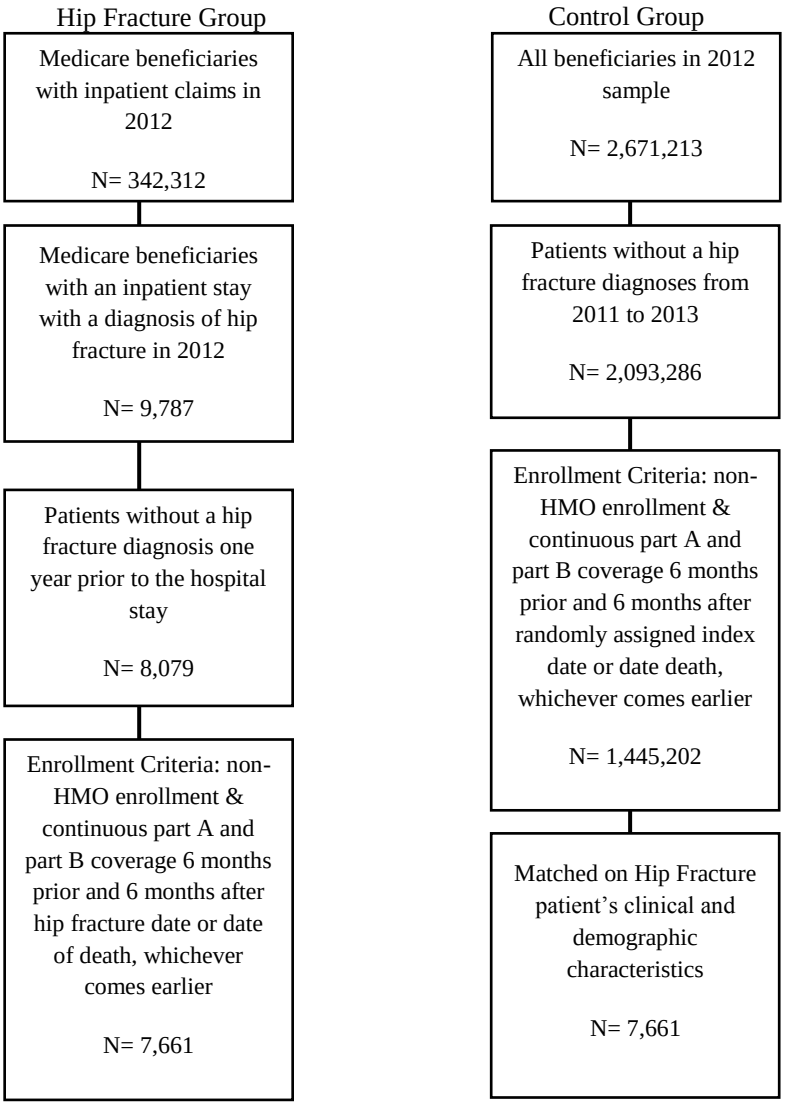
- We included patients without a hip fracture from 2011 to 2013.

For both groups, we excluded beneficiaries who were not continuously enrolled in Medicare Fee-For-Service Parts A and B from 2011 through mid-2013 for estimating the effect of hip fractures on direct treatment costs and we excluded beneficiaries who were not continuously enrolled in Parts A and B from 2011 through 2013 for estimating the effect on nursing home stay.

We used a difference-in-difference approach to estimate acute hospital care costs associated with hip fractures. Because Medicare beneficiaries may incur higher medical costs in any six month period compared to the six month period prior simply from aging, we compared the difference in costs six months before and after in the hip fracture group with the change in Medicare spending for a comparison group. We constructed a comparison group and calculate costs six months before and after a randomly assigned index date. The difference between the hip fracture and comparison groups was our estimated effect of hip fracture on direct treatment costs. However, since the hip fracture group was different from

the comparison group in terms of age, sex, race, and comorbidities, we used propensity score matching to construct a comparison group that was similar to the hip fracture group in age, sex, race, and comorbidities. We used comorbidity indicators from the Centers for Medicare and Medicaid Services hierarchical condition categories model[20], except for the hip fracture indicator. Appendix Chart C.1 describes the cohort selection process and control and intervention group matching approach.

Appendix Chart C.1 Patients Cohort Selection for Acute Hospital Care Cost Estimation



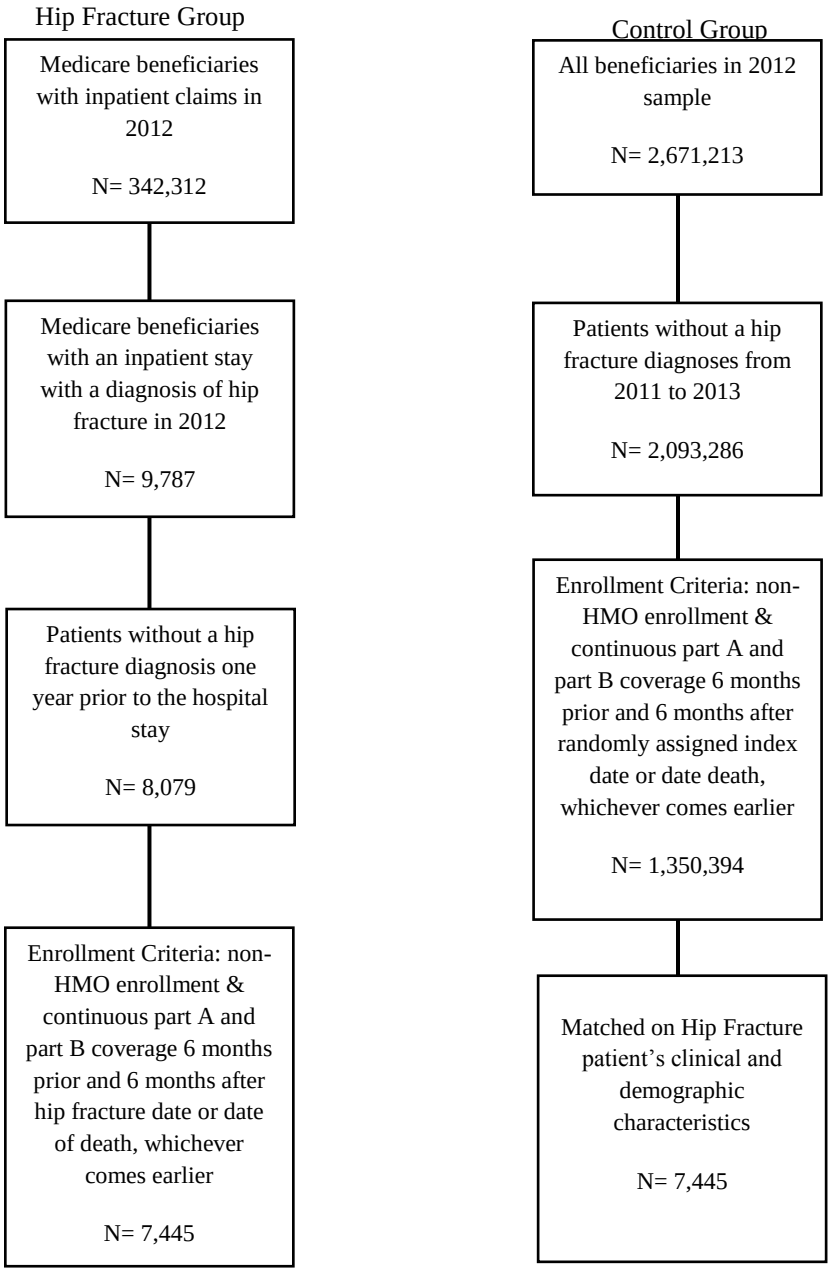
D. Long-Term Custodial Care Utilization Post Hip Fracture

To estimate the effect of hip fracture on nursing home stay, we identify nursing home stays using an algorithm described in two previous studies.[21, 22] Specifically, we identified patients with a nursing home stay by using the relevant Evaluation and Management procedure codes in the carrier claims (Current Procedure Terminology-4 codes 99304-99318)[23] and with a place of service of "nursing facility." We identified and excluded patients with a nursing home stay before hip fracture by applying this algorithm to carrier claims during the one-year period before hip fracture (for the comparison group, we use the one-year period before the randomly assigned index date). We identified patients with a nursing home stay after hip fracture by applying this algorithm to carrier claims during the one-year period after hip fracture (inclusive of the hip fracture date).

To estimate the effect of hip fracture on nursing home use, we calculated the difference in the proportion of patients who were in a nursing home before and after their hip fracture. Because a Medicare beneficiary may be more likely to be in a nursing home in any one-year period compared to the one-year period prior simply from aging, we compared the difference in the proportion in a nursing home in the hip fracture group with the comparison group. This difference between the hip fracture and comparison groups was our estimated effect of hip fracture on nursing home stay. We select comparison patient cohorts and conducted propensity score matching, using similar approaches to that of the acute care cost estimation. Appendix Chart D.1.describes the cohort selection and control and intervention group matching approach.

Appendix D.2. exhibits analysis results of acute care costs, long-term care utilization, and associated mortality from our difference-in-difference models.

Appendix Chart D.1 Cohort Selection for Long-Term Custodial Care Utilization Estimation



Appendix Table D.2. Probabilities and Costs of Post-Hip Fracture Residency

	Community-Dwelling Residency					
	Male			Female		
	Aged 65-69	Aged 70-74	Aged 75+	Aged 65-70	Aged 70-75	Aged 75+
Mean annual total Cost(S.E.)	$45,367*** ($3,809)	$44,566*** ($3,103)	$45,114*** ($1,240)	$39,199*** $(2,211)	42177.531*** (1729.995)	43783.123*** (510.994)
1st Yr. Incremental Mortality	0.157*** (0.040)	0.164*** (0.033)	0.182*** (0.018)	0.063*** (0.023)	0.125*** (0.023)	0.116*** (0.007)
2nd Yr. Incremental Mortality	0.100*** (0.036)	0.010 (0.027)	0.013 (0.013)	0.067*** (0.022)	0.019 (0.016)	0.011** (0.005)
Long-Term Care Utilization	0.160*** (0.034)	0.218*** (0.030)	0.257*** (0.014)	0.222*** (0.028)	0.212*** (0.023)	0.273*** (0.008)
	Long Term Care Residency					
	Male			Female		
Mean Total Cost (S.E.)	$34,967*** ($3,110)			$35,235*** ($1,419)		
1st Yr. Incremental Mortality	0.150*** (0.044)			0.102*** (0.024)		
2nd Yr. Incremental Mortality	-0.032 (0.033)			0.033* (0.018)		

* p<0.10, ** p<0.05, *** p<0.01
Source: Authors' analysis of 2011-2013 Medicare Claims

E. Bisphosphonate intolerance: Oral vs. Injectable

To obtain the proportion of osteoporosis patients who might develop intolerance to oral or injectable bisphosphonates, we examined claims for a 5% sample of Medicare beneficiaries.[23] We then identified osteoporosis diagnosis using ICD-9 code 733.XX, and identified patients who reported adverse events to oral bisphosphonate and IV bisphosphonates with "E933.6" and "E933.7" respectively. We also identified diagnosis of esophagus disease (ICD-9 code: 530.XX) to identify other clinical risk factors for intolerance to oral bisphosphonate, including esophageal stricture, achalasia, or other severe esophageal dysmotility. To minimize bisphosphonate intolerance, we assigned patients who had esophagus diseases or prior adverse events to oral bisphosphonate to injectable Zoledronic acid, and assigned the rest to oral bisphosphonate treatment. Table E.1 exhibits the patient risk profile for developing potential intolerance to oral or injectable bisphosphonates and the final treatment assignment determined in our model.

Appendix Table E.1 Probability and Cost of Post-Hip Fracture Residency

	Number of Patients	Percent of 2012 Medicare Beneficiaries
No Osteoporosis Diagnosis	1,442,984	81.66%
Osteoporosis Diagnosis	324,148	18.34%
Adverse Event To IV Bisphosphonate (A)	34	1% of osteoporosis patient
Adverse Event To Oral Bisphosphonate (B)	89	3% of osteoporosis patient
Esophagus Disease (C)	101,707	31.38%
IV Bisphosphonate : (B) Or (C)	101,763	31.39%
Oral Bisphosphonate	222,385	68.61%

Source: Author's analysis of 2011-2013 Medicare Claims[23]

F. Time to Hip Fracture and Long-Term Care Residency

Appendix Table F.1 exhibits analysis results of time to hip fracture and long-term care utilization by patients using bisphosphonates and those receiving no treatment.

Appendix Table F.1 Mean Time to Hip Fracture and Long-Term Care Residency

		Bisphosphonate	No Treatment	Difference (%)
Mean Time to Hip Fracture				
65 years	Mild Risk	14.24	12.02	-2.22 (-18.5%)
	Moderate Risk	12.27	11.77	-0.5 (-4.2%)
	High Risk	12.45	12.09	-0.36 (-3.0%)
75 years	Mild Risk	13.91	7.37	-6.54 (-88.7%)
	Moderate Risk	9.05	6.61	-2.44 (36.9%)
	High Risk	8.62	7.96	-0.66 (-8.3%)
Mean Time to Long Term Care Residency				
65 years	Mild Risk	16.97	16.51	-0.46 (-2.8%)
	Moderate Risk	16.04	15.8	-0.24 (1.5%)
	High Risk	16.31	16.01	-0.3 (-1.9%)
75 years	Mild Risk	16.92	12.55	-4.37 (34.8%)
	Moderate Risk	10.66	10.11	-0.55 (-5.4%)
	High Risk	10.81	11.08	0.27 (2.4%)

Source: Authors' Analysis of 2011-2013 Medicare Claims Data[23]

G. Methods for Estimating Avoided Hip Fractures

To estimate the number of hip fractures avoided by treating osteoporosis in all women 55-years and older, we first used the results from a study of NHANES data which provides osteoporosis prevalence rates for various age groups (50-59, 60-69, 70-79, and 80+).[24] We then obtained population estimates for women aged 55-59, 60-69, 70-79 and 80+ from an ACS Factfinder table.[25] We calculated the prevalence of osteoporosis for the aforementioned age cohorts. There was not an exact match for the 55-59 age

group, so we used the 50-59 population to calculate the prevalence rate. By multiplying each age group's prevalence rate by its respective total female population we estimate the total number of American women 55-years and older with osteoporosis, approximately 8.6 million women.
From this count, we derive the number of women who take no osteoporosis medication by multiplying the rate obtained from literature, 65%, by the total 8.6 million, resulting in an estimate of 5.58 million women 55-years or older with untreated osteoporosis. We conservatively assume that all of the women with untreated osteoporosis have only mild osteoporosis. If all women with untreated osteoporosis began using bisphosphonates we estimate 941 fractures can avoided per 100,000 mild osteoporosis patients. This means that 0.00941 fractures per person can be avoided when all are treated with bisphosphonates vs no treatment. Multiplying this rate by the estimate for untreated women 55-years or older with untreated osteoporosis results in about 52,543 avoided lifetime hip fractures.

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