筑　波　大　学

博 士 （医 学） 学 位 論 文

Cost-Effectiveness of Combined Oral Bisphosphonate Therapy and Falls Prevention Exercise for Fracture Prevention in the United States

（骨折の予防を目的とした経口ビスフォスフォネート療法と転倒予防運動の併用に関するアメリカにおける費用対効果分析）

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Abstract

Background and Purpose: Osteoporotic fractures increase the risk of fractures, leading to a large economic burden on society worldwide. Incident fractures and associated costs are projected to rise over time, as the global population grows older. Therefore, it is an important priority to determine which strategies to reduce fractures represent good economic value. Although both oral bisphosphonate therapy and falls prevention exercise have been shown to reduce the risk of fractures, it remains unclear whether the combined strategy of oral bisphosphonate therapy and falls prevention exercise is cost-effective compared with either strategy in isolation. The purpose of this study was to examine the cost-effectiveness of the combined strategy of oral bisphosphonate therapy (i.e., alendronate) for five years and falls prevention exercise (i.e., the Otago Exercise Program) for one year compared with either strategy in isolation at a conventionally accepted threshold. To make the results more applicable, we incorporated data from community settings and patient populations as much as possible while keeping the model parsimonious.

Methods: We calculated incremental cost-effectiveness ratios [ICERs] (2014 U.S. dollars per quality-adjusted life year [QALY]), using a Markov microsimulation model among hypothetical cohorts of community-dwelling white women in the United States without prior history of hip, vertebral, or wrist fractures with different starting ages (65, 70, 75, and 80)

over a lifetime horizon from the societal perspective. We included hip, clinical vertebral, wrist, and other osteoporotic fractures (i.e., humerus, distal forearm other than wrist, pelvis, tibia/fibula, and femur other than hip) in the model. We also examined a different scenario, in which the exercise program was offered only to those with osteoporosis in the combined strategy.

Results: At ages 65, 70, 75 and 80, the combined strategy had ICERs of $202,020, $118,460, $46,870, and $17,640 per QALY, respectively, compared with oral bisphosphonate therapy alone. The combined strategy provided better health at lower cost than falls prevention exercise alone at ages 70, 75, and 80. In deterministic sensitivity analyses, results were particularly sensitive to the change in the opportunity cost of participants' time spent exercising. In probabilistic sensitivity analyses, the probabilities of the combined strategy being cost-effective compared with the next best alternative increased with age, ranging from 35% at age 65 to 48% at age 80 at a willingness-to-pay of $100,000 per QALY. The alternative scenario, in which exercise was provided only to those with osteoporosis in the combined strategy, provided favorable ICERs compared with those in base case analyses at ages 65, 70, and 80, and was cost-saving at age 75.

Discussion: Among community-dwelling white women in the United States ages 75 and 80, adding one year of exercise to five years of oral bisphosphonate therapy is cost-effective at a willingness-to-pay of $100,000 per QALY, compared with oral bisphosphonate therapy only. The absolute rates of hip, clinical vertebral, or other osteoporotic fractures increased over the age range in the model, making the absolute reduction in the number of these fractures highest at age 80. We also modeled the value of foregone time participating in the exercise program as declining with advancing age. Thus, the natural history of osteoporotic fracture risk, coupled with the availability of time to exercise relative to alternatives, could explain our findings. The combined strategy is also potentially cost-effective for younger ages (65 and 70) at high risk of fracture (i.e., osteoporosis defined by DXA). To our knowledge, this is the first economic evaluation to examine the combined strategy of oral bisphosphonate therapy and falls prevention exercise compared with either strategy in isolation, which is a notable strength. In contrast, our results may be best applied to U.S. white women, and may not generalize to women of other races/ethnicities, or men, which is one of the limitations. This analysis will help clinicians and policymakers make better decisions about treatment options to reduce fracture risk. In addition, this model can be expanded further to address the cost-effectiveness of different interventions (e.g., other osteoporosis treatments or falls prevention interventions), in a different population (e.g., elderly men), or in a different healthcare setting (e.g., Japan).

Introduction

Osteoporotic fractures not only constitute a major medical and public health concern for older adults, but also impose a large economic burden on society worldwide. Not surprisingly, incident fractures and associated costs are projected to rise over time, as the global population grows older (1). For instance, the burden of osteoporosis for 2005 in the United States was estimated to be more than two million of incident fractures, resulting in nearly $ 17 billion of direct medical costs (more than $ 19 billion if costs for preventing fractures were included). By 2025, these are projected to grow by 50%, exceeding three million of annual incident fractures and $25 billions of the associated costs (2). Therefore, determining which medical and public health strategies to reduce fractures represent good economic value is an important priority.

Treatments for osteoporosis have been the mainstay of fracture prevention. According to recent systematic reviews, there is high-quality evidence showing that bisphosphonates, denosumab, or teriparatide (PTH) reduce the risk of osteoporotic fractures (3, 4). In terms of cost-effectiveness, a recent systematic review demonstrated that osteoporotic drugs were cost-effective in postmenopausal women with osteoporosis when compared with no treatment (5). For example, a five-year course of oral bisphosphonate-like therapy (annual cost of $600) was cost-effective for average risk white women age 70 when compared with no intervention under a willingness-to-pay of $60,000/quality-adjusted life year (QALY), and

cost-saving for those women ages 75, 80, and 85 in the United States (costs were inflated to 2005 U.S. dollars) (6). Another U.S. study showed that oral bisphosphonate therapy for five years (annual cost of $1,050) was cost-effective for average health white women ages 50, 55, 60, 65, 70, and 90 when compared with no intervention under a willingness-to-pay of $50,000/QALY, and cost-saving for those women ages 75, 80, and 85 (costs were inflated to 2008 U.S. dollars) (7). When the cost-effectiveness of bisphosphonate was compared with another osteoporotic treatment, denosumab for 5 years (annual cost of $1,650) was cost-effective compared with generic alendronate (annual cost of $98) under a willingness-to-pay of $100,000/QALY for postmenopausal osteoporotic women, and cost-saving for those women age 75 and over in the United States (costs were inflated to 2012 U.S dollars) (8). Teriperatide (annual cost of $6,720) for two years was dominated by alendronate (annual cost of $894) for five years for U.S postmenopausal white women with severe osteoporosis (costs were inflated to 2003 U.S. dollars) (9). Teriperatide (annual cost of $6,292) for 18 months was also dominated (i.e., higher costs and lower outcomes, such as QALYs) by bisphosphonates (annual cost of $771) for three years in all risk groups examined in another U.S study (costs were inflated to 2005 U.S. dollars) (10).

Prevention of falls is, however, also important to reduce the risk of fractures (11). Recent systematic reviews and meta-analyses suggested that falls prevention exercise programs not only reduce the risk (or rate) of falls, but also reduce those of fractures

associated with falls (12, 13). In terms of cost-effectiveness, a study showed that the Otago Exercise Program for one year was cost-saving compared with usual care in those aged 80 and over because of fewer hospital admissions in New Zealand (14, 15). A recent cost-benefit analysis in the U.S setting also found that the Otago Exercise Program for a year was cost-saving compared with no intervention (16).

Although both oral bisphosphonate therapy and falls prevention exercise have been shown to reduce the risk of fractures, to our knowledge, no large clinical trials have been conducted to examine the effectiveness of combining these two approaches for fracture prevention. In addition, no economic evaluation has been performed to examine the cost-effectiveness of a combined strategy, although oral bisphosphonate therapy consistently and falls prevention exercise, at least in some studies, have been shown to be cost-effective (or even cost-saving) compared with no intervention.

The objective of this study was to examine whether the combined strategy of oral bisphosphonate therapy and falls prevention exercise is cost-effective by conventional standards compared with either strategy in isolation. To make the results more applicable, we incorporated data from community settings and patient populations.

Methods

1) Overview

The reporting of this economic evaluation followed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement (17). We also followed the guidelines for conducting and reporting economic evaluation of fall prevention strategies (18).

We performed a Markov microsimulation model to examine if the combined strategy of oral bisphosphonate therapy and falls prevention exercise is cost-effective by conventional standards compared with either strategy in isolation among hypothetical cohorts of community dwelling non-Hispanic white women with different starting ages (65, 70, 75, and 80), and without prior history of hip, vertebral, or wrist fractures in the United States. Total costs in 2014 U.S. dollars and QALYs were estimated to obtain incremental cost-effectiveness ratios (ICERs), which represent cost per QALY gained for one strategy compared with the others, over a lifetime horizon (until a participant reached age 105, or died). We adopted the societal perspective, in which all costs were considered regardless of who bears them.

In the base case, we assumed a willingness-to-pay threshold of $100,000 per QALY, which is roughly twice the per capita gross domestic product (GDP) of the United States in 2013 ($53,042) (19). In sensitivity analyses, willingness-to-pay thresholds of $50,000 per QALY and $150,000 per QALY were used. These are based on the suggestions by the World

Health Organization Commission of Macroeconomics and Health that reported a reasonable willingness-to-pay may be one to three times per capita GDP (20). We used Treeage Pro Suite 2015 (Treeage Software Inc., Williamstown MA, USA) to program the model and perform analyses.

2) Model Structure

Each cycle lasts one year, and every participant may sustain a hip, clinical vertebral, wrist, or other osteoporotic fracture (i.e., humerus, distal forearm other than wrist, pelvis, tibia/fibula, or femur other than hip) during each cycle. Each participant can have only one fracture per cycle, and can have a maximum of two hip fractures, and an unlimited number of clinical vertebral, wrist, or other osteoporotic fractures over the entire time horizon.

Every participant starts the model in the "no fracture" state. Each cycle lasts one year, and every participant transitions between the health states or remains in the same state based on the assigned transition probabilities. A participant can sustain only one fracture per cycle, and can have a maximum of two hip fractures, and an unlimited number of clinical vertebral, wrist, or other osteoporotic fractures over the entire time horizon. If a participant sustains a wrist fracture or other osteoporotic fracture, a one-time cost and disutility are assigned in whatever Markov state the participant currently resides. If a participant in the "post hip fracture" state sustains a subsequent clinical vertebral fracture, the participant experiences a

one-time cost and disutility associated with the clinical vertebral fracture, but the individual remains in the "post hip fracture" state (Figure 1).

We used tracker variables for fractures and interventions to incorporate memory of previous events from one cycle to the next in the model. To ensure that accounting of costs and utilities was comprehensible, a half-cycle correction was not implemented, as the interventions last up to one year (or two years in sensitivity analyses) and/or five years and each cycle took one year, expecting that Markov approximation errors in calculations, especially associated with death transactions, in the different strategies canceled out eventually (21).

Model inputs included total costs, health-related quality of life, and transition probabilities between four Markov states including no fracture, post hip fracture, post clinical vertebral fracture, and death (Figure 1, Table 1). Literature searches were performed extensively for all the parameters in the model, and inputs were derived from published sources (i.e., meta-analyses, clinical trials, observational studies, cost-effectiveness analyses, websites, or books) that were considered as most relevant, high-quality, and up-to-date estimates. Our own assumptions were chosen only if no reliable published estimate was available.

3) Interventions

a) Overview

The model consisted of a) the combined strategy of oral bisphosphonate therapy for five years and falls prevention exercise for one year, b) oral bisphosphonate therapy only for five years, c) falls prevention exercise only for one year, or d) no interventions (Figure 2). We also examined an alternative scenario, in which the exercise program was applied only to those with osteoporosis in the combined strategy. Data from published meta-analyses were used to obtain the effectiveness of oral bisphosphonate therapy and falls prevention exercise in reducing the risks or the incidence rates of fractures, as applicable.

The relative risks or incidence rate ratios used in this analysis were based on the comparisons between bisphosphonate therapy and no treatment including placebo or concurrent calcium and/or vitamin D groups (concurrent calcium and/or vitamin D would also have to be given in the bisphosphonate therapy group), and between exercise and no-exercise groups (in some studies, social visits may have occurred in the no-exercise group). We did not assume that concurrent vitamin D reduced the risk of falls (12). The relative risk (or incidence rate ratio) reductions of these interventions were assumed to be identical across different ages. We also assumed that there were multiplicative effects between bisphosphonate therapy and the exercise program.

b) Falls Prevention Exercise

Multiple exercise programs have been shown to prevent falls, but no one program is clearly superior to another (12). Therefore, we selected one of the widely available programs, the Otago Exercise Program, to make our analysis more realistic (14, 22-25). Every participant either in the combined strategy or exercise only arms was invited to receive one year of the Otago Exercise Program in the base case. In sensitivity analyses, we examined an alternative scenario in which this exercise program was offered for two years, assuming the same persistence and adherence rates as those in one year.

The Otago Exercise Program combines individually tailored and progressive muscle-strengthening and balance-retraining exercises with a walking program. A physical therapist or a specially trained nurse makes a one-hour home visit and three half-hour home visits over the first two months. Each participant is prescribed a 30-minute program of in-home exercises selected for appropriate and increasing levels of difficulty, and a walking plan. The participants are encouraged to complete the exercises three times a week and to walk outside the home at least twice a week.(14, 24)

The Otago Exercise Program is considered to be highly effective, feasible, and appropriate for older adults with different levels of fall risk, and a recent cost-benefit analysis in the U.S. setting showed that the program provided a positive net benefit and was cost saving compared with no intervention (16). The program was first implemented in New

Zealand, and has been widely disseminated in the United States and worldwide (26).

We assumed that 42% of those initially invited to the exercise program actually accepted an invitation and started the program, based on the studies included in the meta-analysis (24). The meta-analysis included four studies and three of these were used to calculate the proportion of those accepting exercise; the fourth study was not used because it only included participants who took a benzodiazepine, any other hypnotic, or any antidepressant or major tranquilizer at the time of study recruitment. We did not take into account the potential difference in the proportion of those accepting exercise between clinical trials and the community setting, as one of the three studies above was designed in routine clinical practice in the community and the acceptance ratio seemed to be similar to studies conducted in a research setting. In deterministic sensitivity analyses, the proportion of individuals accepting the program was varied between 21% and 63%. We assumed that on average a fracture happened in the middle of a given cycle (i.e., 6 months), and that those who developed a fracture still continued the exercise program. We assumed that those not participating in an exercise program continued not to participate in an exercise program after a fracture. The persistence rate in the Otago Exercise Program was reported to be 89% in one year, and 56% of those who stayed at the program in one year exercised twice or more per week (25). We also did not assume that the potential differences in the persistence or adherence rates between trial and community setting affected the effectiveness of the exercise

program, as there are no reliable data available in the United States regarding the persistence or adherence rates after the programs are implemented in the community.

We assumed that all hip, wrist and other osteoporotic fractures, and one third of clinical vertebral fractures, are caused by falls (27, 28), and that exercise reduced the risks of these fractures in the base case. We also assumed that the proportions of fractures that result from falls are the same for hip, wrist, or other osteoporotic fractures; therefore the effects of falls prevention exercise on fractures are modeled as the same for hip, wrist or other osteoporotic fractures. We modeled the incidence rate ratio of hip, wrist, or other osteoporotic fractures with exercise (0.65, 95% CI: 0.53-0.81), or that of clinical vertebral fractures with exercise (0.88, 95% CI: 0.84-0.94) based on the results of the incidence rate ratio of fall-related injuries associated with exercise from a meta-analysis of individual-level data as the base case (24). We also assumed that the effects of exercise started immediately and disappeared immediately once a participant completed the program (29). We assumed no adverse events from exercise.

c) Bisphosphonate Therapy

In the model, every participant in the combined strategy or bisphosphonate therapy arms received an initial dual-energy X-ray absorptiometry (DXA) measurement of the femoral neck and the lumbar spine. We offered generic alendronate 70 mg once weekly for

five years for those who had osteoporosis defined as a T-score of less than or equal to negative 2.5 either in the femoral neck or the lumbar spine (6, 7, 20, 30). The effectiveness (relative risk reduction) of alendronate for prevention of osteoporotic fractures in postmenopausal women was derived from a meta-analysis, which showed a relative risk of 0.47 (95% CI: 0.26-0.85) for hip fractures, 0.55 (95% CI: 0.43-0.69) for vertebral fractures, 0.50 (95% CI: 0.34-0.73) for wrist fractures, and 0.77 (95% CI: 0.64-0.92) for other osteoporotic fractures.(31)

The National Osteoporosis Foundation recommends bisphosphonates as a pharmacological intervention in postmenopausal women with 1) a history of hip or vertebral fractures, 2) a T-score of bone mineral density (BMD) ≤ -2.5 at the femoral neck or spine after appropriate evaluation to exclude secondary causes, or 3) a T score between -1 and -2.5 at the femoral neck or spine and a 10-year probability of hip fracture ≥ 3% or 10 -year probability of any major osteoporosis-related fracture ≥20% based on the US-adopted WHO Fracture Risk Assessment Tool (FRAX®) algorithm (32). We did not, however, incorporate future fracture risks into the model because the effectiveness of bisphosphonate therapy for populations identified in this manner has not yet been proven in a large clinical trial (20, 33). The prevalence of osteoporosis in non-Hispanic white women with different age ranges (i.e., 65-69 years old, 70-79 years old, and 80 and over years old) in the United States was estimated from published literature that presents the prevalence of femoral neck or lumbar

spine T-score ≤ -2.5 from the National Health and Nutrition Examination Survey (NHANES) 2005-2010 (34). As the article presented values age 60-69 and 70-79, these values were used as reasonable estimates for age 65 and 75 respectively, in order to interpolate the values age 65-69.

Medication persistence and adherence may affect both costs and effectiveness of oral bisphosphonate therapy and are therefore important model parameters (35, 36). Persistence refers to "the duration of time from initiation to discontinuation of the therapy" and adherence, which is a synonym for compliance, refers to "the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen" (37). In U.S. studies, one year after initiation of treatment, about half of patients had discontinued oral bisphosphonate therapy with the range varying significantly across the studies. Persistence with bisphosphonate has not been well described beyond one year (4, 38). In base case analyses, the discontinuation rate was assumed to be 48% by the end of first cycle (one year) (39), and that those who had not discontinued bisphosphonates by the end of the first cycle continued to take bisphosphonates for a total of five years.

Adherence rates to bisphosphonates also varied substantially in the peer-reviewed literature, but rates were higher in clinical trials (mostly greater than 80%, as high as 100%) than observational studies (mostly under or around 50%, as low as 32%) that reflected actual clinical settings (4). We therefore incorporated impact of medication adherence in the model.

A linear relationship was assumed between a relative risk reduction and medication adherence, and conservatively assumed that the relative effectiveness of bisphosphonates in the community is 62.5% (50% community adherence/80% trial adherence) of that of clinical trials. In sensitivity analyses, adherence rates were varied between 32% and 80%, which made relative effectiveness in the community compared with clinical trials between 40% (assuming 32% community adherence/80% trial adherence) to 100% (assuming 80% community adherence/80% trial adherence) (4).

We assumed that not every participant who was initially offered bisphosphonates continued to take the generic version because of participants' preference or intolerance (40), in agreement with the assumptions of previous studies (20, 33). The costs of generic and brand-name alendronate (Fosamax) were different as described below in the Cost section, but the effectiveness, the persistence rate, and the adherence rate were assumed to be the same. The costs were assumed to be proportional to persistence in taking bisphosphonates. We also assumed that those who took bisphosphonates and developed a fracture continued for a total of five years of bisphosphonates from the initiation of bisphosphonates with the same persistence and adherence, as there does not appear to be an association between prior history of fracture and persistence or adherence to bisphosphonates (4). Those who initially did not take bisphosphonates continued not to take bisphosphonates after a fracture in this model (41).

We assumed that those who discontinued their bisphosphonates in the first cycle did not accrue any benefits (30, 33). We also assumed that bisphosphonate therapy was effective at reducing the risk of fractures in the first year through fifth year, and the risk for fracture returned to rates in the absence of bisphosphonate therapy over five years in a gradual linear fashion after completing the therapy, as has been consistently assumed in previous cost-effectiveness analyses (6, 7, 20, 30, 33, 36).

4) Transition Probabilities

a) Fracture rates

We modeled fracture incidence rates based on U.S. hospital discharge data from 2006 and data from Olmsted County, Minnesota, both of which were used for recently updated fracture incidence rates for the U.S. version of FRAX® (42). Because the incidence rates of other osteoporotic fractures (i.e., humerus, distal forearm other than wrist, pelvis, tibia/fibula, or femur other than hip) were not available in this article, these rates were obtained from another published source (43).

To convert the population risk of fracture to the risk for individuals with osteoporosis, the fracture rates of the population were multiplied by a relative risk for the individuals with osteoporosis. The relative risks were calculated by the method that describes how to obtain the risk of fracture of those below a certain BMD threshold (i.e., T score of femoral neck

BMD less than -2.5 SD), compared, compared with that in the general population (44, 45). We used means and SD (standard deviation) of age-and sex-specific (age range 60-69, 70-79, and 80 over years) femoral neck BMD from the NHANES 2005-2008 database, assuming a normal distribution of BMD (46). The reference values for those calculations were obtained from the NHANES III database for femoral neck measurements in white women aged 20–29 years old (47). The 60-69 value and the 70-79 value were used as a reasonable estimate for age 65 and 75 respectively, in order to interpolate the values to obtain the 65-69 value. Age-adjusted relative risks associated with one SD decrement in the hip BMD were estimated to be 1.8 (95% CI: 1.1-2.7), 1.4 (95% CI: 1.4-1.6), and 1.6 (95% CI: 1.4-1.8) for clinical vertebral fractures, wrist fractures, and other osteoporotic fractures, respectively (48). For hip fractures, age-specific relative risks associated with one SD decrement in the femoral neck BMD were provided every 5 years of age (i.e., 65, 70, 75, 80, and 85), and were estimated to be 2.9 (95% CI: 2.4-3.5) for age 65, 2.8 (95% CI: 2.4-3.2) for age 70, 2.6 (95% CI: 2.3-2.9) for age 75, 2.3 (95% CI: 2.1-2.5) for age 80, and 1.9 (95%CI: 1.8-2.1) for age 85, respectively (49). We interpolated linearly to estimate the relative risks between these ages.

We also calculated the relative risk for individuals without osteoporosis compared with the general population by (1-(relative risk associated with osteoporosis*prevalence of osteoporosis))/(1-prevalence of osteoporosis). The risks for fractures in the model were then calculated as follows: (age, sex, and race/ethnicity-specific fracture risk in the general

population)* (relative risk based on the presence or absence of osteoporosis)* (1- relative risk reduction (or incidence rate ratio reduction) provided by the interventions, if any).

In addition, we modeled increased relative risks of second and subsequent fractures associated with prior fractures at the same location (i.e., relative risks were 2.3 for hip, 4.4 for vertebral, and 3.3 for wrist fractures, respectively) (45, 50). We did not consider increased relative risks of second and subsequent fractures associated with other osteoporotic fractures. In a previous cost-effectiveness analysis, an approach was taken in which the same age, sex, and race/ethnicity-specific fracture incidence rates for the second and subsequent fractures were conservatively applied. These two approaches were compared and the results were found to be comparable in the U.S. setting (6).

b) Mortality rates

Background mortality rates were obtained from the 2010 U.S. vital statistics table (51). The table provided the annual mortality rates up to age 100, and the cumulative death rates were 97.0%, 96.8%, 96.5%, and 95.9% by age 100, depending on a starting age of 65, 70, 75, and 80, respectively. We therefore extrapolated the annual mortality rates up to age 105 by assuming that the rate of increase in annual mortality rates between 94-95 years of age and 98-99 years of age was maintained in a linear fashion from 100 to 105 years of age.

The excess mortality rates after a hip fracture (either a first or recurrent hip fracture) in the short- term (within a year) and long- term (starting in the second year and continuing lifelong), defined as background mortality rates*(relative hazard for all-cause mortality after a hip fracture –1), were obtained using a recent meta- analysis (52). We incorporated the excess mortality after a hip fracture lifelong, as the study showed the excess mortality appeared to be stable from the second year onward and did not return to the age- and sex-matched baseline even after 10 years. We conservatively assumed that hip fracture events only contribute to 25% of the excess mortality, as comorbidities appear to play a large role (53, 54). We did not assume excess mortality associated with clinical vertebral, wrist fractures, or other osteoporotic fractures (6, 20, 30, 33). In an alternative scenario, however, we assumed the same impact on mortality after clinical vertebral fractures as after hip fractures.

Mortality rates were calibrated for those without excess mortality associated with hip fractures in order to obtain similar mortality rates for our cohort as a whole (those with and without hip fractures combined, or those with and without hip and clinical vertebral fractures combined in the alternative scenario), when compared with the U.S. vital statistics table.

5) Utilities

We used the generic EQ-5D based on U.S. noninstitutionalized population data to obtain age and sex specific baseline health state utility values (i.e., ages 60-69, 70-79, and 80-89) (55). The values ages 60-69 and 70-79 linearly interpolated to estimate the value ages 65-69. We estimated the value of utility of women aged 90 and beyond by applying the same amount of the decrement of utility between women ages 70-79 and 80-89 to the amount of the decrement between women ages 80-89 and ages 90-105 (i.e., baseline utility: 0.771 for ages 70-79, 0.724 for ages 80-89, and 0.677 for ages 90-105). EQ-5D is a preference-based utility instrument that can describe 243 unique health states and assesses health related quality of life attributes. Generic instruments can make comparisons across different diseases or health statuses possible.

Fractures are associated with disutility, which is a loss in health-related quality of life. We assumed that disutilities associated with hip or clinical vertebral fractures were highest in the year immediately following the fracture, but persisted for the rest of life (41, 56). In contrast, no long-term disutility was assigned to wrist fracture or other osteoporotic fracture beyond one year (57, 58). We obtained multipliers for the proportionate effect of hip and clinical vertebral fractures on utility based on a meta-analysis and a cost-effectiveness analysis, both of which were recently written by Si et al. (41, 56). In Si's meta-analysis, however, the point estimate of utility values for the post-wrist fracture state exceeded those of

the pre-fracture state. The meta-analysis also did not include an estimate of other osteoporotic fracture. Therefore, the multipliers of wrist fracture or other osteoporotic fracture were estimated based on another meta-analysis (57). We focused on fracture prevention in this study, and therefore did not impose any disutility for a fall itself or a fear of falling.

6) Costs

We included costs of bisphosphonates, the falls prevention exercise program, physician visits, DXA scans, fracture-related treatments, and institutional long-term care after a hip fracture. The cost of bisphosphonates was based on the retail cost of generic alendronate (annual cost is $104 at Walmart pharmacy) and the cost of non-generic bisphosphonates (annual cost was estimated to be $1,500) (59, 60). In the base case, we assumed 89% of those who were offered generic alendronate continued to take a generic product, and 11% switched to the branded product, making the annual cost of bisphosphonates $258. This assumption was based on a study that reported the switching patterns of alendronate (i.e., stayed on the branded product, switched to a generic product, and switched to other bisphosphonates) after generic alendronate was released on the market using Medicare prescription drug claims data (40). The study reported that of those who continued bisphosphonates, 10% stayed on the branded product, 89% switched to a generic product, and 1% switched to other bisphosphonates. For simplicity, we assumed that the cost

and the effectiveness of branded alendronate and other bisphosphonates were the same, as the ranges of these costs and effectiveness are similar (4, 60). In deterministic sensitivity analyses, we used a range of cost between $104 (assuming everyone used a generic version) and $1500 (assuming everyone used the brand version). In addition, based on the adherence rate to bisphosphonates in the community (assuming 50% in the base-case) (4), we estimated an annual cost of bisphosphonates in the community at $129 ($258*0.5). We charged cost for three months' supply of generic alendronate (i.e., a single prescription filled) for those who discontinued bisphosphonates within the first year in the base-case.

The cost for exercise consisted of the exercise program cost and the opportunity cost of time spent in the program. The estimated cost for the Otago Exercise Program at base case was obtained from a recent cost-benefit analysis in the U.S setting. In the analysis, the cost for the exercise program was estimated retrospectively based on the descriptions of the intervention in published literature along with direct communications with program developers. The total cost (i.e., advertisement of the program, training physical therapists, delivery the program, and follow-up) was calculated by multiplying the amount of resources used to implement the program by the resource unit cost. Then, the average cost per participant was calculated by dividing the total cost by the number of participants (16).

Time costs (i.e., opportunity cost for time spent in exercise program) of the participants to attend the program were calculated based on the sex-, age-, and race-specific

(65-69, 70-74, and 75+) rates of labor force participation of seniors in 2014 (i.e., white women 65-69: 28.0%, 70-74: 15.9%, 75+: 5.8%) (61), and median weekly earnings of full-time workers by sex and age in 2007 (women 65+: $604/week, inflated to 2014 U.S. dollars) (62). We assumed that a full time-worker worked for 40 hours per week, making her wage $15/hour. We assumed that on average the Otago Exercise Program took a total of two hours per week (based on the finding from a meta-analysis showing that 55.9% reported performing exercise twice or more per week at 12 months (25)) for a total of 48 weeks per year, and estimated the annual time costs of the participant as follows at base case: (hourly wage)*2*48*(proportion of participants in the labor force). In sensitivity analyses, time cost was ranged from zero (no time cost) to full labor force participation.

For the assumed costs of physician visits and DXA scans, allowable charges based on the 2014 Medicare reimbursement for a level 3 physician visit and DXA scan were used (63). We assumed the cost of DXA was $100 in the base case. As the lower bound for sensitivity analysis, we used $49.44 (the 2014 Medicare reimbursement for office-based physicians who are not connected with a facility; the non-facility price for CPT 77080 in the fee schedule lookup). As the upper bound for sensitivity analysis, we used $149.79 ($49.44 + 100.35; the total physician plus facility reimbursement at a facility-based setting for CPT 77080). As the base case, we used the average of the upper and lower bounds, making $100 as the cost for DXA. Every participant had a physician visit in the first year. Those who took

bisphosphonates were assumed to have an additional physician visit each year and to incur the cost of an additional DXA scan two years after the initiation of treatment (6, 30).

We obtained costs for fractures including inpatient, skilled nursing facility, home health, hospice, hospital outpatient, durable medical equipment, and physician/noninstitutional claims from a published article (64). The article estimated both incremental costs (difference between overall healthcare payments in six months before and after fracture), and attributable costs (payment associated with primary fracture diagnosis, i.e., with care specifically related to the fracture). For the base case, we used attributable costs plus 0.25*(incremental costs-attributable cost) for hip, clinical vertebral, and wrist fractures, based on the assumption that these fracture events only contribute to 25% of the difference between incremental and attributable costs. In deterministic sensitivity analyses, we used attributable costs and incremental costs of these fractures as lower and upper ranges.

Long-term care costs associated with hip fractures were assigned. We assumed 12% of those who sustained hip fractures remained at the nursing home beyond one year (65) and those who remained beyond one year required indefinite long-term care. We conservatively assumed that hip fractures themselves were directly responsible for only 25% of long-term care placements, just as we had previously assumed for the attribution of a hip fracture to the mortality risk (in other words, long-term care and/or death would have occurred regardless of the hip fracture in 75% of cases.). We used the average cost for a semi-private room at a

nursing home ($6,991 /month) (66), and estimated $2,517 ($6,991*12*0.12*0.25) per year averaged over all participants in the "post hip fracture" state until death (7, 20). In deterministic sensitivity analyses, the ranges of monthly cost for long-term care were changed and percentage of those who sustained a hip fracture who required indefinite long-term care.

The cost of loss of productivity due to a fracture was not included, as it is intended to be captured in reduced QALYs (67). All costs were presented in 2014 U.S. dollars using the Consumer Price Index for Medical Care for All Urban Consumers, or the Consumer Price Index for All Items for All Urban Consumers, depending on the nature of the cost (68). Costs were assumed to be identical regardless of age unless specified (e.g., time cost).

7) Discounting

We discounted all costs and health benefits at 3% per year for the base case (69). In probabilistic sensitivity analyses, discount rates were ranged between 0% and 5%.

8) Model Simulation and Sensitivity Analysis

a) Base Case Analyses

For base case analyses, we ran the model with 1,000,000 iterations (1,000,000 individuals through the model one at a time).

b) Deterministic Sensitivity Analyses

We conducted deterministic (one-way) sensitivity analyses with 1,000,000 iterations. Different assumptions were evaluated for critical model parameters in deterministic sensitivity analyses, including incidence rate ratio of hip, wrist, or other osteoporotic fractures with exercise, incidence rate ratio of clinical vertebral fractures with exercise, probability of starting the exercise program, relative risk of fractures with bisphosphonates, cumulative persistence rate of bisphosphonates at the end of the first year, relative effectiveness of bisphosphonates in the community, annual costs for bisphosphonates and the exercise program, annual opportunity cost for time spent in the exercise program, direct medical costs for fractures, annual cost for the post-hip fracture state, and prevalence of osteoporosis to examine the robustness of the results when the values of base case assumptions changed. Upper and lower values for deterministic sensitivity analyses and probability distributions were created based on 95% confidence intervals or a reasonable range from the existing literature, or our own assumptions only if no published estimates were available.

c) Alternative Scenarios

We also examined different scenarios in which a) in the combined strategy, the exercise program was offered only to those with osteoporosis (i.e., a T-score of less than or equal to

negative 2.5 either in the femoral neck or the lumbar spine), b) the exercise program was extended to two years (in this scenario, in the second year we assumed the same effectiveness, persistence, and adherence rates and the same total costs as in the first year (both the program cost and the opportunity cost), under the assumption that a participant needed an equivalent number of in-person sessions and telephone follow-ups in the second year as in the first year to continue to exercise), and c) clinical vertebral fractures had the same impact on extra mortality as did hip fractures.

d) Probabilistic Sensitivity Analyses

In addition, we performed probabilistic sensitivity analyses for individuals ages 65, 70, 75, and 80. Probabilistic sensitivity analyses included probability distributions for uncertain key model inputs. Monte Carlo simulation was performed with 200 simulations and 10,000 trials per simulation. Parameter values were randomly selected from the probability distributions. The beta distribution was chosen for incidence rate ratios or relative risks of fractures with interventions, cumulative persistence rate at the end of the first year, utilities, and prevalence of osteoporosis. The gamma distribution was used for relative risks of fractures for individuals with osteoporosis, fracture incidence rates associated with subsequent fractures at the same location, and relative hazard for mortality after a hip fracture. Treeage software can approximate the parameters of some distributions (e.g., beta or

gamma) based on certain statistical values. Means and SDs, which were estimated based on the 95% confidence intervals, were used to obtain the parameters for the beta or the gamma distributions. The triangular distribution was used for the rest of the parameters that required a distribution. Point estimates for mortality rates were used from Centers for Disease Control and Prevention life table, and annual fracture incidences per 1,000 persons without intervention for the U.S. version of FRAX® (42) (Table 1).

Results

1) Model Validation:

a) Mortality

Our model predicted that without an intervention cumulative death rates at age 100 with different starting ages (97.0%, 96.8%, 96.5%, and 95.9% with a starting age of 65, 70, 75, and 80, respectively), were consistent with those in the life table for the U.S. non-Hispanic white women, and 99.6% (starting age 80) or 99.7% (starting ages 65, 70, and 75) died by age 105.

b) Lifetime Fracture Risk

Our model predicted that the probabilities of a woman age 65 having at least one hip, clinical vertebral, or wrist fracture over their lifetime without an intervention were 19.1%, 11.2%, or 16.0%, respectively.

c) Cost-Effectiveness of Oral Bisphosphonate Therapy Compared with No Intervention

Our model showed that bisphosphonates were cost-saving compared with no intervention at all ages examined.

2) Base Case Analysis (Table 2)

At ages 65, 70, 75 and 80, the total costs and QALYs of the combined strategy were $9,990 and 11.532, $10,476 and 9.653, $10,601 and 7.851, and $10,135 and 6.031, respectively, resulting in ICERs of $202,020, $118,460, $46,870, and $17,640 compared with oral bisphosphonate therapy alone. At ages 65, 70, 75, and 80, the total costs and QALYs of falls prevention exercise were estimated to be $9,964 and 11.519, $10,567 and 9.636, $10,784 and 7.829, and $10,523 and 6.008, respectively, making the combined strategy providing better health at lower cost than falls prevention exercise alone at ages 65, 70, and 75. In other words, falls prevention exercise alone was dominated by the combined strategy at those ages.

3) Deterministic Sensitivity Analysis (Figure 3)

In deterministic sensitivity analyses, results were sensitive to the changes in the opportunity cost of time spent exercising at both ages 75 and 80, and changes in the incidence rate ratio of hip, wrist, or other osteoporotic fractures with exercise at age 75, with ICERs of the combined strategy compared with oral bisphosphonate therapy exceeding a willingness-to-pay of $100,000 per QALY when individual parameters were ranged towards their least favorable values. (In the base case analysis, ICERs were less than $100,000 per QALY at ages 75 and 80). On the contrary, at ages 65 or 70, ICERs became less than

$100,000 if any of the following parameters were ranged towards their most favorable values: the opportunity cost of time spent exercising at both ages 65 and 70; the incidence rate ratio of hip, wrist, or other osteoporotic fractures with exercise; the prevalence of osteoporosis; or the cost of the exercise program at age 70. (In the base case analysis, ICERs were greater than $100,000 per QALY at ages 65 or 70).

4) Alternative Scenarios (Table 3)

The first alternative scenario, in which exercise was provided only to those with osteoporosis, provided favorable ICERs compared with those in base case analyses at ages 65, 70, and 80, and was cost-saving at age 75. The second alternative scenario, in which exercise was extended to two years, provided similar ICERs to the base case. The third alternative scenario, in which clinical vertebral fractures had the same impact on extra mortality as hip fractures, also provided similar ICERs to the base case.

5) Probabilistic Sensitivity Analysis (Figure 4)

The acceptability curves provided by probabilistic sensitivity analyses showed that the probabilities of the combined strategy being cost-effective compared with the next best alternative were 35%, 40%, 42%, and 48% for ages 65, 70, 75, and 80 respectively, at a willingness-to-pay of $100,000 per QALY. At all ages, there was a tendency for the

probability of the combined strategy being cost-effective to increase as willingness-to-pay increased from $50,000 per QALY to $150,000 per QALY.

Discussion

Our analysis revealed that at ages 75 and 80 the combined strategy of oral bisphosphonate therapy and falls prevention exercise was cost-effective compared with either strategy alone at conventionally accepted thresholds of willingness-to-pay. The sensitivity of the results to the starting age of the cohort reflects increased absolute rates of hip, clinical vertebral, or other osteoporotic fractures over the age range in the model (42), making the absolute reduction in the number of these fractures highest at age 80, although the effectiveness (i.e., incidence rate ratio) of the exercise program was modeled as constant over all ages in the base case. We also modeled the value of foregone time participating in the exercise program as declining with advancing age, as a function of the rate of the labor force participation. Thus, the natural history of osteoporotic fracture risk, coupled with the availability of time to exercise relative to alternatives, could explain our findings. Previous economic evaluations of the Otago exercise program corroborate these results (15, 16).

The model predicted that the probabilities of a woman age 65 having at least one hip or wrist fracture over their lifetime without an intervention were 19.1%, and 16.0%, respectively. One study estimated that based on the 5% U.S. Medicare sample between 1986 and 1990, the respective risks of a 65 year old white woman sustaining a hip fracture and wrist fracture by age 90 were 16% and 9% (70). This study estimated the lifetime risk until age 105, which may be one of the reasons that this study generated a higher estimate than this

previous work. Although it is still not entirely clear the reason why the estimated lifetime risk of developing a wrist fracture was considerably higher than previously reported, we assume that it probably would not substantially affect the overall results, as in deterministic sensitivity analyses we found the change in the relative risk of wrist fracture with bisphosphonates had just a small impact on the ICERs of the combined strategy when compared with oral bisphosphonates therapy. In addition, one previous cost-effectiveness analysis in the U.S. setting estimated a lifetime risk of wrist fractures for white women age 65 at 17%, which was similar to our estimate (33). This model also predicted that the probability of a woman age 65 having at least one clinical vertebral fracture over her lifetime without an intervention was 11.2%. One previous study in the United States estimated that a 65 year old white woman's risk of developing a vertebral fracture by age 94 was 28% (71), and it has been assumed that 25-33% of vertebral fractures are clinically apparent (72). This result, therefore, appeared to be consistent with that of the previous study.

This study showed that bisphosphonates were cost-saving compared with no intervention at all ages examined. The results of this study agreed with previous studies showing that bisphosphonates were cost-saving compared with no intervention at age 75 and 80 in the U.S. setting (6, 7). Bisphosphonates were, however, shown to be cost-effective (not cost-saving) at age 70 in these two studies and to be cost-effective (not cost-saving) at age 65 in one of these studies. One of the main reasons for the discrepancies between this study and

these other studies at age 65 and 70 is likely because only brand bisphosphonates were available at the time of the previous studies, making costs of bisphosphonates in these studies more expensive than that of our study.

A previous study suggested that the Otago Exercise Program could be more effective (i.e., lower incidence rate ratio for injurious falls) in older populations, especially over age 80, when compared with in younger populations (24). This possibility would reinforce the main finding that the combined strategy might be more cost-effective for older populations (i.e., over age 80), taken together with the results of our deterministic sensitivity analysis showing that ICERs would become more favorable if exercise is more effective (i.e., lower incidence rate ratio) in reducing hip, wrist, or other osteoporotic fractures at age 80.

In the base case analysis, the ICERs of the combined strategy compared with oral bisphosphonate therapy were $46,870, and $17,640 per QALY at ages 75 and 80, respectively. In deterministic sensitivity analyses, the results were sensitive to the changes in the opportunity cost of time spent exercising at both ages 75 and 80, and the change in the incidence rate ratio of hip, wrist, or other osteoporotic fractures with exercise at age 75, with ICERs of the combined strategy compared with oral bisphosphonate therapy exceeding a willingness-to-pay of $100,000 per QALY when individual parameters were ranged towards their least favorable values. If the annual opportunity cost for time spent in an exercise program was set at $1,440, the total annual cost for the exercise program became $1,796.

Compared to a total annual cost for the exercise program of $440 in the base case for ages 75 and 80, it is not surprising that the ICERs were particularly sensitive to a large change in the opportunity cost. The change in the incidence rate ration of hip, wrist, or other osteoporotic fractures with exercise at age 75 resulted in the changes in both costs and effectiveness of the combined strategy, but not in the changes of those in oral bisphosphonate therapy.

On the contrary, at ages 65 or 70, the ICERs of the combined strategy compared with oral bisphosphonate therapy were $202,020, $118,460, respectively. The ICERs became less than $100,000 if any of the following parameters were ranged towards their most favorable values: the opportunity cost of time spent exercising at both ages 65 and 70; the cost of the exercise program, the incidence rate ratio of hip, wrist, or other osteoporotic fractures with exercise; or the prevalence of osteoporosis at age 70. If the annual opportunity cost for time spent in an exercise program was set at $0 at ages 65 and 70, the total annual cost for the exercise program became $356. Compared to a total annual cost for the exercise program of $759 and $585 at ages 65 and 70 in the base case, respectively, it is also not surprising that the ICERs were sensitive to a change in the opportunity cost. Similarly, the cost of the exercise program only affected the cost of the combined strategy without affecting the cost of oral bisphosphonate therapy. The change in the incidence rate ration of hip, wrist, or other osteoporotic fractures with exercise at age 75 resulted in the changes in both costs and effectiveness of the combined strategy, but not in the changes of those in oral bisphosphonate

therapy. Finally, the prevalence of osteoporosis could make a large impact on the costs and effectiveness of the combined strategy and oral bisphosphonate therapy alone by affecting not only the costs for bisphosphonates and for treatment for osteoporotic fractures, but also incidences of the osteoporotic fractures for a total of 10 years; In the mode, we assumed that bisphosphonates reduce the risk of hip, clinical vertebral, wrist, and other osteoporotic fractures (as opposed to the falls prevention exercise that was effective only for hip, wrist, or other osteoporotic fractures, and not for clinical vertebral fractures), and that those who had not discontinued bisphosphonates by the end of the first cycle continued to take bisphosphonates for a total of five years, and the risk for fracture returned to rates in the absence of bisphosphonate therapy over five years in a gradual linear fashion after completing the therapy.

Probabilistic sensitivity analyses showed that in 35% to 48% of iterations, the combined strategy was cost-effective compared with the next best alternative among the four strategies being evaluated. The differences, however, in costs and effectiveness between the four strategies were so close to each other that all of the four strategies became cost-effective in a non-trivial set of iterations at all ages examined. This may reflect our decision to build a model conservatively by trying to incorporate data from community settings as much as possible, and therefore may suggest that patient preference and values are especially important determinants of how clinicians should think about the preferred strategy.

Probabilistic sensitivity analyses also showed that the exercise program alone was least likely to be cost-effective at all ages examined. However, it is important to note that this study does not focus on the cost-effectiveness of an exercise program as a single therapy, compared with oral bisphosphonate therapy. Instead, our intention was to compare the cost-effectiveness of the combined strategy with either strategy in isolation. We offered five years of oral bisphosphonate therapy and one year of falls prevention exercise (most of the previously published studies regarding the Otago exercise program last up to one year (14, 24), therefore making it appropriate to model the exercise program for one year in the base case), and the effectiveness of bisphosphonates lasts up to 10 years from treatment initiation while that of the exercise program lasts only one year from program initiation in the base case. In fact, an alternative scenario in which the exercise program was extended to two years provided more favorable ICERs of the combined strategy compared with oral bisphosphonate therapy at all ages examined. Furthermore, some of those who participated in the exercise program might continue to exercise beyond one year (or two years in the alternative scenario), which would probably provide even more favorable ICERs of the combined strategy compared with oral bisphosphonate therapy.

Under an alternative scenario in which an exercise program was only offered to individuals with osteoporosis (i.e., a T-score of less than or equal to negative 2.5 either in the femoral neck or the lumbar spine), the results were either more cost-effective (i.e., ages 65,

70, and 80), or outright cost-saving (at age 75). This finding suggests that if exercise cannot be offered to the entire population due to resource constraints, targeting exercise for those with osteoporosis may work better from a health economic point of view, especially if fracture reduction is the primary focus.

We noted several limitations. First, our results may be best applied to U.S. white women, and may not generalize to women of other races/ethnicities, or men. We chose to focus on white women for this analysis because white women are a high-risk group for fracture (6). Second, we did not impose any disutility for a fall itself or for fear of falling, as we focused on fracture prevention in this study. In addition, we did not model non-fracture-related benefits from regular exercise, such as cardiovascular benefits. All of these modeling decisions might have underestimated the effects of the interventions. If we assume the exercise program would be effective at reducing other risks that were not included in the model, the ICERs of the combined strategy compared with bisphosphonate therapy would probably be more favorable. Third, we assumed multiplicative treatment effects in the combined strategy, as to our knowledge there has been no large clinical trial to examine the effectiveness of the combined strategy. In addition, we focus only on oral bisphosphonate therapy and the Otago Exercise Program out of available alternatives (e.g., treatments for osteoporosis such as once- yearly zoledronic acid, denosumab, or teriparatide, or other types of falls prevention exercise programs such as Tai-Chi). However, we performed extensive

deterministic sensitivity analyses, potentially addressing the costs, persistence and adherence rates, and effectiveness of at least some of these alternatives. Finally, to keep the model parsimonious, we did not simulate the discontinuation of bisphosphonates beyond the first year (e.g., we assumed that those who completed bisphosphonates at the end of the first year would continue to take bisphosphonates for a total of 5 years), some contraindications (e.g., avoidance of bisphosphonates for those with a creatinine clearance less than 30 mL/min) or adverse events (e.g., gastrointestinal side effects of bisphosphonates) (4).

Despite these limitations, this study has notable strengths. First, to our knowledge, this is the first economic evaluation to examine the combined strategy of oral bisphosphonate therapy and falls prevention exercise. Cost-effectiveness analysis has an advantage of estimating costs and effectiveness of different interventions for lifetime with simulating extremely large number of participants with different starting ages, and calculating ICERs that represent cost per QALY gained for one strategy compared with the others. Second, our model reflects actual clinical settings in the community as much as possible while keeping the model parsimonious. To do so, a conservative approach was taken to estimate parameters. For example, we incorporated medication persistence and adherence in the community into the model to conservatively estimate the effectiveness of bisphosphonates. We also estimated the cost of bisphosphonates more expensive than the generic version, in the case of participants' preference or intolerance. In addition, we realistically modeled only one year of

the exercise program and exercise did not reduce the risk of clinical vertebral fractures as much as that for hip, wrist, or other osteoporotic fractures. Furthermore, we assumed that only 25% of deaths and long-term care placements after a hip fracture were attributable to the hip fracture itself. Third, the model we developed in this study will allow us to perform cost-effectiveness analyses to address not only the alternatives mentioned above, but also new osteoporosis medications, interventions of falls prevention, or a combination of these, in the same U.S. setting or in a different healthcare system such as in Japan in the future.

In conclusion, for community-dwelling U.S. white women ages 75 and 80, adding one year of exercise to five years of oral bisphosphonate therapy is cost-effective at conventionally accepted thresholds, compared with oral bisphosphonate therapy only. The combined strategy of oral bisphosphonate therapy and falls prevention exercise is potentially more cost-effective for older ages (75 and 80), and also for younger ages (65 and 70) at high risk of fracture (i.e., osteoporosis defined by DXA). This study provides new insight about the combined benefits of oral bisphosphonate therapy and falls prevention exercise, and will help clinicians and policymakers make better decisions about treatment options to reduce fracture risk. In addition, this model can be expanded further to address cost-effectiveness of different interventions (e.g., other osteoporosis treatments and/or falls prevention interventions) in a different population (e.g., elderly men), or in a different healthcare setting (e.g., Japan) in the future.

Figure 1: Markov Diagram of Health States and Possible Transitions

Every participant transitions between health states or remains in the same state based on the assigned transition probabilities between four Markov states. Every participant starts the model in the "no fracture" state.

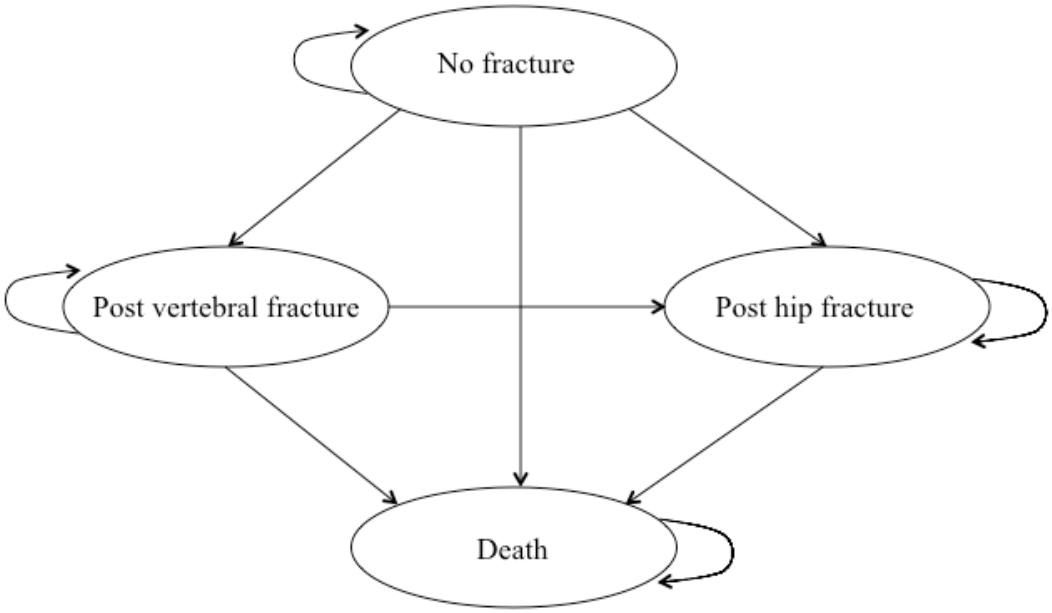


Figure 2: Model Structure

Our model consisted of four strategies: a) the combined strategy of oral bisphosphonate therapy and falls prevention exercise, b) oral bisphosphonate therapy, c) falls prevention exercise only, or d) no interventions. Parameters including probability of starting the program and the prevalence of osteoporosis (bisphosphonates were offered to those with osteoporosis) are presented in Table 1. Every participant starts the Markov diagram in the "no fracture" state as is described in Figure 1.

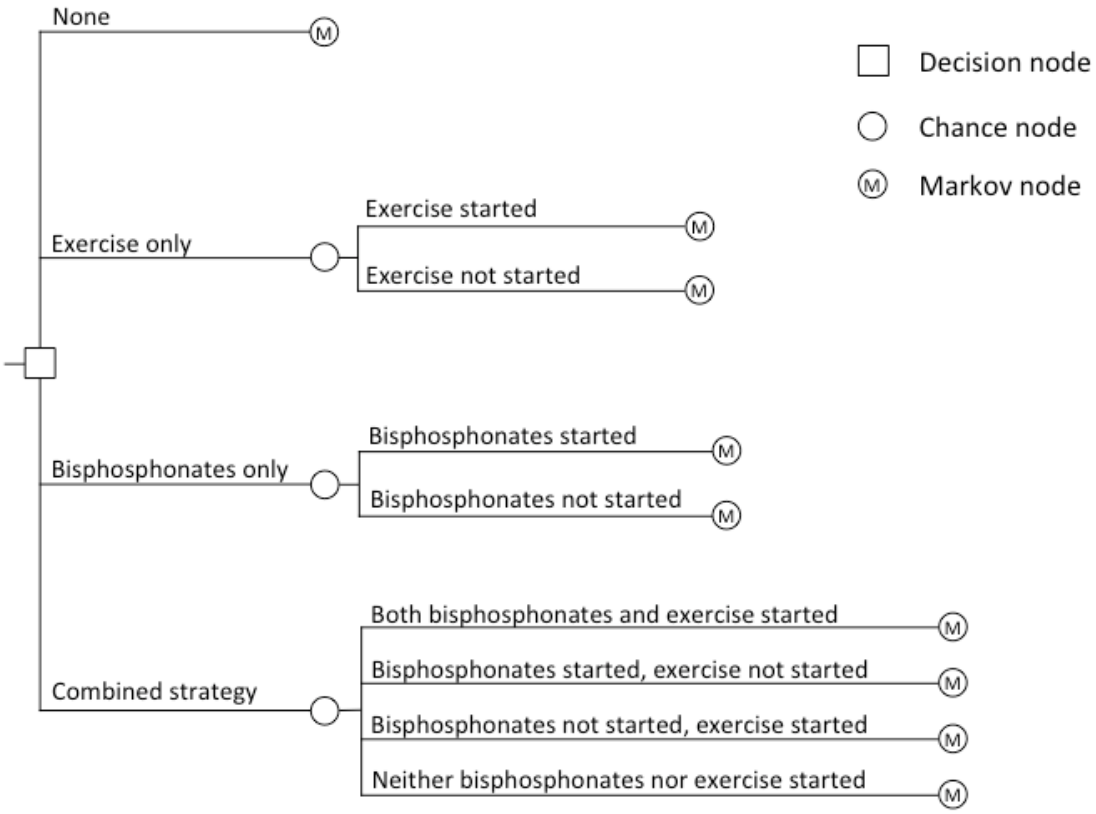


Table 1: Model Parameters

	Value	Range	Distribution	Reference
Exercise (Otago Exercise Program)				
Incidence rate ratio of hip, wrist, or other osteoporotic fractures	0.65	0.53- 0.81	Beta	(24)
Incidence rate ratio of clinical vertebral fracture	0.88	0.84- 0.94	Beta	(24, 27)
Probability of starting program	0.42	0.21-0.63[#]	Triangular	(24)
Length of program (years)	1	1 or 2	N/A	(24)
Bisphosphonate therapy				
Relative risk of hip fracture	0.47	0.26-0.85	Beta	(31)
Relative risk of clinical vertebral fracture	0.55	0.43-0.69	Beta	(31)
Relative risk of wrist fracture	0.50	0.34-0.73	Beta	(31)
Relative risk of other osteoporotic fracture	0.77	0.64-0.92	Beta	(31)
Cumulative persistence rate at the end of the first year	0.48	0.40-0.56	Beta	(39)
Length of treatment (years)	5	N/A	N/A	(6)
Relative effectiveness in community*	0.625	0.4-1.0	Triangular	(4)
Costs (2014 U.S. dollars)				
Annual cost for bisphosphonates	258	104-523	Triangular	(59, 60)
Annual cost for exercise program	356	178-534[#]	Triangular	(16)
Annual opportunity cost for time spent in exercise program (96 hours), age 65-69	403	0-1,440	Triangular	(61, 62)
Annual opportunity cost for time spent in exercise program (96 hours), age 70-74	229	0-1,440	Triangular	(61, 62)
Annual opportunity cost for time spent in exercise program (96 hours), age 75+	84	0-1440	Triangular	(61, 62)
Hip fracture, direct medical cost	26,929	23,059-38,538	Triangular	(64)
Clinical vertebral fracture, direct medical cost	7,476	5,186-14,346	Triangular	(64)
Wrist fracture, direct medical cost	4,110	2,284-9,586	Triangular	(64)
Other osteoporotic fracture, direct medical cost	12,702	9,058-23,631	Triangular	(64)
Annual cost for the post-hip fracture state	2,517	0-5,663[##]	Triangular	(65, 66)
DXA scan (CPT code 77080)	100	49-150	Triangular	(63)
Physician visit (CPT code 99213)	73	67-88	Triangular	(63)
Utilities				
Age 65-69	0.801	0.790-0.813	Beta	(55)
Age 70-79	0.771	0.758-0.784	Beta	(55)
Age 80-89	0.724	0.701-	Beta	(55)

		0.747		
Age 90-105	0.677	0.644-0.710	Beta	(55)
Hip fracture, first year (multiplier)	0.776	0.720-0.844	Beta	(41, 56)
Hip fracture, beyond first year (multiplier)	0.855	0.800-0.909	Beta	(41, 56)
Clinical vertebral fracture, first year (multiplier)	0.724	0.667-0.779	Beta	(41, 56)
Clinical vertebral fracture, beyond first year (multiplier)	0.868	0.827-0.922	Beta	(41, 56)
Wrist fracture first year (multiplier)	0.940	0.91-0.96	Beta	(58)
Other osteoporotic fracture first year (multiplier)	0.910	0.88-0.94	Beta	(58)
Annual fracture incidence per 1,000 persons (without intervention)				
Hip fracture, age 65-69	2.03	N/A		(42)
Hip fracture, age 70-74	3.94	N/A		(42)
Hip fracture, age 75-79	7.93	N/A		(42)
Hip fracture, age 80-84	14.47	N/A		(42)
Hip fracture, age 85+	26.06	N/A		(42)
Clinical vertebral fracture, age 65-69	2.33	N/A		(42)
Clinical vertebral fracture, age 70-74	4.73	N/A		(42)
Clinical vertebral fracture, age 75-79	5.23	N/A		(42)
Clinical vertebral fracture, age 80-84	6.22	N/A		(42)
Clinical vertebral fracture, age 85+	10.95	N/A		(42)
Wrist fracture, age 65-69	8.22	N/A		(42)
Wrist fracture, age 70-74	8.24	N/A		(42)
Wrist fracture, age 75-79	8.35	N/A		(42)
Wrist fracture, age 80-84	8.70	N/A		(42)
Wrist fracture, age 85+	8.49	N/A		(42)
Other osteoporotic fracture, age 65-69	6.60	N/A		(43)
Other osteoporotic fracture, age 70-74	9.84	N/A		(43)
Other osteoporotic fracture, age 75-79	14.44	N/A		(43)
Other osteoporotic fracture, age 80-84	18.06	N/A		(43)
Other osteoporotic fracture, age 85+	26.06	N/A		(43)
Prevalence of osteoporosis (T-score of Femoral Neck or Lumbar Spine ≤2.5)				
Age 65- 69	0.1777	0.14.9-0.206	Beta	(34)
Age 70- 79	0.264	0.232-0.295	Beta	(34)
Age 80+	0.358	0.309-0.407	Beta	(34)

Relative risks of fractures for individuals with osteoporosis				
Hip fracture, age 65-69	3.91	3.28-4.56	Gamma	(44, 49)
Hip fracture, age 70-74	3.13	2.80- 3.47	Gamma	(44, 49)
Hip fracture, age 75-79	2.60	2.39-2.82	Gamma	(44, 49)
Hip fracture, age 80-84	2.04	1.91- 2.17	Gamma	(44, 49)
Hip fracture, age 85+	1.92	1.78-2.05	Gamma	(44, 49)
Clinical vertebral fracture, age 65-69	2.59	1.19-4.27	Gamma	(44, 48)
Clinical vertebral fracture, age 70-79	2.15	1.15-3.15	Gamma	(44, 48)
Clinical vertebral fracture, age 80+	1.82	1.12-2.41	Gamma	(44, 48)
Wrist fracture, age 65-69	1.78	1.78-2.19	Gamma	(44, 48)
Wrist fracture, age 70-79	1.60	1.60-1.88	Gamma	(44, 48)
Wrist fracture, age 80+	1.45	1.45-1.64	Gamma	(44, 48)
Other osteoporotic fracture, age 65-69	2.19	1.78-2.59	Gamma	(44, 48)
Other osteoporotic fracture, age 70-79	1.88	1.60-2.15	Gamma	(44, 48)
Other osteoporotic fracture, age 80+	1.64	1.45-1.82	Gamma	(44, 48)
Relative risks of subsequent fractures associated with prior fractures at the same location				
Hip fracture	2.3	1.5-3.7	Gamma	(50)
Clinical vertebral fracture	4.4	3.6-5.4	Gamma	(50)
Wrist fracture	3.3	2.0-5.3	Gamma	(50)
Annual Mortality Rates				
Age 65	0.0099	N/A	N/A	(51)
Age 70	0.0156	N/A	N/A	(51)
Age 75	0.0256	N/A	N/A	(51)
Age 80	0.0429	N/A	N/A	(51)
Excess Mortality or Nursing Home Placement After a Hip Fracture				
Relative hazard for mortality within a year after a hip fracture	2.87	2.52-3.27	Gamma	(52)
Relative hazard for mortality for second year and beyond after a hip fracture	1.73	1.56-1.90	Gamma	(52)
Proportion of excess mortality after a hip fracture directly attributable to a hip fracture	0.25	N/A	N/A	(53)
Willingness-to-pay (2014 U.S. dollars)				
Willingness-to-pay	100,000	50,000, 150,000	N/A	(20)
Annual discount rate				
Costs	0.03	0, 0.05	Triangular	(69)
Quality-adjusted life-years	0.03	0, 0.05	Triangular	(69)

* Relative effectiveness of bisphosphonates due to lower adherence to bisphosphonates in the community than in the clinical trials.

Sensitivity values 50% lower and 50% higher than the base case value.

Based on our assumptions.

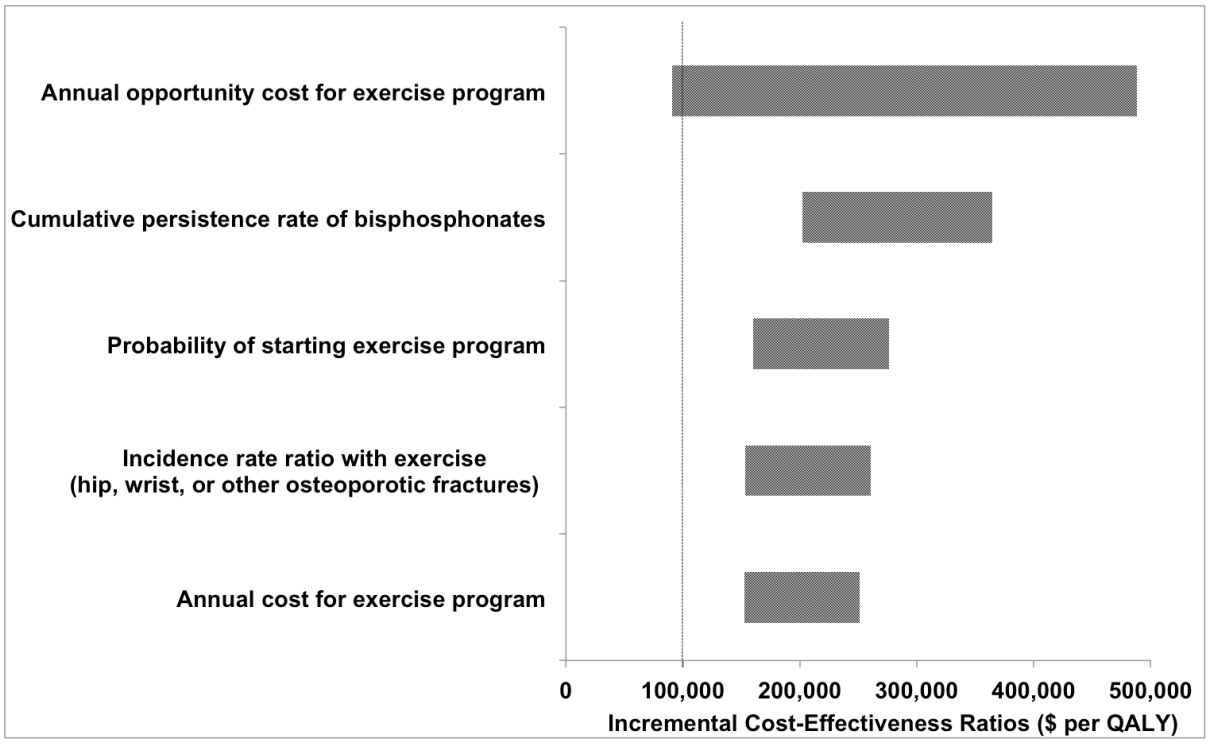
Table 2: The Results of the Base-Case Analyses

	Lifetime Cost, $	Quality-Adjusted Life-Years	Incremental Cost-Effectiveness Ratio
Age 65			
None	9,699	11.518	Dominated
Bisphosphonates	9,683	11.530	Comparator
Exercise	9,964	11.519	Dominated
Combined	9,990	11.532	202,020
Age 70			
None	10,354	9.634	Dominated
Bisphosphonates	10,272	9.651	Comparator
Exercise	10,567	9.636	Dominated
Combined	10,476	9.653	118,460
Age 75			
None	10,718	7.828	Dominated
Bisphosphonates	10,513	7.849	Comparator
Exercise	10,784	7.829	Dominated
Combined	10,601	7.851	46,870
Age 80			
None	10,465	5.999	Dominated
Bisphosphonates	10,052	6.026	Comparator
Exercise	10,523	6.008	Dominated
Combined	10,135	6.031	17,640

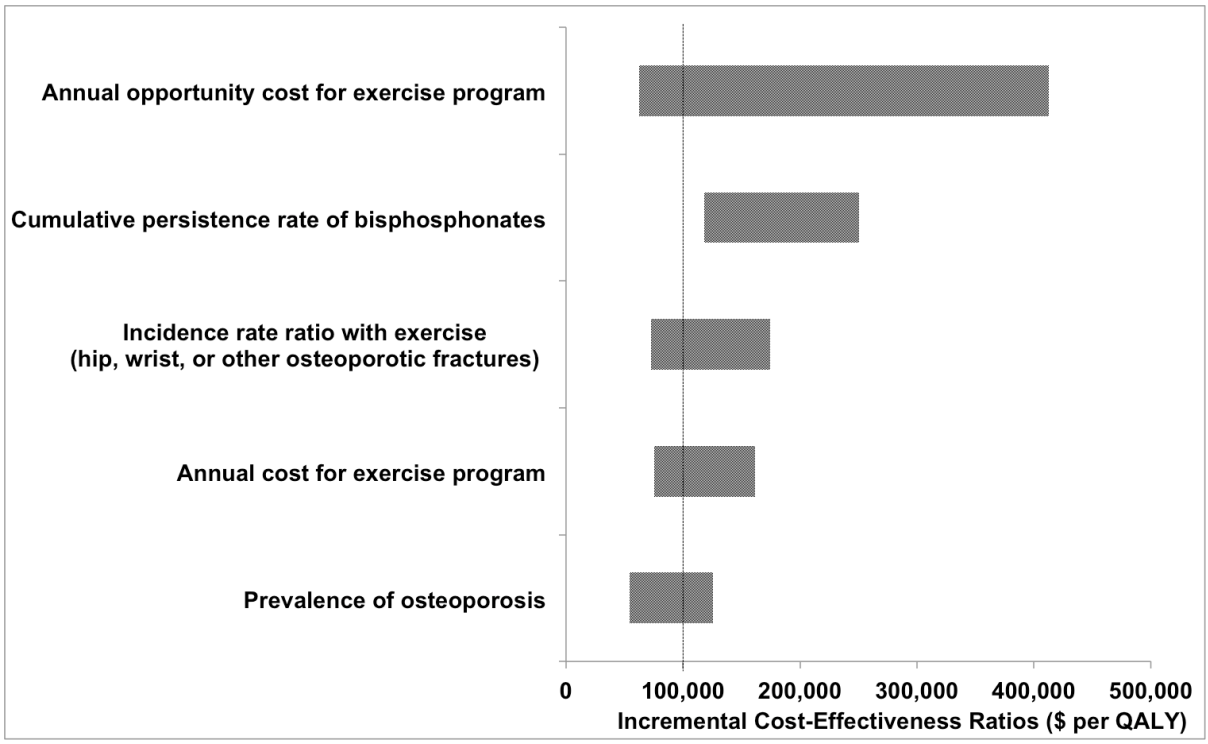
Figure 3: The Results of Deterministic Sensitivity Analyses

The figures present the incremental cost-effectiveness ratios of the combined strategy compared with bisphosphonates alone, when varying the indicated model parameters across their ranges. The vertical hashed line represents $100,000 per QALY. Please refer to Table 1 for the ranges of each parameter. Other osteoporotic fractures included humerus, distal forearm other than wrist, pelvis, tibia/fibula, or femur other than hip.

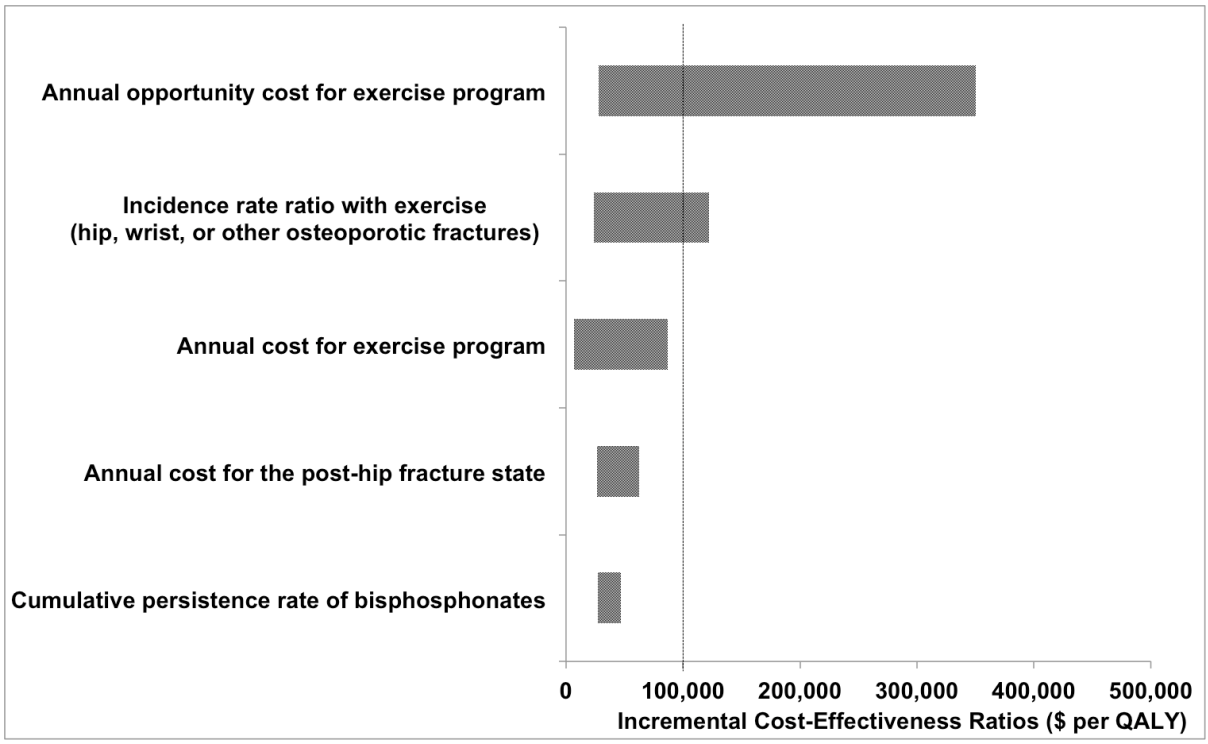
Age 65



Age 70


Annual opportunity cost for exercise program
Cumulative persistence rate of bisphosphonates
Incidence rate ratio with exercise
(hip, wrist, or other osteoporotic fractures)
Annual cost for exercise program
Prevalence of osteoporosis
0
100,000
200,000
300,000
400,000
500,000
Incremental Cost-Effectiveness Ratios ($ per QALY)

Age 75


Annual opportunity cost for exercise program
Incidence rate ratio with exercise
(hip, wrist, or other osteoporotic fractures)
Annual cost for exercise program
Annual cost for the post-hip fracture state
Cumulative persistence rate of bisphosphonates
0
100,000
200,000
300,000
400,000
500,000
Incremental Cost-Effectiveness Ratios ($ per QALY)

Age 80

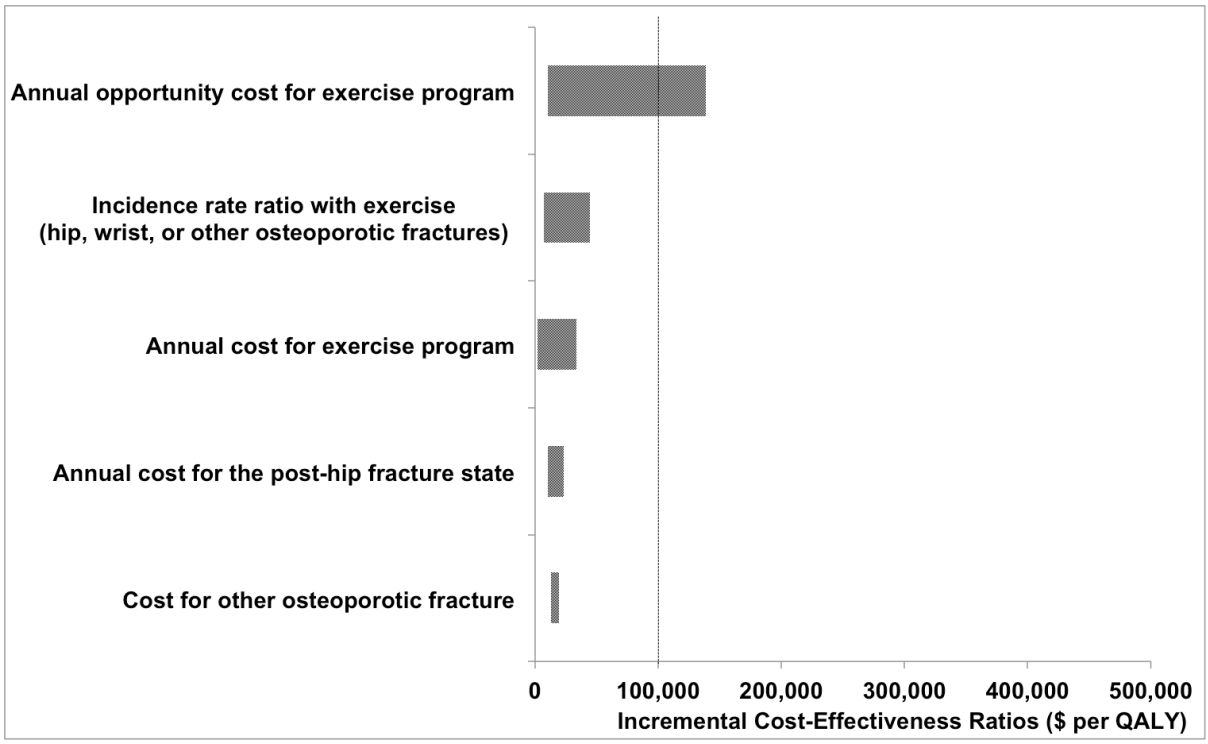

Annual opportunity cost for exercise program
Incidence rate ratio with exercise (hip, wrist, or other osteoporotic fractures)
Annual cost for exercise program
Annual cost for the post-hip fracture state
Cost for other osteoporotic fracture
0
100,000
200,000
300,000
400,000
500,000
Incremental Cost-Effectiveness Ratios ($ per QALY)

Table 3: The Results of the Alternative Scenarios

Age 65

a) Exercise program was offered only to those with osteoporosis			
None	9,699	11.518	Dominated
Bisphosphonates	9,683	11.530	Comparator
Exercise	9,964	11.519	Dominated
Combined	9,746	11.532	49,050
b) Exercise program was extended to 2 years			
None	9,699	11.518	Dominated
Bisphosphonates	9,683	11.530	Comparator
Exercise	10,236	11.520	Dominated
Combined	10,263	11.533	203,660
c) Clinical vertebral fractures incurred the same excess mortality as hip fractures			
None	9,771	11.595	Dominated
Bisphosphonates	9,752	11.610	Comparator
Exercise	10,051	11.596	Dominated
Combined	10,036	11.612	177,940

Age 70

a) Exercise program was offered only to those with osteoporosis			
None	10,354	9.634	Dominated
Bisphosphonates	10,272	9.651	Comparator
Exercise	10,567	9.636	Dominated
Combined	10,317	9.653	30,960
b) Exercise program was extended to 2 years			
None	10,354	9.634	Dominated
Bisphosphonates	10,272	9.651	Comparator
Exercise	10,744	9.637	Dominated
Combined	10,661	9.654	137,300
c) Clinical vertebral fractures incurred the same excess mortality as hip fractures			
None	10,401	9.688	Dominated
Bisphosphonates	10,300	9.714	Comparator
Exercise	10,624	9.689	Dominated
Combined	10,475	9.716	149,360

Age 75

a) Exercise program was offered only to those with osteoporosis			
None	10,718	7.828	Dominated
Bisphosphonates	10,513	7.849	Dominated
Exercise	10,784	7.829	Dominated
Combined	10,501	7.851	Cost-saving
b) Exercise program was extended to 2 years			
None	10,718	7.828	Dominated
Bisphosphonates	10,513	7.849	Comparator
Exercise	10,873	7.832	Dominated
Combined	10,702	7.853	49,580
c) Clinical vertebral fractures incurred the same excess mortality as hip fractures			
None	10,771	7.885	Dominated
Bisphosphonates	10,548	7.912	Comparator
Exercise	10,835	7.885	Dominated
Combined	10,661	7.914	46,060

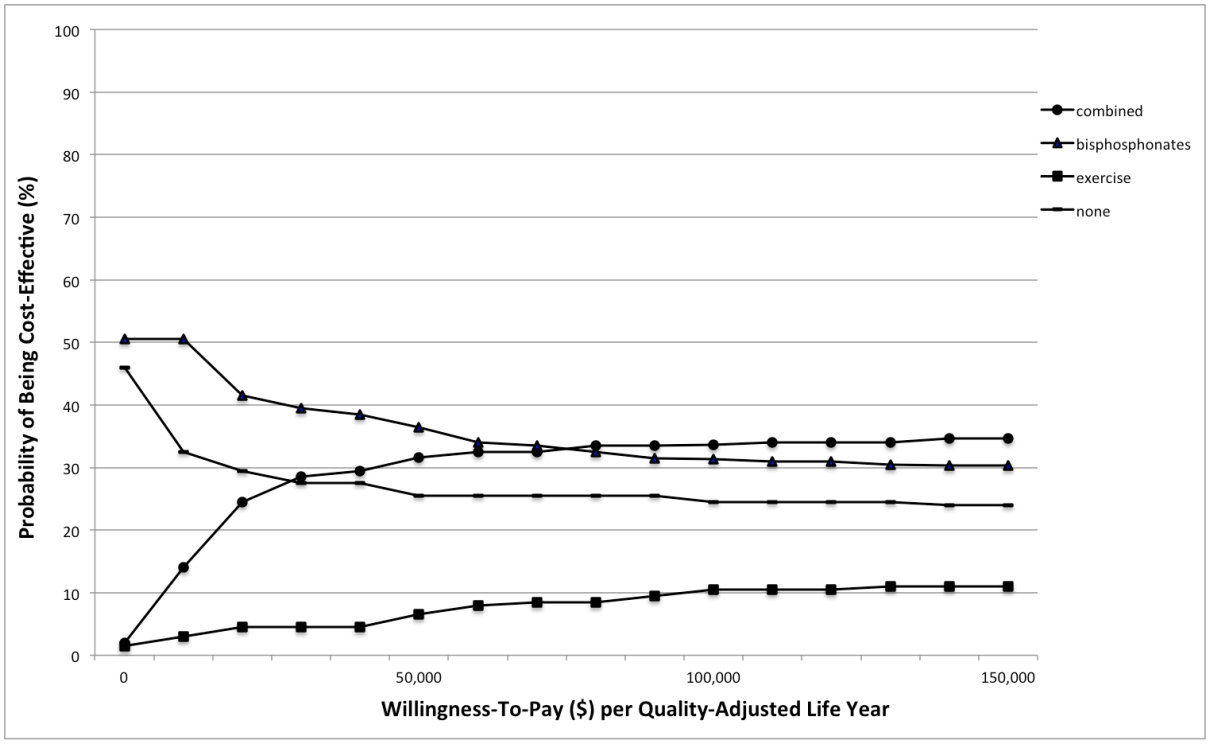
Age 80

a) Exercise program was offered only to those with osteoporosis			
None	10,465	5.999	Dominated
Bisphosphonates	10,052	6.026	Comparator
Exercise	10,523	6.008	Dominated
Combined	10,062	6.030	2,680
b) Exercise program was extended to 2 years			
None	10,465	5.999	Dominated
Bisphosphonates	10,052	6.026	Dominated
Exercise	10,569	6.012	Dominated
Combined	10,197	6.034	20,150
c) Clinical vertebral fractures incurred the same excess mortality as hip fractures			
None	10,508	6.043	Dominated
Bisphosphonates	10,080	6.078	Comparator
Exercise	10,579	6.052	Dominated
Combined	10,156	6.082	16,100

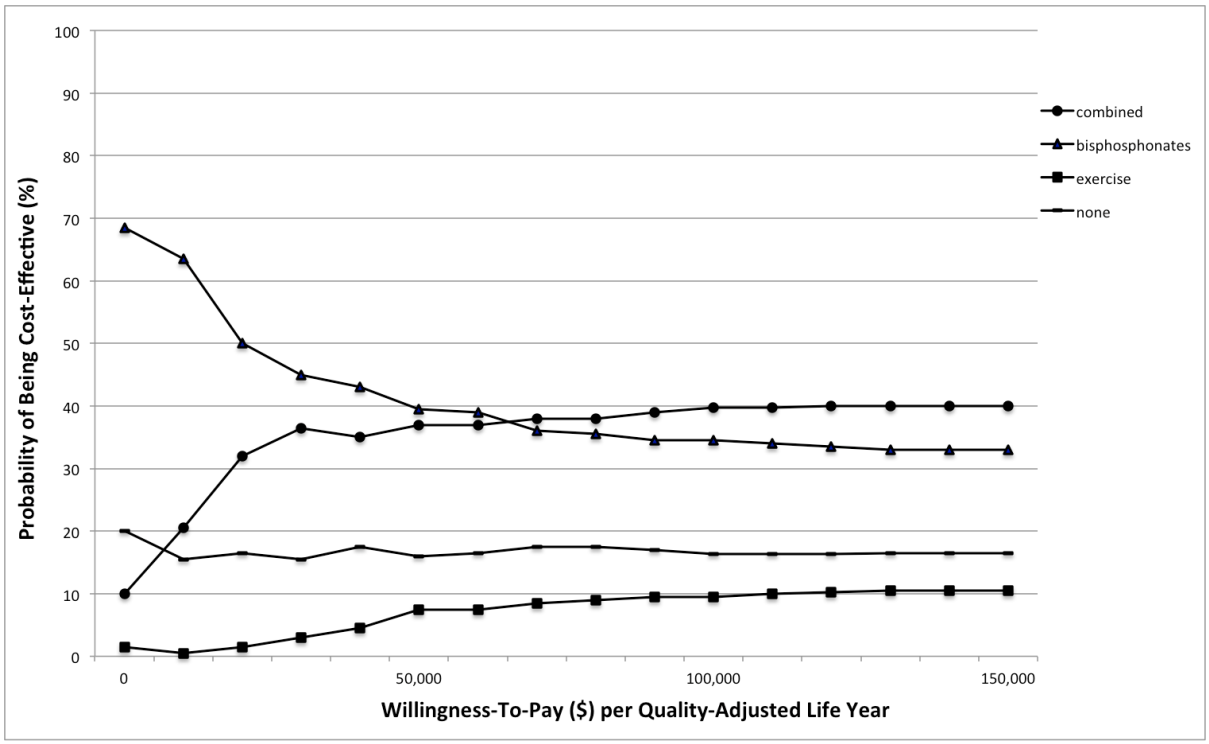
Figure 4: The Results of Probabilistic Sensitivity Analyses

The cost-effectiveness acceptability curves represent probabilities of being cost-effective compared with the next best alternative at different levels of willingness-to-pay per QALY gained.

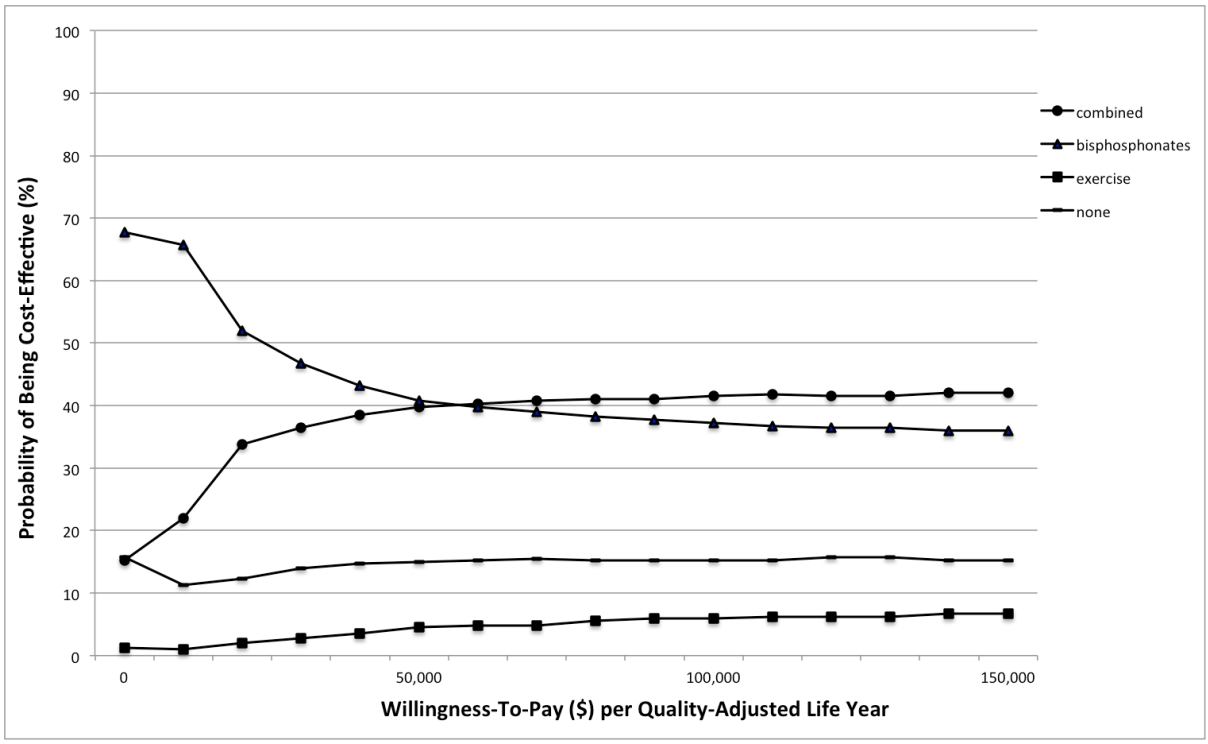
Age 65



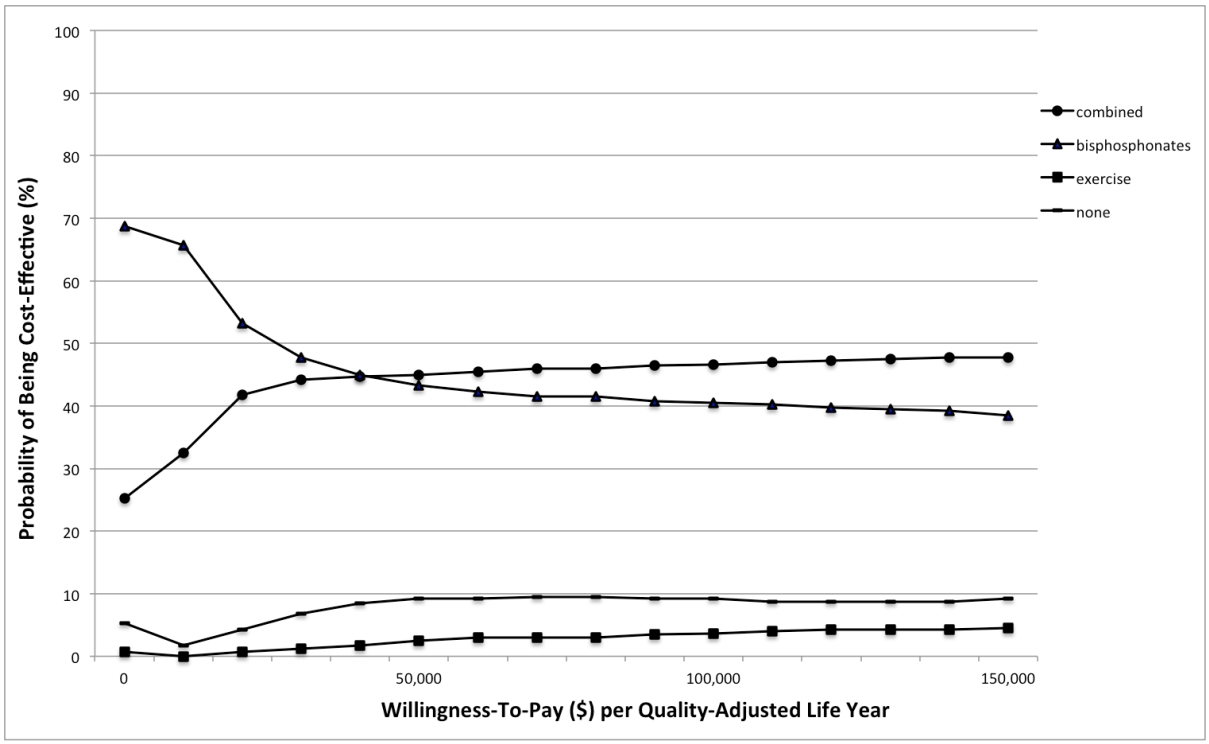
Age 70


100
90
80
70
60
50
40
30
20
10
0
Probability of Being Cost-Effective (%)
0
50,000
100,000
150,000
Willingness-To-Pay ($) per Quality-Adjusted Life Year
combined
bisphosphonates
exercise
none

Age 75


100
90
80
70
60
50
40
30
20
10
0
Probability of Being Cost-Effective (%)
0
50,000
100,000
150,000
Willingness-To-Pay ($) per Quality-Adjusted Life Year
combined
bisphosphonates
exercise
none

Age 80


100
90
80
70
60
50
40
30
20
10
0
Probability of Being Cost-Effective (%)
0
50,000
100,000
150,000
Willingness-To-Pay ($) per Quality-Adjusted Life Year
combined
bisphosphonates
exercise
none

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