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Abstract

Fractures are associated with high economic costs, increased mortality and loss of health related quality of life. Studies have shown that individuals with prior fractures have an increased risk of experiencing subsequent fractures. Therefore secondary fracture prevention appears useful to reduce further fractures in high risk individuals, e.g., in individuals with a prior hip fracture. A clinical trial (HORIZON-RFT) showed that a yearly dose of 5mg intravenous zoledronic acid (IZA) had a fracture-reducing effect in individuals with a prior hip fracture. As to our knowledge no evidence about the cost-effectiveness of IZA is available, the objective of this study is to evaluate the cost-effectiveness of 5mg IZA in women with a previous hip fracture in comparison to no intervention. For this reason a previously published discrete event simulation model which simulates the natural occurrences of different fractures was enhanced. The main enhancements of the model were the inclusion of medication persistence and potential residual treatment effects of IZA. Model input data in terms of epidemiologic, economic and medication effectiveness data was taken from multiple sources. Quality adjusted life years (QALY) were used as effect measure. Costs were considered from a societal perspective for the year 2009. Costs and QALYs were discounted by 3%. As main outcome we calculated the incremental cost-effectiveness ratio (€/QALY) and constructed cost-effectiveness acceptability curve (CEAC) to represent the parameter uncertainty around our results. In the base-case analysis the model showed an ICER of 11,602 €/QALY with incremental costs and QALYs of 21.8€ and 0.0018762 QALYs, respectively. At ICER thresholds of 12,500 €/QALY and 80,000€/QALY the CEAC showed a probability for cost-effectiveness of 48% and 93%, respectively. The result of the model suggest that yearly 5 mg intravenous zoledronic

acid is a cost-effective intervention in postmenopausal women after a hip fracture.

Keywords: Cost-effectiveness, fractures, zoledronic acid, discrete event simulation JEL

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Introduction

The lifetime risk of an osteoporotic fracture is about 40 to 50% for women aged 50 years [1]. Fracture patients are confronted with a reduction in health-related quality of life (HRQoL) [2] and increased mortality [3]. The oldest patients are additionally at increased risk of losing their independence after a fracture and therefore often require long-term support from professional or informal care givers [4], or even have to be institutionalized in a nursing home [5]. Furthermore, osteoporotic and osteoporosis-related fractures cause high economic burden [6-9]. Effective pharmaceutical anti-fracture treatment is available for individuals with high fracture risk, i.e. persons with clinical risk factors [10], a previous vertebral fracture [11] or low bone mineral density (BMD) [12-15].

The first step in the treatment process is to identify persons at high fracture risk. Fracture risk assessments are usually done using fracture risk assessment questionnaires, e.g. FRAX® [16] or DVO questionnaire [17] to assess clinical risk factors, in combination with an osteodensitometry to determine BMD. Depending on the applied assessment, physicians have to decide whether a person is eligible for pharmaceutical treatment or not [17]. However, potential high risk persons, e. g. persons with osteoporosis, often do not have physical symptoms [18] and therefore might not consult a physician to evaluate their fracture risk, which hampers a systematic primary fracture prevention.

In secondary fracture prevention the identification process seems easier, because persons with fragility fractures coming to clinical attention are identified as high fracture risk patients per se [19] without additional screening. Studies have shown that postmenopausal women with a previous hip fracture have a 2.4 times increased risk of suffering from a subsequent fracture compared to women without previous hip fractures [20]. One possible secondary prevention strategy to avoid subsequent

fractures is to systematically treat hip fracture patients with 5mg intravenous zoledronic acid (IZA). A randomized, double-blinded, placebo-controlled trial showed that the treatment of hip fracture patients with 5mg IZA led to a relative risk reduction of 35% in the occurrence of further clinical fractures over three years [21]. Despite the shown effectiveness of IZA in reducing subsequent clinical fractures in patients with a hip fracture [21], to our knowledge neither national nor international studies have analyzed the cost-effectiveness of IZA in hip fracture patients. Yet, this analysis could be important for health care decision makers in order to assess the value for money of IZA. Therefore, the aim of this study was to evaluate the cost-effectiveness of 5mg IZA in postmenopausal women (aged 50 years and older) with a first hip fracture from a societal perspective in Germany, using a discrete event simulation (DES) model.

Methods

Study overview

In this study the cost-effectiveness of 5mg IZA compared to no intervention was analyzed based on a DES which simulates the natural occurrence of six fracture types [22]. Cost-effectiveness was estimated using incremental cost-effectiveness ratios (ICER) [23]. Effects were measured using quality-adjusted life years (QALYs) [23]. Direct costs were calculated form a societal perspective in 2009 Euros (€). Indirect costs due to health-related productivity losses were not considered, because they showed low relevance in a previously conducted cost-of-illness study [22]. All costs and effects were discounted by 3% in the base case analysis [24]. A lifetime time horizon (until age of 100) was chosen to account for possible long-term consequences of IZA. The intervention was designed as follows: Women aged 50 years or older with a first hip fracture received a yearly dose of 5mg IZA up to 3 years. The intervention was compared to no IZA after surgical repair for hip fracture. No

intervention as comparator was chosen because no other interventions have analyzed the anti-fracture effectiveness in individuals after a hip fracture [25]. Postmenopausal women (aged 50 years or older) were chosen as target population because around 75% of hip fractures occur in this population group in Germany [26].

Model structure

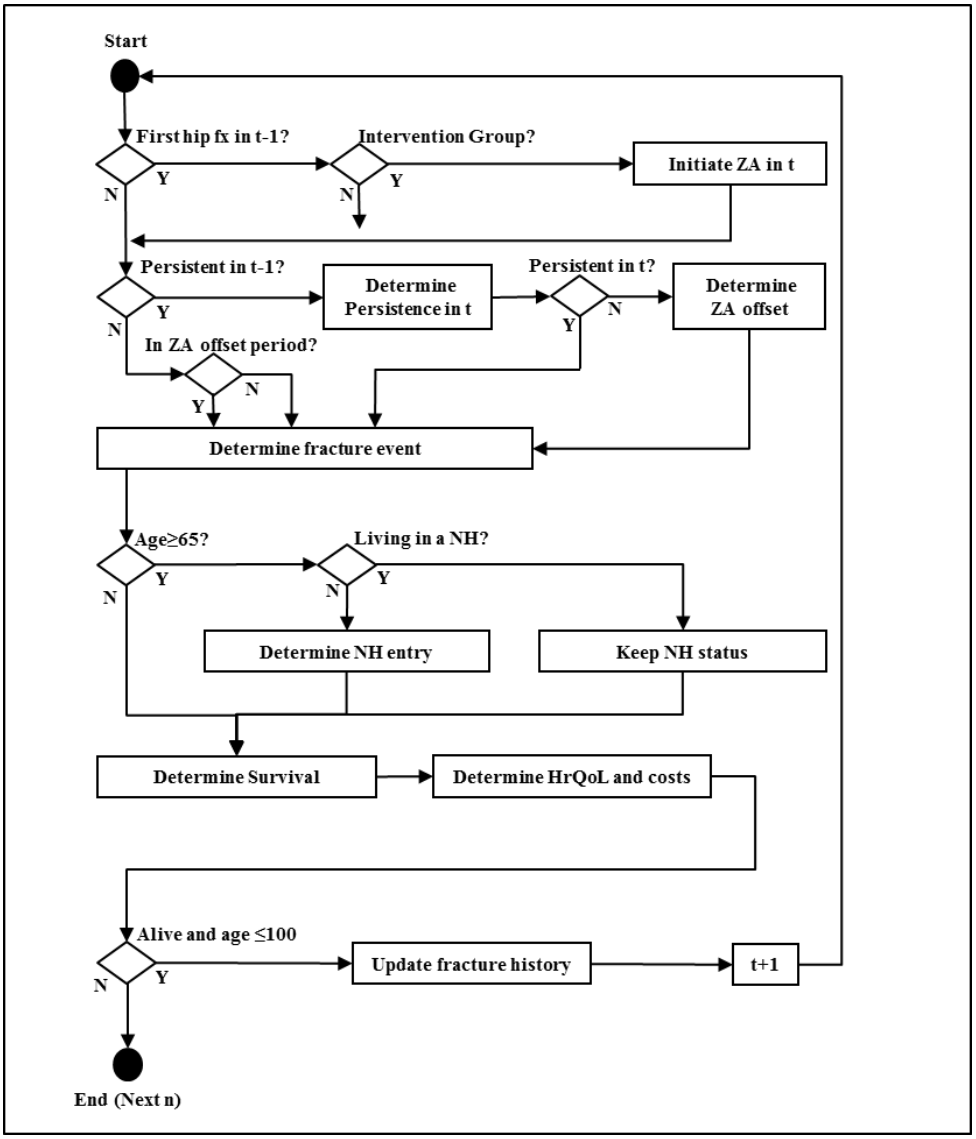
A previously published and validated individual-based "time driven" DES model [22] was used. In the base case analysis we simulated 400,000 individuals (n) and applied a "full common random numbers approach" [27] to reduce variability in ICER results. Stability was tested by comparing results of 50 independent simulation trials (m) (50 x 400,000).

DESs are conceptualized with events which are discrete and can occur simultaneously [28]. Individuals are called entities and have different constant or dynamic attribute profiles, e.g. age or risk factors. Depending on these profiles event probabilities are determined. Reversely, events can change the attributes profile, which technically implements individuals' history in the simulation [28]. In a "time driven" DES time is modeled with constant intervals [29] similar to cycles in a Markov model [30]. A Markov structure was not chosen because too many mutually exclusive health states would have been necessary to reflect all possible situations. In this "time driven" DES (interval length t = 1 year) six different fracture events (hip, other femur, clinical vertebral, humerus, pelvis and wirst) can occur. The occurrence of these fractures is dependent on age, history of previous fractures, residential status (community dwelling or nursing home) and IZA treatment status (IZA effect in the persistent phase of treatment and IZA effect after treatment discontinuation (offset effect)). Starting at the age of 50 in a community-dwelling setting, a woman can be institutionalized in a nursing home (firstly at the age of 65 years) during the simulation, which has an increasing effect on mortality and fracture risk as well as a decreasing effect on HRQoL. The institutionalization itself is dependent on age and

the presence of fractures. Furthermore, individuals' survival depends on age, residential and fracture status (previous and acute fracture). Fracture-related costs and HRQoL were modeled as attributes.

At the start of each simulation (n) it is predefined if a woman had any previous fractures before the age of 50. In case the first fracture occurs during the simulation process, the model changes the woman's attributes profile from "no previous fracture" to "with previous fractures" which increases the subsequent fracture risk. A treatment with IZA is initiated in year t if a woman experienced a hip fracture in the year t-1. Figure 1 shows how the individuals flow through the model per time interval t, where rhombuses represent decision points and rectangles initializations of events. The model was constructed in Matlab R2012a (The MathWorks, Inc., Natick, MA, USA) in combination with Excel 2010 (Mircosoft Corporation, Redmond, WA, USA).

Figure 1: Model flow chart



Legend Figure 1: ZA=Zoledronic acid, NH= Nursing home, End=Death event, HRQol= Health-related quality of life

Fracture risk

The six fracture types were defined according to the International Classification of Diseases (ICD-10): hip S72.0-2, other femur S72.3-9, clinical vertebral S12.0-2/S12.7/S22.0-1/S32.0, humerus S42.2-4, pelvis S32.1-8 and wrist S52.5-6. The average fracture risks of the German female population aged 50 years and older are shown in Table 1. A detailed description of the estimation method can be found in a previous publication [22].

Table 1: Fracture probabilities for the female general population by fracture type and age

Fracture type	Age-specific probabilities			Distribution	Source
Hip	*50-54:* 0.00038 *55-59:* 0.00071 *60-64:* 0.00104	*65-69:* 0.00187 *70-74:* 0.00334 *75-79:* 0.00772	*80-84:* 0.01605 *85-89:* 0.02791 *90-94:* 0.03625 95+: 0.03960	*None*	*[22]* *Supp.**
Other femur	*50-54:* 0.00010 *55-59:* 0.00014 *60-64:* 0.00021	*65-69:* 0.00033 *70-74:* 0.00054 *75-79:* 0.00102	*80-84:* 0.00162 *85-89:* 0.00262 *90-94:* 0.00324 95+: 0.00382	*None*	*[22]* *Supp.**
Clinical vertebral	*50-54:* 0.00095 *55-59*: 0.00144 *60-64:* 0.00192	*65-69:* 0.00316 *70-74:* 0.00456 *75-79:* 0.00634	*80-84:* 0.01132 *85-89:* 0.01378 *90-94:* 0.01339 95+: 0.01052	*None*	*[22]* *Supp.**
Wrist	*50-54:* 0.00221 *55-59*: 0.00390 *60-64:* 0.00491	*65-69:* 0.00620 *70-74:* 0.00684 *75-79:* 0.00866	*80-84:* 0.00973 *85-89:* 0.00916 *90-94:* 0.00740 95+: 0.00530	*None*	*[22]* *Supp.**
Humerus	*50-54:* 0.00085 *55-59*: 0.00143 *60-64:* 0.00194	*65-69:* 0.00272 *70-74:* 0.00360 *75-79:* 0.00530	*80-84:* 0.00716 *85-89:* 0.00872 *90-94*: 0.00861 95+: 0.00795	*None*	*[22]* *Supp.**
Pelvis	*50-54:* 0.00018 *55-59:* 0.00028 *60-64:* 0.00038	*65-69:* 0.00071 *70-74:* 0.00127 *75-79:* 0.00285	*80-84:* 0.00544 *85-89:* 0.00890 *90-94:* 0.01172 95+: 0.01118	*None*	*[22]* *Supp.**

* *Supp. = Electronic supplementary material*

Fracture risk depends on individuals' attribute profiles, thus the average fracture risks were adjusted for different profiles. Studies showed that individuals with a previous fracture have an increased fracture risk compared to those who never suffered from a previous fracture [19]. To estimate the fracture risk for women without a previous fracture, we calculated the relative risk reduction for those without previous fractures compared to the general population ($RR_{withoutFx}$) and multiplied $RR_{withoutFx}$ with the age-dependent average fracture risks. The following formula was used to estimate

$RR_{withoutFx}$ [31]:

$$RR_{withoutFx(i)} = \frac{1}{(1+(RR_{AnyFx}-1)*Pr_{PrevFx(i)})}$$

Where RR_{AnyFx} represents the relative fracture risk of getting any subsequent clinical fracture in individuals with a previous fracture compared to those without a previous fracture (RR_{AnyFx} 1.84 (1.72-1.96); Log-Normal distribution) [19] and $Pr_{PrevFx(i)}$ the prevalence of previous fractures (age (i) 50 (23%) - age 90 (48%), with linear increase; uniform distribution +/-30%) [19]. If a woman experienced a clinical non-hip fracture in the model for the first time, it was assumed that the risk for a hip fracture increases by RR 1.77 (1.49-2.11; Log-Normal distribution) and for other fractures by RR 1.85 (1.70-2.01; Log-Normal distribution) [19]. If a woman experienced a hip fracture at first the risk for a subsequent hip fracture increases by RR 2.3 (1.5-3.7; Log-Normal distribution), for a vertebral fracture by RR 2.5 (1.8-3.5; Log-Normal distribution), and for other fractures by RR 1.9 (not available; (1.4-2.7) assumed based on RR range from vertebral fracture RR) [20]. Modeling the fracture risk after a hip fracture is an important issue in determining the cost-effectiveness of IZA after a hip fracture. In order to show the impact of different assumptions of post-hip fracture risk on ICER results, we performed sensitivity analyses assuming upper and lower confidence intervals of RRs after hip fracture.

Institutionalized persons have a higher fracture risk compared to community-dwelling persons [32]. The relative fracture risk (fracture type-specific (fx)) of women living in a nursing home ($RR_{Nurs(fx)}$) and those who do not ($RR_{NoNurs(fx)}$) compared to the female general population (see Supplementary Table 1) were estimated based on data from a large German sickness fund (AOK Bayern). A description of the dataset and calculation method can be found elsewhere [22]. Dependent on the actual attributes profile (residential status) in the model, RR_{Nurs} or RR_{NoNurs} were combined with the actual fracture risk of this woman.

Probabilities of institutionalization in nursing homes

There is evidence that elderlies have an increased risk of institutionalization into a nursing home after having fragility fractures compared to fracture free elderlies at the same age [5]. A new entry in a nursing home was modeled using age-dependent all-cause and fracture-dependent institutionalization probabilities. All-cause probabilities were calculated based on German official care statistics [33], by transforming the age-dependent shares of institutionalized women into institutionalization probabilities [34]. To estimate the probability of institutionalization into a nursing home after a fracture, data from a large German mandatory sickness fund (AOK Bayern) was used (see Table 2). It was assumed that the institutionalization was fracture attributable if a community-dwelling woman was institutionalized 3 months after a (hospitalized) fracture for the first time. A new entry in a nursing home was firstly possible at the age of 65. Similar to other modeling studies we assumed that institutionalized women reside in a nursing home for the rest of their lives [35].

Table 2: All-cause and fracture type-specific institutionalization probabilities by age

Type	**Age-specific probabilities (95% confidence intervals)***		**Distribution**	**Source**
All-cause	*65-69:* 0.0017	80-84: 0.0150	*Model*	*[22]*

(any reason)	*70-74:* 0.0023 75-79: 0.0061	85-89: 0.0368 90-94: 0.0669 95+: 0.1130	*intern*	*Supp.*
Hip	*65-69:* 0.032 (0.016-0.047) *70-74:* 0.048 (0.038-0.057) 75-79: 0.078 (0.069-0.087)	80-84: 0.143 (0.133-0.153) 85-89: 0.208 (0.194-0.221) 90-94: 0.299 (0.276-0.322) 95+: 0.427 (0.380-0.475)	*Beta*	*[22] Supp.*
Other femur	*65-69:* 0.032 (-0.004.0690) *70-74:* 0.051 (0.027-0.075) 75-79: 0.092 (0.065-0.118)	80-84: 0.161 (0.131-0.191) 85-89: 0.260 (0.214-0.307) 90-94: 0.354 (0.272-0.437) 95+: 0.271 (0.146-0.399)	*Beta*	*[22] Supp.*
Clinical vertebral	*65-69:* 0.008 (-0.001-0.017) *70-74:* 0.022 (0.014-0.030) 75-79: 0.055 (0.045-0.065)	80-84: 0.104 (0.091-0.117) 85-89: 0.166 (0.145-0.187) 90-94: 0.254 (0.209-0.299) 95+: 0.379 (0.275-0.482)	*Beta*	*[22] Supp.*
Wrist	*65-69:* 0.004 (-0.0005-0.008) *70-74:* 0.007 (0.003-0.010) 75-79: 0.026 (0.020-0.033)	80-84: 0.046 (0.037-0.055) 85-89: 0.081 (0.064-0.098) 90-94: 0.175 (0.128-0.221) 95+: 0.268 (0.152-0.384)	*Beta*	*[22] Supp.*
Humerus	*65-69:* 0.012 (0.003-0.021) *70-74:* 0.020 (0.014-0.027) 75-79: 0.039 (0.030-0.047)	80-84: 0.084 (0.073-0.096) 85-89: 0.155 (0.136-0.175) 90-94: 0.313 (0.267-0.358) 95+: 0.332 (0.231-0.433)	*Beta*	*[22] Supp.*
Pelvis	*65-69:* 0 020 (-0.002-0.043) *70-74:* 0.032 (0.019-0.046) 75-79: 0.077 (0.061-0.093)	80-84: 0.128 (0.111-0.145) 85-89: 0.175 (0.153-0.197) 90-94: 0.244 (0.207-0.281) 95+: 0.359 (0.278-0.440)	*Beta*	*[22] Supp.*
A more detailed description of input parameters can be found in source [22] (Supp.=electronic supplementary material). Only significant values were applied.*				

Mortality

Mortality was modeled using official German generation survival tables for women aged 50 in the year 2009 [36] adjusted for residential status (see Supplementary Table 2). Comorbidity adjusted fracture excess mortality (relative risks by year 1 to 10 following a fracture and age) for all fracture types, excluding wrist, was taken from a Canadian study [3]. If two fractures occurred in the same year we assumed the highest fracture-specific relative mortality risk.

Treatment effectiveness

The effectiveness data of 5mg IZA after hip fracture was taken from the HORIZON-RFT [21] clinical trial. In this randomized, double blinded, placebo-controlled trial, enrolled patients aged 50 years or older (76.7% women), unwilling to take oral bisphosphonates, received a 15 minutes infusion of 5 mg zoledronic acid or placebo within 90 days after surgical repair of a hip fracture. Additionally, all participants (intervention and control group) received a single loading dose of vitamin d as well as a daily oral supplementation of vitamin d (800 to 1200 IU) and calcium (1000 to 1500mg) during the study period. The trial showed a hazard ratio (HR) (risk reduction) for any fracture of 0.65 (0.50-0.84), non-vertebral fracture of 0.73 (0.55-0.98), hip fracture of 0.70 (0.41-1.19) and clinical vertebral fracture of 0.54 (0.32-0.92) [21] (see Table 3). HRs were estimated over a three year time horizon. In our model we assumed that the treatment effect of IZA was constant for all infusions a woman received, e.g. if a woman stopped taking IZA after 2 yearly infusions we assumed that the yearly treatment effect of these two years was the same as reported in the HORIZON-RFT study. This is a conservative assumption, because the HR estimation method was based on an intention to treat analysis including discontinuation of treatment within 3 years. A population of fully persistent individuals over 3 years might have shown a higher anti-fracture effect than it was shown in the HORIZON-RFT study.

Table 3: Parameters and assumptions regarding treatment effectiveness and costs of the intervention

	Parameter	**Distribution**	**Source**
Anti-fracture effect by fracture type	**Hazard Ratios (95% Confidence intervals)**		
Hip	0.70 (0.41-1.19)	*Log-Normal*	*[21]*
Clinical vertebral	0.54 (0.32-0.92)	*Log-Normal*	*[21]*
All others	0.73 (0.55-0.98)	*Log-Normal*	*[21]*
Reinfusion rate	**Percentage % (Interval)**		
First and second infusion	*50 (30-70)*	*Uniform*	*[37, 38]*
Offset duration	**Years (Interval)**		
	3 (0-6)	*Uniform*	*[39]*
Intervention cost	**In 2009 euro**		
IZA costs per year + one physician visit	*544.1*	*None*	*[40-43]*

Effectiveness of IZA after discontinuation

Studies have shown a tendency that the effect of IZA continues after treatment discontinuation [39, 44]. A post-randomized study found a relative fracture risk reduction for clinical fractures of 32% (2%-53%) after three years in individuals who received only one infusion of IZA. Individuals who received three yearly infusions had a similar relative risk reduction of 34% (23%-53%) [39]. The extension of the HORIZON-RFT (conducted in women with osteoporosis, extension from 3 to 6 years) showed that the relative risk reduction in hip, clinical vertebral and non-vertebral fractures in women receiving IZA for 6 years were similar to those who received IZA for 3 years only, except for risk reductions in morphometric vertebral fractures [44]. These two studies support the assumption that IZA has a prolonging effect on fracture risk reduction after discontinuation (offset effect). In the base case analysis we assumed an offset period of 3 years, based on the study results from Reid et al. [39] (see Table 3). As there remains uncertainty about the "true" offset effect of IZA after discontinuation, different offset durations were tested in sensitivity analyses. Similar to other modeling studies we assumed that the treatment effect decreases linearly to the risk level of an untreated woman after the offset period [45, 46].

Persistence and compliance

Persistence was defined as "the duration of time from initiation to discontinuation of therapy" and compliance as "the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen" [47]. The advantage of yearly IZA is, once a person received one infusion, this person is fully compliant for one year. Nevertheless, if the treatment duration is 3 years, non-persistence beyond the first year is possible. To our knowledge, there are few studies analyzing the reinfusion rates (persistence) after the first infusion of IZA. One study reported that 36.3% [37] of persons with a first infusion of IZA received a second, whereas another study

showed a reinfusion rate of 68% [38]. For this reason, we conservatively assumed that 50% (30%-70%, uniform distribution) of first IZA users took a second and third infusion (see Table 3). Persistence and compliance were implemented in the model based on a method described by Ström et al. [46].

Costs

Costs were calculated from a societal perspective using multiple sources (see Table 4). An inflation correction to the year 2009, using the consumer price index [48], was applied if necessary. Fracture-specific hospital costs were estimated based on German diagnosis related groups (DRGs) [49, 50] and capital costs [22, 43]. Post-hospital rehabilitation costs were calculated using average lengths of stay data [51] and unit costs per day [52]. Costs for outpatient care (physician visits (including outpatient surgeons), physiotherapeutic treatments and analgesics) were calculated combining German unit costs [43, 53] and resource use data from a German economic evaluation [54]. In the case an individual required hospitalization after a fracture (based on hospitalization probabilities; see Supplementary table 3), costs for acute hospital treatment, outpatient aftercare, and if necessary costs for (inpatient) rehabilitation (based on rehabilitation probabilities; Supplementary table 3) were tracked. If no hospitalization was required, only costs for outpatient care were considered.

Table 4: Cost per fracture case by fracture type and health care sector in 2009 €

Cost category	Hip	Other femur	Clinical Vertebral	Humerus	Pelvis	Wrist	Distribution	Source
Hospitalization (with outpatient aftercare)	*8,554*	*8,395*	*6,324*	*5,764*	*5,005*	*3,794*	*Gamma**	*[22] Supp.*
Rehabilitation (if required after hospital stay)	*2,187*	*2,187*	*2,092*	*2,337*	*2,177*	*2,337*	*None*	*[22] Supp.*
Exclusive outpatient (without hospitalization)	*n.a.*	*n.a*	*1,614*	*835*	*963*	*835*	*Gamma*	*[22] Supp.*
Professional home care**	*2,174*	*2,174*	*2,212*	*937*	*2,174*	*525*	*Gamma*	*[22] Supp.*
Informal home care**	*2,361*	*2,361*	*2,061*	*2,961*	*2,361*	*581*	*None*	*[22] Supp.*
Nursing home (per year)	*25,759*	*25,759*	*25,759*	*25,759*	*25,759*	*25,759*	*None*	*[22] Supp.*

**Only outpatient aftercare costs were varied with Gamma distribution; a more detailed description of input parameters can be found in source [22] (Supp.= electronic supplementary material). **Only applicable in community-dwelling women aged 65 and older*

The number of average hours of professional and informal care after a fracture were taken from a burden of disease study from Austria as a proxy for missing data from Germany [55]. Hours of informal care were valued with the market cost approach (proxy good method) [56], using the hourly gross salary of an employee in the field of care for elderly and disabled persons [57]. The hourly salary was increased by the employer share of social contribution [58]. Costs per hour for professional home care were taken from a German source [59]. Average costs for fracture-related professional home and informal care were only tracked for community-dwelling women older than 65 years.

Yearly nursing home costs, weighted by level of care, were taken from the official care statistic 2009 [33] and increased with capital costs [60]. A model intern parallel simulation [61] was applied to determine fracture attributable nursing home costs. An institutionalization for any reason and due to fractures was simulated in parallel. Only time in nursing home related to fractures was tracked as fracture attributable, a half cycle correction [30] of nursing home costs was applied if necessary.

Intervention costs were estimated under the assumption that each infusion of IZA requires one family physician visit (17.91€ (2009) [43]). Costs for IZA (Aclasta®, 561.6€) were taken from a German medication price list [40] and were decreased by manufacture (6%, [41]) and pharmacy discounts (1.75€, [42]) (see Table 3). Intervention costs were tracked in the year an infusion of IZA was initiated.

Health-related quality of life

EQ-5D index values of community dwelling individuals, calculated based on the index of Dolan [62], were taken from a representative German HRQoL study using the EQ-5D [63]. EQ-VAS scores of women living in a nursing home were derived from a study surveying HRQoL of 342 inhabitants of 8 German nursing homes [64]. Reductions in HRQoL in the first and following years after a fracture were modeled combining fracture-specific HRQoL –multipliers with community-dwelling or nursing home utility weights. HRQoL-multipliers for hip, vertebral and wrist fractures were taken from an international systematic review [2], multipliers for humerus and pelvis fractures from a study by Kanis et al. [65] (see Table 5). If two or more fractures occurred at the same time, the lowest HRQoL-multiplier was applied.

Table 5: Age-related utility weights by residential status and fracture-specific utility multipliers

	Utility weight by age (confidence intervals)	Distribution	Source
Residential status			
Community dwelling*[1]	*50-54:* 0.918 (α=1153.4; β=103.2) *55-64:* 0.881 (α=969.0; β=130.9) *65-74:* 0.823 (α=603.1; β=129.9) *75+:* 0.745 (α=367.1; β=125.5)	*Beta*	*[63]*
Nursing home	*65-74:* 0.530 (0.477-0.583)*[2] *75-84:* 0.500 (0.450-0.550)*[2] *85-94:* 0.550 (0.495-0.605)*[2] *95+:* 0.650 (0.585-0.715)*[2]	*Beta*	*[64]*
Fracture type	**Utility multipliers (95% confidence interval)**		
Hip	*First year :* 0.797 (0.770-0.825) *Subsequent years:* 0.899 (0.855-0.910)	*Beta*	*[2]*
Other femur	*First year :* 0.797 (0.770-0.825) *Subsequent years:* 0.899 (0.855-0.910)	*Beta*	*[2]*
Clinical Vertebral	*First year:* 0.720 (0.660-0.775) *Subsequent years:* 0.931 (0.916-0.946)	*Beta*	*[2]*
Wrist	*First year :* 0.940 (0.910-0.960) *Subsequent years:* 1.000 (1.000-1.000)	*Beta*	*[2]*
Humerus	*First year:* 0.794 (0.715-0.873)*[3] *Second year:* 0.973 (0.876-1.000)*[3]	*Beta*	*[65]*
Pelvis	*First year*: 0.794 (0.715-0.873)*[3] *Second year:* 0.815 (0.734-0.897)*[3]	*Beta*	*[65]*

**[1] Values directly received from HH König *[2]Median EQ-VAS, confidence interval assumed +/-10% from average value; *[3] confidence interval assumed +/-10% from average value. A more detailed description of input parameters can be found in source (electronic supplementary material) [22] .*

Sensitivity analyses

In order to assess uncertainty in our modeled ICER, we performed deterministic and probabilistic sensitivity analyses (PSA). Cost-effectiveness acceptability curves (CEAC) [66] were used to present parameter uncertainty (second-order uncertainty) as a result of PSA. Distributional assumptions of each parameter [67], for which parameter uncertainty was expected because of sample errors are shown in Table 1 to Table 5. As we used an individual-based simulation approach, there is the possibility that the

CEAC is biased by first order uncertainty [68], that is uncertainty introduced by random variability in ICER estimates [69]. To overcome this potential bias, we estimated corrected CEACs using a hybrid-Bayesian approach suggested by O'Hagan and Stevenson [70]. In total we simulated 1,000 individuals (n) with 1,500 different parameter sets (M) to estimate corrected CEACs.

Results

In our base case analysis we found an ICER of 11,602 €/QALY with incremental costs and QALYs of 21.8€ and 0.0018762 QALYs, respectively (Base case: 3 year treatment duration, 3 years offset effect, 50% reinfusion rate for second and third infusion, 3% discount rate). The intervention strategy showed discounted costs of 4,691€ and 18.29920 QALYs, whereas "No intervention" showed discounted costs of 4,670€ and 18.29733 QALYs.

The results of the deterministic sensitivity analysis are shown in Table 6. In total the ICER ranged from dominance to 55,654 €/QALY. Applying the lower confidence interval values of the relative fracture risk after hip fracture for subsequent clinical fractures, the ICER increased to 21,002€/QALY (S01), applying the upper confidence value resulted in dominance (S02). Assuming a 30% decrease in fracture probabilities increased the ICER to 25,465 €/QALY (S03). A secular trend of 1% fracture risk increase per year resulted in an ICER of 308 €/QALY (S04). Varying fracture costs for hospital treatment and nursing home by ±30% (S05-S08) showed an ICER range from 7,885 €/QALY to 15,319€/QALY. Assuming no fracture attributable nursing home costs resulted in an ICER of 18,199 €/QALY (S09). The ICER was less sensitive to changes in fracture-related HRQoL-multipliers (applying upper and lower confidence bounds) (S10-S11). Assuming that fractures do not increase mortality the ICER decreased to 8,774€/QALY (S12). The impact of assuming different reinfusion rates for the second and third infusion led to an ICER variation of 14,185€/QALY to 8,947€/QALY for 70% (S13) and 30% (S14) reinfusion rates, respectively. The increase of the ICER with higher reinfusion rates is mainly explained by the offset assumption of 3 years. Assuming a reduced anti-fracture effect of IZA by 10% (S15) and 30% (S16) increased the ICER to 17,032€/QALY and 29,152€/QALY, respectively. The largest ICER of 55,654€/QALY resulted when no anti-fracture effect of IZA was assumed for subsequent hip fractures (S17). Decreasing the intervention costs for IZA by 30% (S18) and 50% (S19) led to dominance. Assuming no offset effect of IZA after treatment discontinuation resulted in an ICER of 32,237€/QALY assuming 1 year of

treatment (S20), 26,931€/QALY assuming 5 years of treatment (S21), and 24,332€/QALY assuming 10 years of treatment (S22). Keeping the offset effect at 3 years and assuming 1 year treatment duration led to an ICER of 4,516€/QALY (S23), 19,796€/QALY assuming 5 year treatment duration (S24), and 21,853€/QALY assuming 10 year treatment duration (S25). Increasing the offset effect to 6 years led to dominance assuming 1 year treatment duration (S26), 13,978€/QALY assuming 5 year treatment duration (S27), and 19,883€/QALY assuming 10 year treatment duration (S28). A lifelong treatment with IZA resulted in an ICER of 22,271€/QALY (S29). Assuming discount rates of 0% (S30) and 5% (S31) in costs and QALYs led to ICER's of 6,098€/QALY and 17,266€/QALY, respectively.

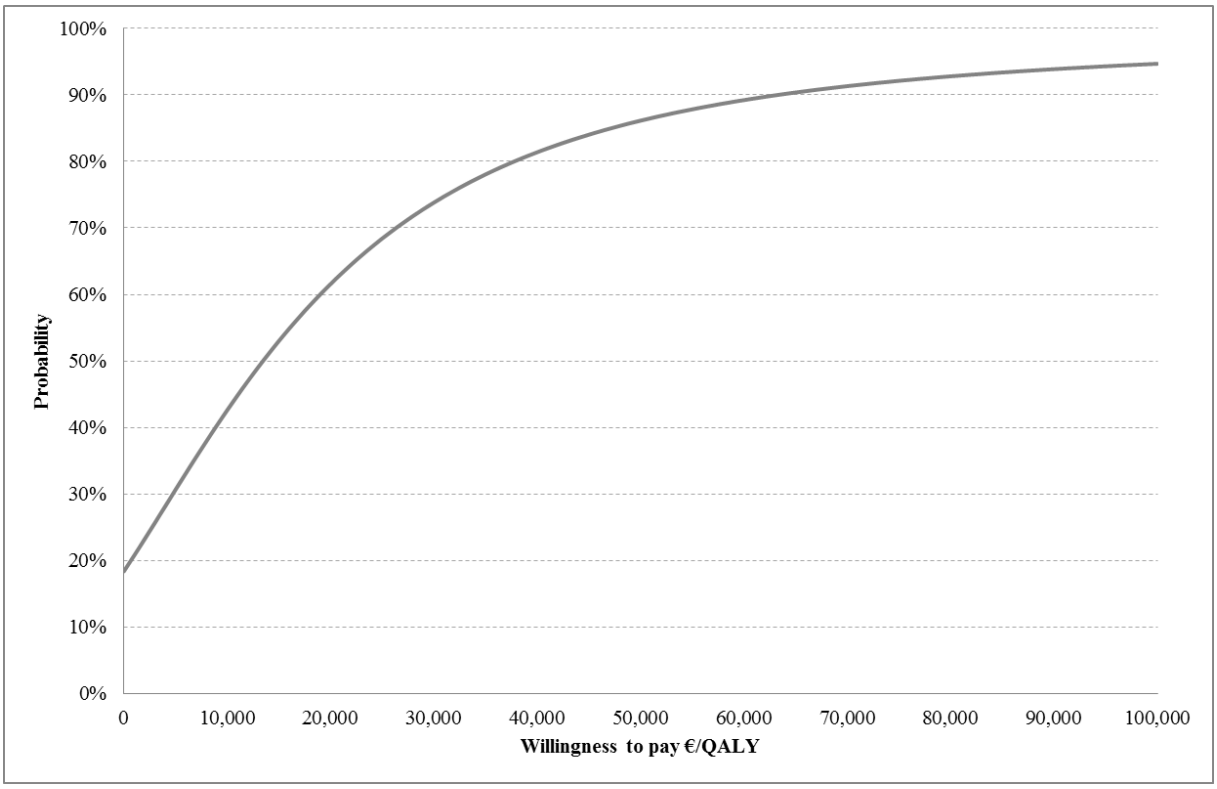
Table 6: Deterministic sensitivity analysis

Variants (S)	**ΔCost**	**ΔQALY**	***ICER (€/QALY)***
Fracture risk			
(S01) Fracture risk increase after hip fracture; applying RRs lower CI	30.6	0.00145631	*21,002*
(S02) Fracture risk increase after hip fracture; applying RRs upper CI	-0.5	0.00275319	*DOM*
(S03) 30% decrease of fracture risk (all fractures)	25.2	0.00098939	*25,465*
(S04) Secular trend in fracture risk (+1% yearly)	1.1	0.00348893	*308*
Fracture costs			
(S05) 30% increase of acute hospital costs	14.8	0.00187625	*7,885*
(S06) 30% decrease of acute hospital costs	28.7	0.00187625	*15,319*
(S07) 30% increase nursing home costs	18.1	0.00187625	*9,623*
(S08) 30% decrease nursing home costs	25.5	0.00187625	*13,581*
(S09) No fracture attributable nursing home costs	34.1	0.00187625	*18,199*
Fracture-related HRQoL			
(S10) HRQoL multipliers lower CI value	21.8	0.00196027	*11,105*
(S11) HRQoL multipliers upper CI value	21.8	0.00178756	*12,178*
Mortality			
(S12) No fracture attributable mortality	10.5	0.00119446	*8,774*
Treatment effectiveness			
(S13) Reinfusion rate 70%	29.4	0.00207552	*14,185*
(S14) Reinfusion rate 30%	14.8	0.00165103	*8,947*
(S15) 10% decrease of treatment effectiveness	28.6	0.00167805	*17,032*
(*S16)* 30% decrease of treatment effectiveness	38.7	0.00132703	*29,152*
(S17) No effect of IZA on subsequent hip fractures	49.6	0.00089125	*55,654*
Intervention costs			
(S18) 30% decrease of intervention costs	-0.9	0.00187625	*DOM*
(S19) 50% decrease of intervention costs	-16.0	0.00187625	*DOM*
Treatment duration and offset (100% reinfusion rate)			
(S20) Treatment duration: 1 year; Offset: 0 years	22.3	0.0006921	*32,237*
(S21) Treatment duration: 5 years; Offset: 0 years	78.8	0.0029273	*26,931*
(*S22)* Treatment duration: 10 years; Offset: 0 years	114.4	0.0047029	*24,332*
(S23) Treatment duration: 1 year; Offset: 3 years	5.8	0.0012747	*4,516*
(S24) Treatment duration: 5 years; Offset: 3 years	66.3	0.0033489	*19,796*
(*S25)* Treatment duration: 10 years; Offset: 3 years	107.4	0.0049128	*21,853*
(S26) Treatment duration: 1 year; Offset: 6 years	-16.4	0.0020504	*DOM*
(S27) Treatment duration: 5 years; Offset: 6 years	53.0	0.0037882	*13,978*
(*S28)* Treatment duration: 10 years; Offset: 6 years	101.0	0.0050799	*19,883*
(S29) Treatment duration: Lifelong; Offset: 0 years	149.3	0.0067048	*22,271*
Discount rate			
(S30) 0%	36.6	0.00600522	*6,098*
(S31) 5%	15.5	0.00089767	*17,266*

DOM = Dominance

The results of the PSA are presented in Figure 2 as a corrected CEAC, where the y-axis shows the probability of cost-effectiveness and the x-axis the willingness to pay value per one QALY in €. For a willingness to pay of 0€ per QALY the probability of cost-effectiveness is around 18%, i.e. 18% of the 1500 simulation trials (M) were cost-saving. For willingness to pay thresholds of 30,000€/QALY, 50,000€/QALY and 75,000€/QALY the probability of cost-effectiveness is around 74%, 86%, and 92%, respectively.

Figure 2: Cost-effectiveness acceptability curve



Validation

As an internal validation we compared modeled fracture rates with the input fracture rates. Due to adjustments of relative risks after a hip fracture in the actual model we found slightly higher fracture rates compared to our previous model [22]. The functionality and correctness of program code was tested using debugging mode for different scenarios and also by reverse calculations (test code), e.g. average health sector-specific fracture costs were calculated based on the model output data and

were compared with the input cost data.

Discussion

In Germany, there is currently no ICER threshold in order to decide if a new intervention is cost-effective or not. International ICER thresholds were often indirectly derived from country-specific reimbursement decisions and range from 12,700€/QALY to 80,000€/QALY (except of New Zealand with a range from 1,400€/QALY to 7,200€/QALY) [71]. For an ICER threshold range of 12,700€/QALY to 80,000€/QALY IZA can be seen as a cost-effective intervention considering our base case results of 11,602€/QALY. For ICER thresholds of 12,500 €/QALY to 80,000€/QALY the probability of cost-effectiveness was 48% and 93%, respectively.

The effect of treatment discontinuation (offset effect) had an important impact on the ICER. Although studies showed a tendency of an offset effect of IZA after treatment discontinuation, there is still uncertainty about the true duration and progression of this effect. One study analyzed the treatment offset of IZA based on a post-hoc analysis of a subgroup which was included on the basis of a post-randomization characteristic and should therefore be interpreted with caution [39]. Interestingly, our analysis showed that only one infusion of IZA after surgical repair of a hip fracture was moderately cost-effective when no offset effect of IZA was assumed (32,237€/QALY*)* and highly cost-effective (4,516€/QALY) to dominant when 3 to 6 years offset effect was assumed. This is an important finding from a clinical perspective. If health care professionals would systematically consider IZA as treatment option after hip fracture, QALYs can be gained as good value of money also when only one infusion of IZA is initiated.

To our knowledge, there are no other studies available which analyzed the cost-effectiveness of IZA in postmenopausal women after hip fracture. Yet, two other studies analyzed the cost-effectiveness of IZA in the management of postmenopausal osteoporosis [72, 73]. Akehurst et al. [72] analyzed the cost-effectiveness of 5mg IZA in women aged 50, 60, 70 and 80 with osteoporosis (T≤2.5) and a previous fracture

for three countries (Finland, Norway and Netherlands) in comparison with branded risedronate, alendronate, ibanodronate (oral and intravenous (iv)) and generic alendronate, using a lifetime discrete event model. In Finland, IZA dominated all branded agents and was cost-effective in comparison to generic alendronate. In Norway, IZA dominated branded risedronate and ibandronate as well as branded alendronate at age classes over 70. Moreover, IZA was cost-effective in comparison to generic alendronate and branded alendronate (age classes under 70). In the Netherlands, IZA dominated branded ibandronate (iv), branded ibandronate (oral, age 70, 80) and risedronate (age 70, 80); IZA was not cost-effective (> 80,000 €/QALY (threshold for Netherlands)) in comparison to generic alendronate in all age classes. Fardellone et al. [73] estimated the cost-effectiveness of IZA in postmenopausal women with osteoporosis compared to current treatment strategies in France using a simulation approach. They found that IZA was more effective in reducing fractures and also had lower total fracture-related medical costs in comparison to current treatment.

Limitations

Models are reduced pictures of reality and should always be interpreted with respect to their assumptions and ensuing limitations. In our model we assumed that all postmenopausal women receive IZA after their first hip fracture. In real clinical practice this would not be the case, since some women were not eligible for IZA due to pre-existing medical conditions e.g. renal dysfunction and hypocalcemia [74] or because they currently take other anti-osteoporosis treatments. Furthermore, we did not include IZA-related side effects. This assumption was based on the results from the HORIZON-RFT trial [21], which found no significant difference in severe adverse events (cardiovascular, cerebrovascular and renal events) between the IZA and placebo group. Significant group differences were found in less severe side effects like myalgia and pyrexia which were treated with low-cost acetaminophen [21] and

therefore may have marginal effects on ICER results. The HORIZON-RFT trial has also shown significant lower mortality rates in individuals treated with IZA [21]. However, this effect was not modeled because the causality of IZA in reduction of mortality is not fully clear [75]. Furthermore, the HORIZON-RFT did no report a significant fracture risk reduction in subsequent hip fractures [21]. This non-significant reduction may be explained by the early cessation of the study because the pre-specified efficacy boundaries were reached before the planed study duration was finished (power problem). As suggested by Briggs and O'Brien [76] we applied the "non-significant" mean value (RR: 0.7) in the base case analysis and applied the confidence intervals as input data for PSA. Men were not included in our study, this was mainly because 75% of hip fractures occur in women [26], who therefore are the largest target group for IZA after a hip fracture. A crude estimate of the cost-effectiveness of IZA after hip fracture in male patients can be found in the deterministic sensitivity analysis (S03), where we reduced fracture risk by 30% [77]. Utility weights of women living in a nursing home were only available as EQ-VAS median scores and not as mean values [64]. Since no other studies were available we applied median data as best available evidence. Limitations and strengths regarding our modeling approach have been discussed previously [22].

Policy Implications

Despite the shown effectiveness and potential cost-effectiveness of IZA in preventing subsequent fractures after a first hip fracture, there is evidence that the post-hip fracture management is suboptimal. A study from the USA [78] showed that in 2011 only 20.5 % of hip fracture patients received osteoporosis medication within 12 month after discharge form hospital. Unsatisfactorily, the authors of this study found a decreasing trend of osteoporosis medication use rates from 40.2% in 2002 to 20.5% in 2011 [78]. Similar results were found by a multinational study, analyzing 60,393 postmenopausal women from Europe (43%, including Germany), USA (45%) as well as

Canada and Australia (12%) [79, 80]. The authors of this study reported that only 26% of the women with a hip fracture received anti-osteoporotic treatment beyond the first year of follow up [80]. Elliot-Gibson et al. [81] analyzed practice patterns in the management of patients with osteoporosis after fragility fractures. As main barriers of optimal anti-osteoporosis management they summarized, that there is often ambiguity about the responsibility for treatment initiation between health professionals (e.g. family physician or surgeon). Furthermore, there are concerns in terms of treatment costs, availability and cost of osteodensitometry, effectiveness of medication, potential side effects, and patients' acceptance [81]. Vogel et al. [82] interviewed 328 German trauma surgeon clinics about the post management of osteoporotic fractures, and reported that only 8.7% of the clinics monitor the long-term (post- hospital) success and continuation of recommended therapy, which is possibly one reason for a post-fracture treatment gap in Germany. They ascribed the low post-hospital monitoring rate of 8.7% to the sectorial boundaries between inpatient and outpatient care in the German health care system as well as to a lack of networking between hospital surgeons and outpatient physicians [82]. However, there are options to reduce sectorial boundaries and confusion in treatment responsibility between health professionals. As recommended by the "Capture the fracture campaign" of the International Osteoporosis Foundation [83] fracture liaison services (FLS) can help to overcome the gap in post-fracture treatment. The main objectives of FLS are to identify patients with an initial fracture (case finding), to perform a risk assessment and to initiate a tailored and guideline-based treatment (e.g. IZA after hip fracture) as well as to apply methods which enhance therapy adherence [83]. FLS are mostly coordinated by a clinical nurse acting as a case manager linking experts involved in the acute and post fracture management (fall prevention service, orthopedics, osteoporosis experts and primary care physicians, and patients) [83]. A successful implementation of FLS has therefore the potential to overcome sectorial boundaries and can help to decrease the treatment gap with anti-fracture agents.

Conclusion

In this cost-effectiveness analysis we found that a systematical implementation of 5 mg IZA after surgical repair of hip fracture in comparison to no anti-fracture treatment after hip fracture would result in a favorable ICER of 11,602 €/QALY. The study also showed that only one infusion of IZA showed moderate cost-effectiveness of 32,237€/QALY when no treatment offset was assumed, which was a conservative assumption. From a health economic perspective, decision makers in Germany should consider IZA as a standard treatment after hip fracture to prevent subsequent clinical fractures as good value for money.

Supplementary tables

Supplementary Table 1: Relative fracture risk of women living in a nursing home (RR_{Nurs}) and those not (RR_{NoNurs}) compared to the female general population by fracture type

Fracture type	**RR_{Nurs} by age (95% Confidence interval)***		**Distribution**	**Source**
RR hip	*65-69:* 9.13 (7.27-11.46) *70-74:* 7.12 (6.23-8.12) 75-79: 4.00 (3.68-4.36)	*80-84:* 2.33 (2.21-2.46) *85-89:* 1.65 (1.57-1.73) *90-94:* 1.17 (1.11-1.24) 95+: 0.95 (0.87-1.04)	*Log Normal*	*[22] Supp.*
RR other femur	*65-69:* 9.04 (5.38-15.20) *70-74:* 6.47 (4.65-9.00) 75-79: 3.65 (2.89-4.62)	*80-84:* 2.08 (1.76-2.47) *85-89:* 1.79 (1.54-2.07) *90-94:* 1.41 (1.19-1.66) 95+: 1.23 (0.99-1.55)	*Log Normal*	*[22] Supp. AOK*
RR vetebral	*65-69:* 2.66 (1.62-4.36) *70-74:* 2.23 (1.65-3.02) 75-79: 1.44 (1.18-1.75)	80-84: 1.22 (1.08-1.39) 85-89: 0.92 (0.81-1.03) 90-94: 0.86 (0.74-0.99) 95+: 0.84 (0.67-1.06)	*Log Normal*	*[22] Supp.*
RR humerus	*65-69:* 3.25 (2.29-4.61) *70-74:* 2.10 (1.62-2.72) 75-79: 1.74 (1.49-2.05)	80-84: 1.37 (1.23-1.53) 85-89: 1.02 (0.91-1.14) 90-94: 1.01 (0.89-1.15) 95+: 0.93 (0.76-1.14)	*Log Normal*	*[22] Supp.*
RR pelvis	*65-69:* 1.90 (0.79-4.59) *70-74:* 4.25 (3.10-5.81) 75-79: 2.70 (2.23-3.62)	80-84: 1.65 (1.46-1.87) 85-89: 1.24 (1.12-1.38) 90-94: 1.01 (0.90-1.14) 95+: 0.90 (0.75-1.07)	*Log Normal*	*[22] Supp.*
Fracture type	**RR_{NoNurs} by age (95% Confidence interval)***		**Distribution**	**Source**
RR hip	*65-69:* 0.95 (0.88-1.02) *70-74:* 0.92 (0.87-0.98) 75-79: 0.91 (0.87-0.94)	*80-84:* 0.89 (0.86-0.92) *85-89:* 0.87 (0.84-0.91) *90-94:* 0.93 (0.88-0.97) 95+: 1.04 (0.96-1.12)	*Log Normal*	*[22] Supp.*

RR other femur	*65-69:* 0.95 (0.80-1.13) *70-74:* 0.93 (0.82-1.06) 75-79: 0.92 (0.83-1.02)	*80-84:* 0.91 (0.83-1.00) *85-89:* 0.85 (0.76-0.94) *90-94:* 0.82 (0.71-0.96) 95+: 0.82 (0.65-1.04)	*Log Normal*	*[22] Supp.*

**Only significant values were applied, Supp.= Electronic supplementary material*

Supplementary Table 2: Mortality rates by residential status and fracture type

Type	**Mortality rate**			**Distribution**	**Source**
Community dwelling*	50-54: 0.00260 55-59: 0.00347 60-64: 0.00441	65-65: 0.00595 70-74: 0.00909 75-79: 0.01422	80-84: 0.02497 85-89: 0.04631 90-94: 0.09531	*None*	*[22] Supp.*
Nursing home*	65-74: 0.11012 75-84: 0.12581 85-79: 0.13950	80-84: 0.15070 85-89: 0.18629 90-94: 0.24225		*None*	*[22] Supp.*
Fracture-related	See original source [3] (table 5**)			*Log Normal*	

********To many values to report, co-morbidity adjusted values were used, Supp.= electronic supplementary material, estimated based on general female population mortality and relative mortality risk for community-dwelling women and women living in an nursing home [22].*

Supplementary Table 3: Fracture-specific hospitalization and rehabilitation probabilities

Fracture type	**Probabilities**	**Distribution**	**Source**
	Hospitalization (α; β)		
Hip	1.0	*None*	*Assumed*
Other femur	1.0	*None*	*Assumed*
Clinical Vertebral	0.47 (α =24.4; β=27.6)	*Beta*	*[22]*
Wrist	0.58 (α =30; β=22)	*Beta*	*[84]*
Humerus	0.87 (α =45; β=7)	*Beta*	*[84]*
Pelvis	0.75 (α =180.91; β=59.66)	*Beta*	*[85]*
Fracture type	**Rehabilitation** (α; β)		*See also [22]*
Hip	0.310 (α =20708; β=46076.7)	*Beta*	*[51]*
Other femur	0.310 (α =20708; β=46076.7)	*Beta*	*[51]*
Clinical Vertebral	0.053 (α = 966; β=17206.7)	*Beta*	*[51]*
Humerus	0.079 (α = 2609; β=30293.2)	*Beta*	*[51]*
Pelvis	0.120 (α = 3263; β=22991.8)	*Beta*	*[51]*
Wrist	0.009 (α = 305; β=34892.7)	*Beta*	*[51]*

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