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Cost and impact for different degrees of implementation of the S3-guideline on osteoporosis in Germany

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Abbreviations

ACER	Average cost-effectiveness ratio
BMD	Bone mineral density
DVO	Dachverband der Deutschsprachigen Wissenschaftlichen Osteologischen Gesellschaften e.V. (German Umbrella Organisation of Osteology Associations)
DXA	Dual-energy X-ray absorptiometry
EBM	Einheitlicher Bewertungsmaßstab (Uniform Assessment Standard by the National Association of Statutory Physicians)
G-BA	Gemeinsamer Bundesausschuss (German Federal Joint Committee)
GDP	Gross domestic product
GP	General physician
ICER	Incremental cost-effectiveness ratio
NNT	Number needed to treat
PTH	Parathyroid hormone
PZN	Pharmazentralnummer (pharmaceutical product identifier number)
QALY	Quality adjusted life year
RKI	Robert Koch-Institut
SERM	Selective estrogen receptor modulator
SEK	Swedish krona
SHI	Statutory health insurance
WHO	World Health Organization
YPLL	Years of potential life lost

1 Introduction

Osteoporosis is a disease that is characterized by the occurrence of fractures due to reduced bone stability caused by depletion of supporting bone structures.[1] It can be a consequence of diseases, treatments, hormonal changes and ageing.[2] If not fatal, the resulting fractures may severely restrict the patients in their daily activities and cause serious pain.[3]

Every year approximately 885 000 new cases of osteoporosis arise in Germany.[4] The overall number of fractures attributable to osteoporosis in 2010 was estimated at 115 248 and the numbers are expected to more than double by the year 2050.[5] Especially hip fractures have a detrimental effect on health. In 2002 3 485 osteoporosis related hip fractures in Germany are estimated to have resulted in death, which corresponds to 22 724 years of potential life lost (YPLL).[6] The decrease in quality of life, especially after multiple fractures, is comparable to other chronic conditions such as diabetes and arthritis.[7] The high mortality and morbidity following osteoporotic fractures provide a strong motive to attend to this public health issue.

As the disease is “clinically silent” up to the fracture, screening approaches are being researched, but currently mass-screening has not been proven effective in reducing morbidity or mortality.[8] The measurement of bone mineral density, a common screening method, has a similar predictive value on fractures as blood pressure measurement has on stroke.[9] In Germany the guideline of the “Dachverband der Deutschsprachigen Wissenschaftlichen Osteologischen Gesellschaften e.V.” (DVO, the German Umbrella Organisation of Osteology Associations) with its orientation toward individual fracture risk, instead of considering solely bone mineral density, attempts an age- and risk factor-specific stepwise screening approach for osteoporosis, but the implementation is not comprehensive.

Osteoporosis is an interdisciplinary challenge, involving trauma surgery as well as general physicians (GPs), physiotherapists and nutritionists amongst others.[10] The involved parties need to work hand in hand to ensure a high quality of treatment. However, in Germany the treatment of osteoporosis is still characterized by under-treatment and inappropriate treatment.[11] The developers of the S3-guideline on osteoporosis aim to change this by

1 Consensus development conference: Prophylaxis and treatment of osteoporosis 1991: 114
2 Kanis et al. 2013a: 28
3 Faßbender et al. 2003: 1615
4 Hadji et al. 2013: 53
5 Bleibler et al. 2013: 840; Konnopka et al. 2009: 1120
6 Konnopka et al. 2009: 1120
7 Adachi et al. 2010: 809
8 Altkorn, Cifu 2015
9 Kanis et al. 2013a: 27
10 Faßbender et al. 2003: 1616
11 Faßbender et al. 2003: 1615

giving age group- and risk-specific recommendations. Besides improving the quality of treatment, guidelines are also intended, from a political standpoint, to facilitate economic feasibility of health care.[12] Since funds are limited, it is important to allocate funds as effectual as possible.[13]

In this thesis the methods of health technology assessment, that is, systematic compilation of study results and synthesis of evidence in an analytic framework,[14] are applied to the issue. In a model the outcomes of different degrees of implementation of the S3-guideline on osteoporosis are simulated, based on studies on osteoporosis prevalence, fracture and mortality rates. The essential aspects of the disease, including epidemiology, burden of disease, natural history and available treatments are provided in chapter 2. The following chapter provides insight into the S3-guideline, after which the research question is defined. The modelling approach is described in chapter 4, including considerations in constructing the model and a detailed overview of the eligible studies, as well as deliberations on which data are to be applied in the model. The results of the model are provided in form of three scenarios (chapter 5), and the model is subjected to a sensitivity analysis (chapter 6). The results are scrutinised in the next chapter and compared to other studies (chapter 7) before reaching a conclusion in the closing remarks.

2 Osteoporosis

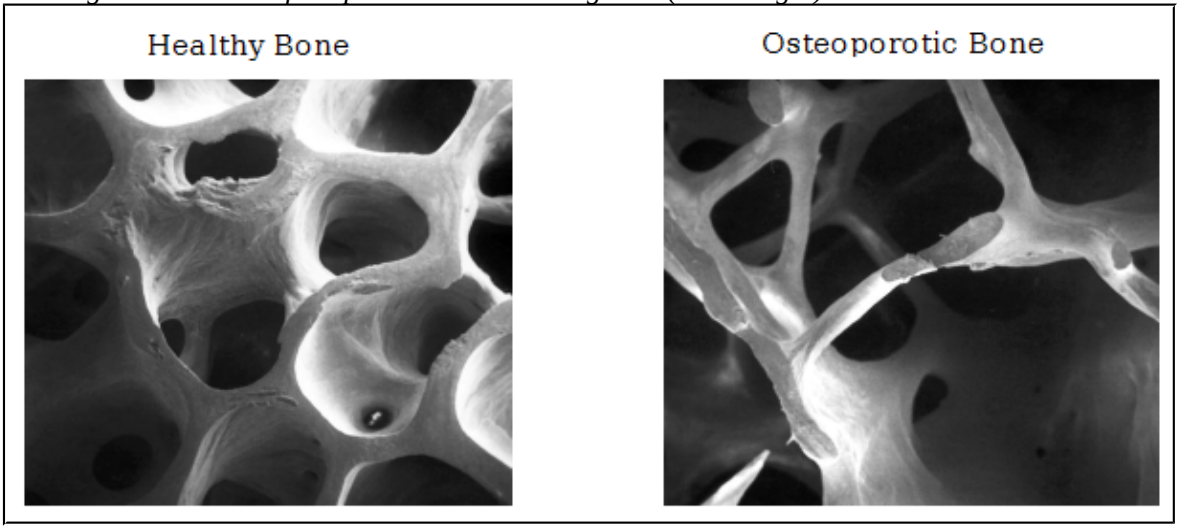
Osteoporosis is a condition characterised by low bone mineral density and deterioration of bone tissue thereby compromising the micro-architecture and stability of the skeletal system. This leaves the affected individual prone to fragility fractures.[15] The most common osteoporotic fracture sites are the spine, hip and forearm, but fractures can also occur in other bones.[16] While research on osteoporosis became an area of scientific interest as early as 1948, its relevance as a public health issue has only been recognized in recent decades.[17]

There have been various attempts at defining and classifying the disease. This is probably due to the unsymptomatic progression which complicates the diagnosis. In general all definitions draw on one or more of the following elements: bone mass or bone mineral density (BMD), bone structure (see figure 1), and fractures.[18] In 1991 the Consensus Development Conference agreed on the following definition:

> *"Osteoporosis is a disease characterized by low bone mass, microarchitectural deterioration of bone tissue leading to enhanced bone fragility, and a consequent increase in fracture risk"*[19]

12 Ollenschläger et al. 2001: 481
13 Zethraeus et al. 2007: 10
14 Philips et al. 2006: 356
15 Kanis et al. 2013a: 24
16 Kanis et al. 2013a: 24
17 Marcus et al. 2013: 21
18 Kanis, Gluer 2000
19 Consensus development conference: Prophylaxis and treatment of osteoporosis 1991: 114

Figure 1: Images of healthy trabecular bone (left) and of porose osteoporotic trabecular bone showing deterioration of the plates and connecting rods (on the right).



Source: Electron-microscopical image showing biopsies of the iliac crest taken from Dempster et al. 1986

In 1994, the World Health Organization (WHO) issued a report defining the criteria for diagnosis of osteoporosis by T-scores.[20] The T-score compares the BMD value of an individual to a reference population, commonly the female National Health and Nutrition Examination Survey (NHANES) III study population (20-29 year-olds).[21] The T-score is calculated by subtracting the reference BMD from the result of the individual BMD measurement and dividing the outcome by the standard deviation.

$$T-score = \frac{Measured\ BMD - Young\ adult\ mean\ BMD}{Young\ adult\ \ population\ SD} \qquad (1)$$

The 1994 consensus paper states that a T-score of -1 to -2.5 should be considered low bone mass (osteopenia) and a T-score lower than -2.5 is to be considered as osteoporosis. A T-score below -2.5 concurrent with a fracture is termed severe osteoporosis.[22] The values were chosen arbitrarily picking a cut-off at which osteoporosis is the exception in women before menopause and were especially designed for epidemiological purposes.[23] At the time of establishment the T-scores were of importance for awareness and conformity within diagnoses.[24] But T-scores have the disadvantage of having a low sensitivity concerning fracture probability, and many individuals with bone mineral density above the osteoporotic range will contract a fracture.[25] While the WHO definition acknowledges that bone structure is relevant for the occurrence of fractures, the WHO diagnosis criteria do

20 World Health Organization 1994
21 Looker et al. 1998; Kanis, Gluer 2000
22 Kanis et al. 1994
23 Kanis et al. 2013b; Kanis, Gluer 2000: 196
24 Leslie, Lix 2014: 2
25 Hernlund et al. 2013: 20

not include it, as it is not easily measurable clinically.[26] This may change in the future as methods to assess bone structure become available.[27]

Bone mineral density measurement can be used to infer the amount of bone, since the ratio of minerals and collagen within the bone normally stays the same. This ratio can, however, be impacted by poor nutrition and diseases such as osteomalacia, osteopetrosis, osteoarthritis and osteoarthrosis, which will lead to false conclusions.[28] For BMD measurements to be meaningful, a differential diagnosis is therefore necessary. BMD can be applied for diagnosis, risk prediction and monitoring of treatment effect.[29]

BMD can be measured by various methods. Currently, dual energy x-ray absorptiometry (DXA), which measures the calcium content of the bone tissue, is the gold standard. The derived T-scores have a 95% CI of ±1 which can have a strong impact on diagnosis. Other bone densitometry techniques are also available and have been found to be of use in predicting fractures. However the correlation of the differing measurement techniques is not good.[30] Therefore, despite its drawbacks, DXA is the only form of densitometry which is reimbursed by the statutory health insurance in Germany.[31]

Within an individual BMD varies between sites. The proximal femur and lumbar spine are the sites mainly measured, the proximal femur being less susceptible to age related deformities and therefore established as the diagnostic reference site.[32] The outcome is areal density given in grammes per square centimetre. The areal BMD cannot completely explain the variance in bone strength.[33] This indicates that besides bone mass other factors are also relevant for the presence of osteoporosis.

2.1 Burden of Disease

The prevalence of osteoporosis and osteoporotic fractures in Germany is unknown. Regarding the German population aged 50 and above, estimates arrive at values ranging from 13% to 39% of the population having osteoporosis, with women having a higher prevalence than men.[34] The bandwidth of the estimates is probably due to the differing reference populations and the multitude of methods, such as random population surveys

26 Hernlund et al. 2013: 5
27 Kanis et al. 2013a: 25
28 Schulz, Manns 1992; Kanis et al. 2013a: 25
29 Hernlund et al. 2013: 5,17
30 Blake, Fogelman 2009
31 Gemeinsamer Bundesausschuss (Berlin) 2013
32 Hernlund et al. 2013: 5f.; Kanis, Gluer 2000, 195
33 Kanis et al. 2013a: 25
34 Robert Koch Institut 2014; Hadji et al. 2013; Häussler et al. 2007; Fuchs et al. 2013; Scheidt-Nave, Starker 2005, 1342; Acker 2013; Sondergeld 2015; Bassgen et al. 2013; Brecht, Schädlich 2000

(Studie zur Gesundheit von Erwachsenen in Deutschland (DEGS)[35], Telefonischer Gesundheitssurvey 2003 (GSTel03)[36], Gesundheit in Deutschland aktuell (GEDA)[37]), with the issues of recall bias and responder bias, or analyses of claims data of the statutory health insurance (Bone Evaluation Study (BoneEVA)[38], Bone Evaluation Study (BEST)[39]) (see table 1). These have the problem of providing information only with respect to a limited number of variables excluding clinical values, as well as not being representative for the general population due to selection differences.

Table 1: Estimated prevalences in selected studies for age related subgroups of the female German population (in %).

Study	**Overall (50+)**	**50-59**	**60-69**	**70-79**
DEGS	13.1	4.1	12.7	25.2
	Overall (50+)	**50-64**	**65-74**	**75+**
GSTel03	14.2[a]	10.0[b]	17.1	23.7
GEDA	14.5	7.8	20.5[c]	-
BEST	24	17	32	48
BoneEVA	39.0	23.3	46.7	59.2

[a] *Prevalence for female population 45+*
[b] *Prevalence for female population 55-64*
[c] *Prevalence for female population 65+*

While the differences shown above presumably mainly result from the differing populations and methods, they could, however, also indicate a high number of undiagnosed cases in the German population, seeing that BEST and BoneEVA also included fractures of people previously undiagnosed.

The BEST study estimates approximately 885 000 new cases of osteoporosis each year within the German population. In the age group 74 years and above the incidence is estimated to be 5.8% for women and 2.3% for men.[40]

2.1.1 Fractures

Fractures are the clinical outcome of osteoporosis and in many cases the first sign of the disease. The most common fractures are forearm fractures, hip fractures and vertebral fractures (see table 2).[41] These fragility fractures *"are associated with substantial pain and suffering, disability and even death for the affected patients and substantial costs to society."*[42] Having sustained a fracture increases the probability of sustaining a further

35 Fuchs et al. 2013
36 Scheidt-Nave, Starker 2005: 1342
37 Robert Koch Institut 2014
38 Häussler et al. 2007
39 Hadji et al. 2013
40 Hadji et al. 2013: 53
41 Häussler et al. 2007
42 Svedbom et al. 2013: 76

fracture in the future.[43] Many patients sustaining a fracture or a fall experience fear of falling and partly even depressive episodes as a consequence. This may lead to protective behaviour such as inactivity which in turn increases the fracture risk.[44]

Table 2: Share of fractures by fracture site amongst osteoporotic patients of the TK (2006-2009).

Fracture site	**Share amongst osteoporotic patients**
Forearm	13.8 %
Thoracic spine, ribs, sternum	12.7 %
Lumbar spine, pelvis	8.9 %
Femur	7.9 %
Shoulder, humerus	6.7 %
Lower leg	4.5 %
Wrist, hand	2.9 %
Patients fractured	52.0 %

Source: BEST Study[45]
As some patients sustained multiple fractures the portion of patients fractured is lower than the summed up numbers by fracture site.

Regarding the total numbers, it appears that a high burden of fractures is borne by persons with an osteopenic bone mineral density as they sustain more than half of all fractures even though their relative risk of sustaining a fracture is lower. This is caused by the large share of the population being osteopenic.[46]

For 2003 the BoneEVA study estimates that 333 322 osteoporosis patients in Germany experienced at least one fracture.[47] Currently, fewer men than women sustain a fracture each year. This is partially due to demographic characteristics; therefore the number of men sustaining fractures is expected to increase in the next decades.[48]

The incidence of fractures differs between European countries, with the highest incidences of hip fractures in Denmark and Sweden (235 and 213 per 100 000 of the population) and the lowest in Romania and Poland (85 and 94 per 100 000 of the population). The incidence for hip fracture is 141 per 100 000 people in Germany[49] Hernlund et al. report that in 2010 95 672 women and 34 178 men in Germany experienced a femur fracture.[50] In 2013 172 587 femur fractures were treated in hospitals in Germany.[51] A portion of these femur fractures will, however, have been due to accidents with a high impact, such as car collisions, and not osteoporosis. In women aged 65 to 74 69 % of femur fractures are

43 Pasco et al. 2006: 1047; Schumacher et al. 2014: 143
44 Berlin Hallrup et al. 2009: 381; Faßbender, Pfeilschifter 2008: 64–66; Cauley 2013: 1246; Karlsson et al. 2013: 748
45 Hadji et al. 2013
46 Pasco et al. 2006: 1047
47 Häussler et al. 2007: 80
48 Häussler et al. 2007: 83
49 Hernlund et al. 2013: 55.
50 Hernlund et al. 2013: 59.
51 Statistisches Bundesamt 2015d: 46

attributed to osteoporosis, in women over the age of 75 89 % of femur fractures are assumed to be caused by osteoporosis.

The mortality linked to osteoporosis is mainly caused by fracture incidents. It is estimated that 14 of 100 000 women of the general population in Germany die of a hip fracture each year.[52] Mortality rates after fracture are highest for hip fractures (with 16-26 % of fracture patients deceased after one year[53]) followed by vertebral fractures. The older a patient is the more likely death due to fracture becomes. The risk of death after fracture is highest in the first months after fracture after which it declines, while still being increased compared to the general population for many years.[54]

2.1.2 Quality of Life

The GSTel03 survey highlighted that women with osteoporosis rate their health status to be bad or very bad more often than women without osteoporosis.[55] A difference in quality of life between unfractured osteoporotic patients and osteopenic patients was also identified in Austria.[56] Lange and colleagues found that German insurants who sustained a vertebral fracture already incurred higher costs in the year prior to their fracture than age and sex matched insurants.[57] These finding indicate that even prior to fracture osteoporosis may already affect the health and quality of life of patients.

Besides this, experiencing a fracture certainly impacts the quality of life of the patients, leading to short and long-term limitations, and may also impact the living conditions by necessitating assistive care.[58] Hip and spine fractures have the strongest impact on quality of life of all fractures.[59] Hip fractures also have the most devastating effect on independence and are the most expensive.[60] Of formerly mobile hip fracture patients only approximately half are able to walk without an assistive device one year after the fracture.[61] Around 40 % of admissions to long-term care facilities are connected to a fall incident.[62]

2.1.3 Cost of Osteoporosis

The yearly direct costs incurred by osteoporosis are estimated at € 5.4 billion for Germany. Fractures were identified as the drivers of cost in Germany with inpatient costs making up more than half of direct costs. The population aged 75 years and above, who contract the

52 Hernlund et al. 2013: 65
53 Berry et al. 2007; Bondo et al. 2013
54 Leboime et al. 2010; Haentjens et al. 2010
55 Scheidt-Nave, Starker 2005: 1342
56 Jahelka et al. 2009: 238
57 Lange et al. 2014: 2439
58 Pasco et al. 2005: 2050
59 Roux et al. 2012: 2867
60 Hernlund et al. 2013: 5ff.; Kanis et al. 2013a: 24; Häussler et al. 2007: 82
61 Endres et al. 2006: 93ff.; Pasco et al. 2005: 2049
62 Faßbender, Pfeilschifter 2008: 64

most osteoporotic fractures, therefore had the highest contribution to the total cost. Other cost driving categories were long term care and medication. Long-term care due to osteoporosis and subsequent fragility fractures is estimated at approx. 5 % of overall long-term care expenditure. The bulk of medication cost was generated by analgesics prescriptions.[63] This could indicate room for improvement of preventive treatment.

In another study direct and indirect cost of only osteoporosis attributable fractures were estimated at € 1 billion.[64] In a European compendium the economic burden of osteoporosis in Germany is estimated at € 37 billion, with about two thirds being due to acute fracture treatment.[65] Overall, osteoporosis patients are assumed to be responsible for 3.5 % of expenditure of the health insurance (SHI and private insurances) in Germany.[66]

2.2 Treatment

Loss of bone mass is part of the natural ageing process and can be exacerbated by hormonal changes leading to menopause. The resulting fractures, and to some extent also the degree of bone mass reduction, can be reduced by eliminating lifestyle risk factors, as is the case with many widespread diseases. With regard to osteoporosis the following two lifestyle changes are of particular importance: firstly, performing weight bearing physical activity which decreases the thinning of the plates and rods of the bone, as well as preventing falls,[67] and secondly, keeping a healthy diet thereby providing the body and especially the bones with the essential vitamins and minerals.[68] But pharmaceuticals can also be an important component of prevention.[69]

Basic treatment of osteoporosis consists of securing adequate amounts of calcium and vitamin D. Ideally, this is achieved by a balanced diet and sunlight exposure, however, if this is not the case, supplementation is recommended in Germany.[70] The evidence for supplementation is thin[71] and has recently been tackled.[72]

Apart from this baseline treatment, additional pharmaceutical intervention may be warranted. Two main approaches exist, firstly inhibiting bone resorption (anti-resorptives) or secondly promoting the formation of bone. Anti-resorptives are more common and

63 Häussler et al. 2007: 81f.
64 Bleibler et al. 2013: 841
65 Svedbom et al. 2013: 2
66 Häussler et al. 2007: 81
67 Morgan et al. 2013: 8
68 Kurth, Pfeilschifter 2007: 685; Howe et al. 2011; Cameron et al. 2014; Giangregorio et al. 2013; Dachverband Osteologie DVO e.V. 2014: 147
69 Wells et al. 2011: 2010b
70 Dachverband Osteologie DVO e.V. 2014: 147
71 Avenell et al. 2014
72 Grey, Bolland 2015

include a multitude of medications with differing modes of action.[73] One of the oldest agents, an anti-resorptive, used for osteoporosis treatment is hormone replacement therapy.[74] However, due to the increased risk of heart attacks and breast cancer, hormone replacement therapies are now only prescribed in severe cases of climacteric affliction, with the additional benefit of preventing bone deterioration, or if other treatment options are not viable.[75] Similarly selective estrogen receptor modulators (SERMs) are mainly prescribed to post-menopausal women at risk of osteoporotic fractures who also have a high risk of developing invasive breast cancer. In Germany currently only raloxifene, marketed under the names “Evista” and “Optruma”, is available.[76] The mode of action of estrogens is complex and still being researched.[77]

The most commonly prescribed class of agents to prevent bone deterioration is bisphosphonate. Bisphosphonates were approved for osteoporosis treatment in the 1990s. They bind to the bone and inhibit osteoclasts (bone resorbing cells). The bisphosphonates remain in the bone for some time after treatment has been discontinued.[78] This leads to a protective effect even after treatment has ceased. Amongst the many bisphosphonates there are four mainly prescribed active components: alendronate, risedronate, zoledronate, ibandronate. They were shown to reduce the vertebral fracture risk and in part also the non-vertebral and hip fracture risk.[79] The effects continue in the years after the end of the treatment. Gastric issues are a common side-effect. Reports of adverse events such as osteonecrosis of the jaw and subtrochanteric fractures have increased, however the safety profile of these drugs is still considered good.[80]

A newly approved agent is denosumab, a RANKL inhibitor. Treatment can decrease bone turnover and increase BMD to a stronger extent than bisphosphonates, however, the effect wears off more quickly.[81] Treatment with denosumab positively influences the risk of vertebral and hip fractures.[82] Another agent, strontium ranelate, was approved for osteoporosis treatment in Germany in 2004. Based on bone marker measurements, it is assumed that strontium ranelate has both an anti-resorptive as well as a stimulating effect on bone formation. However, due to adverse effects[83] and missing head-to-head studies with bisphosphonates, it is set apart as a third choice option by the German Joint Federal Committee (G-BA), which decides on which services are to be reimbursed by the statutory health insurances (SHI).[84]

73 Russell 2015: 118
74 Kanis et al. 2013a: 39
75 Dachverband Osteologie DVO e.V. 2014: 192; Marjoribanks et al. 2012
76 Kurth, Pfeilschifter 2007: 688
77 Russell 2015: 118
78 McClung et al. 2013
79 Wells et al. 2010b: 2011; Russell 2015: 120
80 Dachverband Osteologie DVO e.V. 2014: 220
81 Russell 2015: 117f.
82 Boonen et al. 2011: 1729f.
83 Reginster et al. 2009
84 Gemeinsamer Bundesausschuss (2007)

The only approved bone forming agents are based on the human parathyroid hormone (PTH). After stimulating solely bone growth at first, it later prompts both resorption as well as formation, maintaining an increase of bone matter and possibly improving bone micro-architecture. This makes it a favourable choice for high risk patients. Studies indicate that the effect of PTH may wear off after 18 months, calling for anti-resorptives to retain the improved BMD, but further research is warranted.[85] Side-effects include dizziness, nausea and cramps.[86]

2.2.1 Adherence

A common issue of osteoporosis therapy is the low adherence of patients, especially as long-term treatment is assumed necessary to reduce fracture rates.[87] There are many possible causes for the low adherence rates ranging from intolerable side-effects to low risk perception and lack of knowledge of consequences of osteoporosis.[88] In general patients also seem to have a higher threshold of valuing risk acceptable before instigating treatment than health care professionals.[89]

In the hope of increasing adherence, compounds have been developed which do not have to be taken on a daily basis. Hadji and colleagues found that adherence still was not good and whether treatment regimen was weekly or monthly did not have any effect. Daily treatment regimens, however, had an even higher cessation of treatment rate.[90]

But not only treatment regime is of relevance to patients. Given the choice between a weekly treatment which reduces hip and vertebral fractures and a monthly treatment reducing only the vertebral fracture rate most study participants (82%) opted for the more efficacious treatment instead of the more convenient treatment form.[91]

Adherence is influenced by the treatment itself, as well as the individuals' perception, which may be influenced by knowledge and whether they feel they are being taken seriously.[92] There is no evidence of a healthy adherers' bias concerning medication compliance.[93]

85 Cosman, Lindsay 2013: 1949, 1958
86 Cosman, Lindsay 2013: 1951
87 Hadji et al. 2012
88 Huas et al. 2010: 5
89 Douglas et al. 2012: 2139
90 Hadji et al. 2012: 227
91 Keen et al. 2006: 2378
92 Huas et al. 2010: 3
93 Cadarette et al. 2011; Harris et al. 2009; Hughes et al. 2001; Nowson 2010; Silverman, Gold 2011; Wang et al. 2014

2.2.2 Under-treatment

In Europe, USA and Canada the burden of disease due to osteoporosis is high, while measures to combat the disease and measures of fracture prevention are insufficiently applied.[94] Under-treatment of osteoporosis is common. Even in patients presenting with a fragility fracture, less than 50 % are followed up with a BMD scan, an osteoporosis diagnosis or treatment.[95]

Slightly older data from a nationwide telephone survey indicate that in Germany more than 40 %[96] of women diagnosed with osteoporosis are not treated for the condition.[97] At EU level the comparison of prescription data with the population profile illustrates a treatment gap of 77 % for German women.[98]

In their analysis of claims data Häussler and colleagues found an even bigger treatment gap. Only about 20 % of patients diagnosed with osteoporosis were receiving treatment, half of which were treated with bisphosphonates. Younger female patients were receiving treatment more often (31 %) than the older female patients (19 %).[99] Häussler and colleagues come to the conclusion that especially older, self-dependently living osteoporotic persons in Germany are undertreated. This also includes patients with an osteoporotic fracture. At the most, one third of elderly fracture patients were actually diagnosed with osteoporosis.[100] Hadji and colleagues also identify a large discrepancy between patients with an osteoporotic fracture and those being treated for osteoporosis. Over the study duration of 3 years many persons had multiple fractures, which indicates a necessity for optimization of osteoporosis treatment.[101]

3 S3-Guideline on Osteoporosis

The German S3-guideline on osteoporosis was developed by the “Dachverband der Deutschsprachigen Wissenschaftlichen Osteologischen Gesellschaften e.V.” (DVO) the German Umbrella Organisation of Osteology Associations.[102] “S3” indicates that the guideline is based on a systematic review and is evidence-based. The included recommendations are consensual and have been derived in a structured process involving the appropriate medical societies and professional associations.[103] The aim of the guideline is to support physicians in diagnosing and treating osteoporosis on the basis of current

94 Hernlund et al. 2013: 5
95 Giangregorio et al. 2006; Elliot-Gibson et al. 2004; Freedman et al. 2000
96 The much higher medication in the study could be due to a recall bias, as those who are treated will be the ones who remember that they were diagnosed with osteoporosis. Also it is not clear whether supplements were counted as medication.
97 Scheidt-Nave, Starker 2005: 1346
98 Svedbom et al. 2013: 81
99 Häussler et al. 2007: 80
100 Häussler et al. 2007: 83
101 Hadji et al. 2013: 53
102 Dachverband Osteologie DVO e.V. 2014: 18
103 AWMF online (n.d.)

evidence. The guidelines do not constitute rules, physicians should apply their own judgement to each case, but the evidence-base does provide good reasoning for employing the guidelines as decision guidance.[104] Application of the guidelines is not compulsory.

The German S3-guideline on osteoporosis applies the WHO diagnosis criteria of T-scores, but starting in 2006 a paradigm change has taken place. Treatment is no longer to be prescribed solely based on T-score, which gives a population based fracture risk, but instead based on individual risk of fracture.[105] This is an advancement, as the ultimate goal in osteoporosis treatment is the prevention of fractures and not the increase of BMD. Compared to the previous guideline the importance of treating older patients is stressed.[106]

The German algorithm is based on published studies. Effectively, the guideline is a step-wise screening tool with risk dependent diagnostics and treatment recommendations. Based on the general risk of population groups – defined by age and sex – specific risk factors of an individual are assessed, and if the individual risk is elevated, subsequent tests are performed, depending on the outcome treatment is initiated. Intervention based on fracture risk is preferable as the same BMD at different ages will have a differing 10-year fracture risk.[107] Research is, however, still being aggregated on the interaction of the various risk factors.[108] Based on the 10-year fracture risk, intervention thresholds can be defined. These differ from country to country and are influenced by regional prevalence, differing fracture risks, medication effectiveness, as well as, in some countries, cost-effectiveness calculations.[109]

Outside of Germany similar developments have taken place driven by the development of the FRAX® tool developed by the World Health Organization (WHO) Collaborating Centre for Metabolic Bone Diseases at the University of Sheffield (UK) in 2008[110]. This is also an algorithm with which to calculate the 10-year probability of hip fracture as well as major fracture (defined as fractures of hip, spine, wrist, upper arm) based on the presence of risk factors and/or BMD. The underlying data stem from eight large trials and the outcome is calibrated to specific countries based on the national age specific relative risks and mortality rates, as they are competing risks.[111] Many national guidelines have been adapted to incorporate fracture risk assessment. Both the UK and US guidelines apply FRAX®. In the UK the National Osteoporosis Guideline Group (NOGG) recommends the consideration of treatment of all persons with a prior fragility fracture and the utilization of FRAX® without BMD measurement to assess the 10-year risk of postmenopausal women

104 Bartl, Bartl 2015: 6
105 Hernlund et al. 2013: 6; Dachverband Osteologie DVO e.V. 2006: 79; Piatek et al. 2013: 596
106 Dachverband Osteologie DVO e.V. 2006
107 Kanis et al. 2013b: 1612
108 Kanis et al. 2013b: 1617
109 Bolland, Grey 2010; Rendl et al. 2013; Kanis, Gluer 2000: 198
110 Online at: http://www.shef.ac.uk/FRAX/index.aspx [12.09.2015].
111 Kanis et al. 2013b: 1611–1612

and men over the age of 50 with (at least) one clinical risk factor. [112] The US guideline takes an opposite approach. Every woman over the age of 65 is eligible for a free BMD scan, as are younger postmenopausal women with risk factors, men over the age of 70 and any person with a fragility fracture after the age of 50. For women with a bone density in the osteopenic and osteoporotic range the fracture risk is assessed using FRAX® and treatment is recommended if the 10-year fracture probability is higher than 3 % for hip fracture or 20 % for major fractures.[113]

3.1 Recommendations of the S3-Guideline on Osteoporosis

The German S3-guideline gives general advice on osteoporosis prophylaxis, fracture risk assessment, diagnosis procedure and treatment. It also provides information on exacerbating medications and diseases and respective treatment alternatives.

General prophylaxis, i.e. healthy diet, physical activity, controlled sun exposure and smoking cessation, is recommended for the whole population.[114] Diagnostic activities focusing on osteoporosis should be performed if the fracture risk assessment indicates a risk of 20 % or more of sustaining a fracture in the next ten years. This is dependent on age and sex as well as the presence of various, weighted risk factors. Basic diagnostics should also be performed if an individual has already sustained a fracture. The diagnostic activities include assessment of treatable fracture risk factors (e.g. calcium or vitamin D deficiency, fall risk increasing medication), checking for signs of vertebral fractures (if applicable following up with imaging), DXA densitometry, basic blood work, and in older patients an assessment of muscle strength.[115]

Until recently bone mineral density testing was only reimbursed in Germany if the individual had already contracted a fragility fracture. This regulation was amended in 2013, and now reimbursement of bone mineral density testing of persons without fracture is possible if pharmaceutical treatment is being deliberated, dependent on the outcome of the DXA examination.[116]

On the basis of the results of the diagnostic procedures fracture risk is reassessed. In persons with a 10-year fracture risk of 20 – 30 % according to the DVO fracture risk assessment, a re-assessment of bone mineral density is advised at a later time. The time frame is dependent on the BMD value and the risk profile of the individual.[117] If an individual has a fracture probability of 30 % or more, treatment of osteoporosis is

112 National Osteoporosis Foundation (NOF) 2013: 15f.; Johansson et al. 2012; Leslie, Lix 2014: 17
113 National Osteoporosis Foundation (NOF) 2013; Leslie, Lix 2014: 17
114 Dachverband Osteologie DVO e.V. 2014: 175
115 Dachverband Osteologie DVO e.V. 2014: 160f.
116 Gemeinsamer Bundesausschuss (Berlin) 2013
117 Dachverband Osteologie DVO e.V. 2014: 241

recommended. The fracture risk derived in the DVO algorithm refers to fractures of the spine and hip. Based on an estimated 50 % efficiency of the medication this constitutes a number need to treat (NNT) of 13 – 22 people for one person to profit from treatment.[118]

Patients receiving treatment should initially visit their prescribing physician every three to six months because of possible adverse effects, but regular DXA examination is not necessary. The guideline does not give a recommendation for a specific medication, instead it lists the evidence-base for the efficacy of the various agents in preventing the different fractures. Physicians are advised to take the effects and side-effects, effect duration, drug administration and price into consideration when prescribing a treatment.[119] Duration of treatment is at the discretion of the attending physician.[120]

3.2 Implementation of the S3-Guideline on Osteoporosis

Guidelines, which are the most common form of implementing evidence-based medicine, are subject to scepticism. By some they are regarded as a threat to professional autonomy and a danger for patient-specific treatment, even though they constitute guidance and not rules.[121]

As of 2003, 39 % of primary care physicians in Germany interviewed as part of the "Healthcare Monitor" agreed with the statement that patients were best off if treated without guidelines, but based on the knowledge of the needs and patient possibilities. On the other hand 43 % felt that patients are best treated "on the basis of scientific knowledge in the form of guidelines". The compromise statement that treatment should be based on a fair "balance of scientific recommendation, individual need and current possibilities" gained agreement from 80 % and disagreement from 5 % of the physicians. In the same study 55 % of physicians stated that they applied guidelines and 22 % stated that they employed guidelines only as an exception. The guidelines were found to be not practical enough (21 %) and 14 % of physicians also claimed that the content was not supportable. This shows a split opinion within the group of primary health care physicians with physicians who have been practising for a longer time and those in small practices with few staff members being more sceptical.[122] Besides from fears for professional freedom, the scepticism may also stem from the unclear implications of guidelines for liability law[123] and the possibility of financial recourse.[124]

118 Dachverband Osteologie DVO e.V. 2014: 183
119 Dachverband Osteologie DVO e.V. 2014: 212
120 Dachverband Osteologie DVO e.V. 2014: 247
121 Schmacke 2002
122 Butzlaff et al. 2006: 50
123 Ollenschläger et al. 2001: 474
124 Karstens et al. 2015

The dissemination of guidelines in Germany is passive. Physicians themselves need to take action by reading journals, consulting the internet and participating in conferences.[125] Low motivation and lack of knowledge of the guidelines are the most important reasons for not applying guidelines. By making the Asthma-guideline the topic of an attendance-based training with continuing medical education credits the knowledge on the topic, as well as application of the guideline, was found to increase.[126]

Concerning the guideline on osteoporosis, a survey by the Robert Koch-Institut (RKI) found that 51.7 % of the partaking general physicians stated that they had good knowledge of the S3-guideline on osteoporosis, many of them applying the guideline without encountering problems. In contrast 22.6 % declared that they did not know the guideline at all. These values may be influenced by social desirability, and are therefore probably overestimating the guideline implementation. Budgetary restrictions were a common concern and were expressed as an obstacle in the application of the guideline.[127]

Similarly only 35 % of hospitals with trauma surgery have a standardised course of action for diagnosis and treatment of osteoporosis after a (possibly) osteoporotic fracture. Concerning diagnostic procedure the standards of 30 % of these hospitals correlated to the actions recommended by the S3-guideline on osteoporosis. The hospital-specific standardised course of action for treatment for osteoporosis agreed with the S3-guideline in 51 % of the hospitals.[128]

This suggests that the degree of implementation of the S3-guideline shows room for improvement. This is especially of importance as the treatment of osteoporosis, in the years prior to the development of the first guideline, was described as characterised by under-treatment and inappropriate treatment.[129]

3.3 Research Question

Fractures have a considerable effect on the quality of life and the life span of osteoporosis patients. The S3-guideline, which was one of the first to incorporate the paradigm change in osteoporosis understanding and treatment, could considerably improve the treatment of osteoporosis. However, it is unclear to which extent the guideline is actually adopted and how strongly the application affects health outcomes of patients. As it has been theorized that guidelines may be cost-saving,[130] the effect on the payor side is also of interest. Therefore, in this thesis the two following questions are to be examined:

125 Ollenschläger et al. 2001: 478
126 Redaèlli et al. 2015
127 Chenot et al. 2007: 586f.
128 Vogel et al. 2008: 872f.
129 Faßbender et al. 2003: 1615; Bestehorn et al. 2003
130 Kosimbei et al. 2011

How do different degrees of implementation affect the health outcomes concerning osteoporosis and would increasing the degree of implementation be cost-effective or even cost-saving?

4 Method

Due to the paradigm change incorporated in the S3-guideline the current state of research does not provide for much data material pertaining directly to the thresholds stated within the guideline. Also, little data is available on the degree of implementation in Germany. The stated research question is therefore to be examined on the basis of a model. Models are applied when studies are too cumbersome or expensive, like for example monitoring treatment effects over a cohort's lifetime. They combine data from different sources and can provide the framework for decisions under uncertainty besides identifying relevant areas for future study.[131] Simplification is the advantage as well as limitation of models. The aim is to reduce complexity while still including all relevant information, thereby achieving a parsimonious model.[132] But models can only provide estimates and are conditional on the quality of the input data.[133]

Within health economics various model types are employed, each with their specific assets and drawbacks. They either simulate the aggregate level using cohorts, such as the decision tree and many types of Markov models, or run several simulations on the individual patient levels e.g. microsimulation, discrete event simulation.[134] While micro level simulations have the advantage of being able to incorporate the patient history and providing probabilistic results, they also require large amounts of specific data and calculation power.[135] And even these models cannot fully include the impact of issues such as patient behaviour and genetics.[136]

For this thesis, as detailed data on the issue as well as available calculation power was limited, a combined decision tree and cohort Markov model was developed. This approach was also applied because of the advantage of being able to meet the challenges of modelling a chronic disease over time. The model was constructed and calculated with the spreadsheet software Libre Office Calc, version 4.3.7.2.

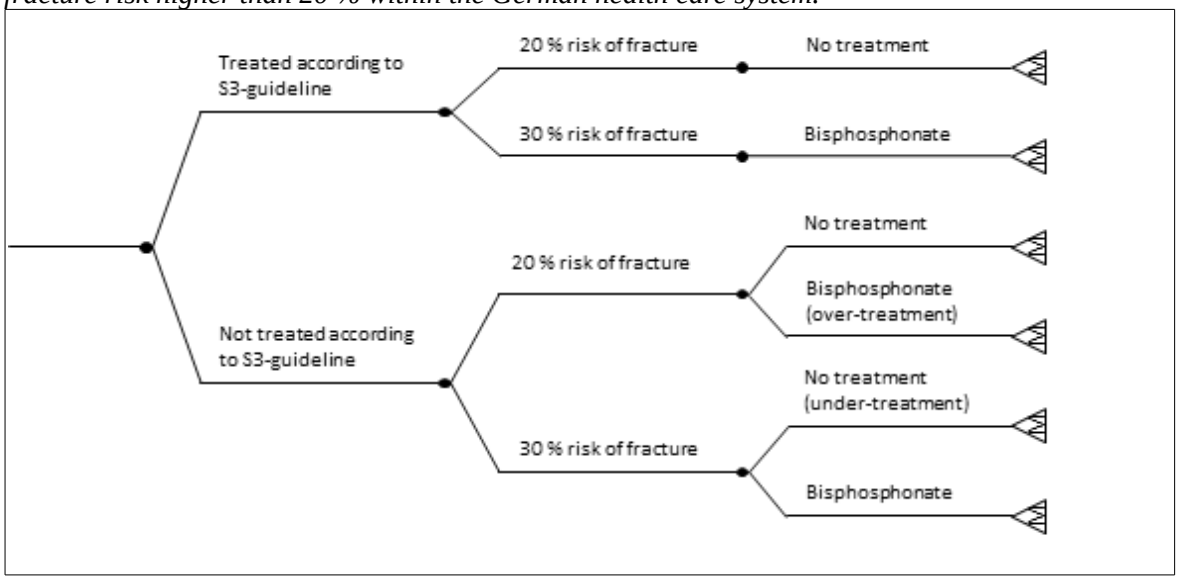
131 Sun 2007: 750; Drummond 2007: 277f.
132 Drummond 2007: 300; Briggs et al. 2011: 45
133 Drummond 2007: 305–307
134 Marsh et al. 2012: 2
135 Bleibler et al. 2014: 2
136 Bala, Mauskopf 2006: 346

4.1 Structure of the Model

The costs and effects of the various degrees of implementation of the S3-guideline are modelled from the perspective of the statutory health insurance in Germany, as they are the main payor, insuring 88 % of the German population in 2011.[137] A decision tree model and a Markov model are combined to simulate the treatment impact of the S3-guideline on osteoporosis. The patients pass through the decision tree which models the allocation of the patients to the treatment groups according to the S3-guideline and non-S3-guideline treatment, after which their treatment and survival is modelled in the Markov model. The aim is not to compare cost and effect of S3-treatment versus non-S3-treatment but to compare the outcomes of possible different degrees of implementation.

In the decision tree (see figure 2) the first node is the probability of treatment according to the guideline. Unlike in most decision tree models the first node here is not a decision but a chance node. On the micro level it is, of course, a decision of the individual physician whether he or she reads up on the current guidelines and applies them. On the macro-level, however, which is to be simulated here, whether a patient is treated by a physician applying the S3-guideline or not, is, at least partly, due to chance. As there is only limited information on the extent of the application of the guideline[138] three scenarios will be modelled with differing degrees (30 %; 50 %; 70 %) of implementation.

Figure 2: Decision tree showing the possible treatment allocation of patients with a 10 year fracture risk higher than 20 % within the German health care system.



Of those treated according to the guideline all will receive a DXA bone density measurement, as the 10-year risk of fracture is 20 % or greater. With the bone density measurement the 10-year fracture risk estimation will be refined. According to the

137 Bundeszentrale für politische Bildung 2013: 4
138 Vogel et al. 2008; Chenot et al. 2007

guideline people over the age of 70 with a T-score of -2.5 or lower should be treated as their 10-year risk of fracture is minimum 30 %. Patients with a 10-year fracture risk of 20-29 % are given basis therapy consisting of lifestyle advice (nutrition information and sunlight exposure for vitamin D and calcium). The guideline also includes other risk factors besides a low T-score, however, these are not included in the model due to lack of data.

Of those treated by physicians who do not apply the S3-guideline, a lower percentage is diagnosed with osteoporosis and BMD measurement is not as common.[139] Patients will either be treated or not treated, resulting in either guideline conform or under- or over-treatment, depending on underlying risk status.

The time horizon of the decision tree is set to zero, as it is only applied for allocation. With the transition to the Markov model the time horizon begins.

After establishing the number of patients in the subgroups of the cohort, each subgroup is transferred to a Markov model and modelled separately (see figure 3). Markov models are especially suited to simulate chronic diseases over a long time.[140] The main structure of the Markov model is based on the reference model published by Zethraeus and colleagues[141] and the adapted model by Müller and Gandjour[142]. The reference model was initially chosen in order to facilitate comparability of the results with current research. However, since the S3-guideline also includes initiation of treatment after the occurrence of a femur or vertebral fracture, since these fractures are risk factors for subsequent fractures, amendments had to be made, leading to differing model structures. In addition, the occurrence of a second hip fracture was also included in the model.

In health economics a Markov model consists of distinct health states between which a patient can transition. States are depicted as ovals, and the possible transitions between states are indicated by arrows. A patient can only be in one state at a time.[143] The transition occurs once per cycle and is dependent only on the prior health state, not the entire patient history; this is the Markovian assumption of memorylessness.[144] Therefore, the population within one health state should be homogeneous.[145] This constitute a challenge as patients may experience an assortment of fractures which in turn influence the probability of experiencing other fractures. Results therefore pertain to an average patient.

139 Chenot et al. 2007: 589
140 Briggs, Sculpher 1998: 399
141 Zethraeus et al. 2007
142 Mueller, Gandjour 2009
143 Briggs, Sculpher 1998: 399
144 Bala, Mauskopf 2006: 347
145 Marsh et al. 2012: 2

Figure 3: Markov model showing the possible health states and transition paths

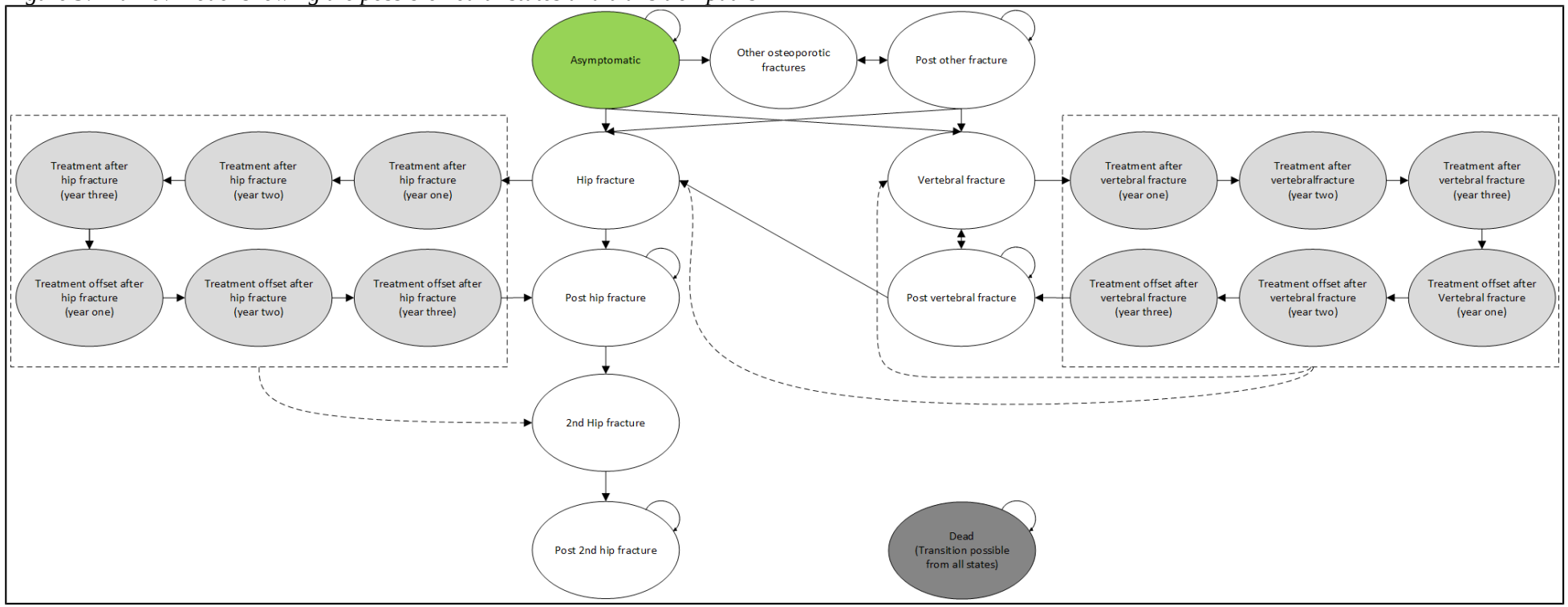


Figure legend
Transition to the state "dead" is possible from all other states. Arrows have been omitted for better readability.
Transition from each of the six states within a dashed box (- - -) is possible along the respective dashed arrows.

The states of a Markov model depict clinically important health conditions[146]. Each of the subgroups start in the “asymptomatic” state. From here transition to three different fracture states is possible, as well as transition to death or remaining in the asymptomatic state, as illustrated in figure 3. Hip and vertebral fractures are distinguished due to their strong impact on quality of life, mortality and cost, while all other osteoporotic fractures are subsumed in the state “other fracture”. Differences in impact within these other fractures do exist, but can be disregarded due to their minor magnitude compared to the difference to hip and vertebral fracture. Another simplification is that the fracture state is left after one cycle even though it is theoretically possible to experience a fracture every year, or even more often. Patients then transition to the respective post fracture state. This enables the modelling of decreased quality of life after a fracture, as well as possible subsequent costs.

The DVO guideline states that a woman over the age of 70 with a T-score higher than -2.5 and no other risk factors should not be treated with bisphosphonates as the 10-year risk is below 30 %. However, if this woman sustains a fracture of the hip or vertebrae nevertheless, her subsequent 10-year fracture risk is 30 % (or higher) and therefore treatment with bisphosphonates would be indicated. This is incorporated into the model with tunnel states. Studies show that adherence to bisphosphonates is low[147] and there is disagreement concerning whether low adherence should be included in cost-efficiency modelling[148]. To cautiously accommodate the low adherence to bisphosphonates only a three year medication phase is modelled, as well as a post-treatment phase (offset-time) with the same duration as the treatment in which the effect of the bisphosphonates slowly wanes in a linear decline.[149] After this the patients transition to the respective post fracture state, which is equal to no treatment. Transition to another fracture state, while less likely, is still possible from the tunnel states. For the sake of clarity these transition arrows are not depicted individually, but are combined and shown as the dashed box surrounding the tunnel states and the attached arrow. In the future, adherence could be directly incorporated into the model by including transitions from each of the treatment and treatment-offset tunnel states to the respective post-fracture state, thereby modelling the premature cessation of the medication regime. The treatment states have the advantage of being able to model later differences in treatment adjustment additional to the initial treatment decision.[150]

After sustaining a fracture all other types of fractures can occur. However, since the quality of life after a hip fracture is lower than after a wrist fracture, and as a Markov model has no memory of prior states, here, in order to keep the model simple, only the occurrence of a hip or vertebral or “other fracture” after an “other fracture”, hip or vertebral fracture after vertebral fracture and second hip fracture after hip fracture are modelled. This leads to a

146 Briggs, Sculpher 1998: 399; Philips et al. 2006: 359
147 Hadji et al. 2012
148 Hughes et al. 2001; Hiligsmann et al. 2009: 692; Hernlund et al. 2013: 32
149 Zethraeus et al. 2007: 14f.; Bartl, Bartl 2015: 8
150 Bala, Mauskopf 2006: 351

slight underestimation of those fractures with little or only short term quality of life reduction and lesser cost compared to those fractures which are included.

Death is a possibility from every health state. The arrows showing these transitions have been omitted for better clarity of the diagramme. It is not possible to leave the absorbing state of death.[151]

Markov cycle length was set to one year.[152] This enables the capturing of the increased mortality in the first six months following a fracture. In order to avoid under- or over-estimation of life years and since fractures occur not only at the end of the year a half cycle correction was applied.[153] This is done by adding half a cycle before the first cycle; as a result the transitions take place in the middle of a cycle, thereby equalizing under- and overestimation.[154] The Markov model is simulated over a time horizon of 30 years until the women reach the age of 100 or have died.[155] The outcomes of interest are fracture events as well as cost and quality adjusted life years (QALYs).

4.2 Populating the Model

For the identification of transition probabilities a literature review was conducted with PubMed.gov, a service searching Medline and other life science databases. The reference lists of the identified articles were hand searched and complementary selective internet searches and searches in the German statistical databases were carried out. The search terms were: mortality after *fracture; quality of life after *fracture, refracture, *fracture after *fracture, mortality after *fracture, fracture prevention/reduction bisphosphonate, osteoporosis, T-score, quality of life, cost of fracture. Only articles published in German and English language were included. Data pertaining to Germany were treated preferentially for populating the model. Studies with a focus on co-morbidities which are also risk factors (e.g. diabetes, inflammatory bowel disease) were excluded.

4.2.1 Probabilities

The change in the understanding of osteoporosis and treatment recommendations brought about by the S3-guideline “Osteoporosis” in Germany,[156] and the FRAX Model on an international level, provide a challenge in populating the model as most epidemiological studies do not measure the 10-year fracture incidence or fracture risk, but only apply the WHO definition using T-scores. In order to incorporate the epidemiological data into the

151 Briggs, Sculpher 1998: 400
152 Briggs, Sculpher 1998: 399
153 Briggs et al. 2011: 33; Sonnenberg, Beck 1993: 329
154Briggs, Sculpher 1998: 403
155 O'Mahony et al. 2015
156 Piatek et al. 2013: 596

model the starting age of the model population was set at 70 years. In Germany women aged 70 are estimated to have an average 10 year fracture risk of 20 % due to age alone. Women aged 70 with a T-score of -2.5 are estimated to have an average 10-year fracture risk of 30 %.[157] For other age groups and men the percentages of persons with a fracture risk of 20 % and 30 % can currently not be derived from epidemiological studies.

The cohort size was set to 10 000. In cohort models the population size is arbitrary, as the probabilities dictate the expected outcomes, therefore a cohort size was chosen which corresponds to general practice.[158]

4.2.1.1 Decision Tree

The women are simulated as being aged 70 and generally healthy, exhibiting no known risk factors for osteoporosis. Only five publications were found providing prevalences of osteoporosis in Germany based on actual bone mineral density measurements (see table 3). The cross-sectional data stems from three specified towns in Germany, as well as from a cross-sectional study with participants from 20 different towns. Two of the publications are based on the BASE II study (Berlin), but at differing time-points and therefore differing levels of participant recruitment. Berkemeyer and colleagues approached all of the registered population above the age of 75 living in Herne. Those willing to attend a clinical examination were included in the study.[159] The other studies examined participants aged 60 and above who had become aware of the respective studies through notifications and came forward based on their interest.[160]

The number of included female participants varies, as does the proportion of the population with a T-score lower than -2.5. This may in part be due to the differing DXA equipment and the differing measurement sites. In the studies examining more than one site the lowest value was decisive as to whether the threshold had been crossed or not, as is recommended by the DVO.[161] The lower portion of the population with a T-score of or below -2.5 in the study by Berkemeyer and colleagues may be due to the measurement of only the left hip. Low values tend to be more common at the spine.[162] Effect of equipment cannot be determined here. Generally it is found that the dual-energy X-ray absorptiometers produced by GE Healthcare (Lunar) provide higher values on average than the instruments produced by Hologic.[163]

157 Dachverband Osteologie DVO e.V. 2014: 185
158 Briggs et al. 2011: 33
159 Berkemeyer et al. 2009: 2
160 Luhn 2012: 9; Piatek et al. 2013: 597; Acker 2013: 21; Sondergeld 2015: 19
161 Dachverband Osteologie DVO e.V. 2014: 185
162 Sondergeld 2015: 31
163 Pearson et al. 2002: 951

Table 3: Publications giving proportion of women in Germany with a T-score below -2.5 (WHO definition of osteoporosis).

Publication	**Population**	**Partici-pants[a] (n)**	**Age**	**T-score ≤ -2.5**	**Measurement site**	**DXA instrument**
Berkemeyer et al. 2009	Herne (2005-2006)	197	75+	13.7 %[b]	Left femur neck	Lunar Prodigy
Luhn 2012	20 German towns (2002)	1197	60-95	28.5 %[c]	Spine, femur neck	Lunar DPX-NT
Piatek et al. 2013	Magdeburg (2009-2010)	94	59-81	25.6 %	Spine, femur neck, total hip	Hologic QDR-1000
Acker 2013	Berlin (2009-2010)	318	60-84	20.1 %	Spine, femur neck, total hip	Hologic QDR 4500
		82	70-84	22.0 %		
Sondergeld 2015	Berlin (2009-2013)	626	60-84	19.0 %	Spine, femur neck, total hip	Hologic QDR 4500

[a] *only female participants included in the table*
[b] *own calculation based on 27 identified cases of osteoporosis at the spine.*
[c] *own calculation based on 305 identified cases of osteoporosis at the spine.*

For the decision tree a probability of 25 % of having a 10-year fracture risk of 30 % was applied. This value was chosen as it matches that study with the largest population undergoing a DXA scan. As women from different towns were examined, regional differences become less pivotal. Since this value is based on women aged 60 and above, it can be assumed that the actual probability of women aged 70 years may even be a little higher.

In comparison, Müller and Gandjour estimate that 33 % of the population aged 70 would be prescribed medication if treated according to the S3-guideline (2006). This estimate is slightly higher as it also includes the effect of clinical risk factors,[164] which are not included in this model. A similar value (33.8 %) is also given by Sondergeld concerning the total prevalence of osteoporosis in females in the BASE II study based on the 2009 edition of the S3-guideline, while the prevalence of osteoporosis based solely on T-scores is lower.[165]

The probability of being diagnosed with osteoporosis and treated with bisphosphonates in the non-S3 population was inferred from surveys (see table 4). Concerning the share of patients with osteoporosis who are not diagnosed with osteoporosis divergent numbers exist, from the same underlying study population no less, ranging from 25 - 66 %.[166] For populating the model the value of interest, however, is not the number of undiagnosed cases of osteoporosis, but how many of the persons with a 10-year fracture risk of more than 30% are treated with bisphosphonates in the non-S3 population.

164 Mueller, Gandjour 2009: 1109
165 Sondergeld 2015: 33
166 Acker 2013: 44; Sondergeld 2015: 33

Table 4: Publications on the diagnosis and treatment of osteoporosis in women by physicians in Germany.

Publication	**Population**	**Participants female (n)**	**Age**	**Osteoporosis[a]**	**Undiagnosed osteoporosis[b]**	**Treated for osteoporosis[c]**
Acker 2013	Berlin (2009-2010)	318	60-84	20.1 %	66 %	10.8 %[f]
Sondergeld 2015	Berlin (2009-2013)	626	60-84	19.0 %	25 %	
Häussler et al. 2007	Gmünder Ersatzkasse	-[d]	50+	39.0 %	-	24 %
			65-74	46.7 %	-	[g]
Hadji et al. 2013	TK	-[e]	50+	24%	-	21-32 %[h]

[a] *Share of people with a T-score of or below -2.5 or with an osteoporosis diagnosis, depending on study.*
[b] *Share of people undiagnosed of those with a T-score of or below -2.5.*
[c] *Share of people treated for osteoporosis (any type of treatment including prescribed calcium and vitamin D supplements) of those with a T-score of or below -2.5 or with an osteoporosis diagnosis, depending on study.*
[d] *Approximately 1,5 million insurants (both sexes).*
[e] *Approximately 1.7 million insurants (both sexes).*
[f] *Only treatment with antiresorptives. Also 12,5% were treated with Vitamin D and Calcium, overlap not specified.*
[g] *Not stated. In the age group 50-64 31% and in the age group 75+ 19% of women were treated for osteoporosis. The value for the age groups 65-74 lies in between.*[167]
[h] *Includes male patients.*

As the identified studies are quite recent it is appropriate to assume that some of the patients included have been treated based on the S3-guideline. Nonetheless, the medication rate in general, including supplements, is low with at most one third of osteoporosis patients receiving some form of treatment. Based on the S3-guideline 100 % of the people diagnosed with osteoporosis should be treated with bisphosphonates, which is approximately 25 % of the total population aged 70. In the studies a bisphosphonate medication rate of only around 10 % of people diagnosed with osteoporosis is described.[168] Even with the inclusion of other osteoporosis treatments, including supplements, the recommendation is not met.[169] For the model, women attended to by a physician without knowledge of the S3-guideline, or choosing not to abide by it, the treatment rate with bisphosphonates is modelled as 10 % which is consistent with the publications of Acker as well as Häussler and colleagues.

4.2.1.2 Markov Model

The values assigned within the Markov model are generally the same for the subgroups with the exception of the overall fracture risk (20 % or 30 % of fracture within 10 years) and the probability of being treated with bisphosphonates after a hip or vertebral fracture. Transitions from each state need to sum up to 100 %. The number of persons in a given state over the duration of 30 years were calculated separately for each subgroup and then summed up for each implementation scenario.

167 Häussler et al. 2007: 80
168 Acker 2013: 44; Häussler et al. 2007: 80
169 Häussler et al. 2007: 80; Acker 2013: 44; Hadji et al. 2013: 53

Probability of fracture

The probability of fracture is dependent on the risk profile of the subgroup. Therefore the 10-year fracture risk was converted to a constant rate with the following formula

$$r = \frac{-\ln(1-p)}{t} \qquad (2)$$

where *r* is the constant rate, *p* is the probability over a period of time and *t* is the period of time, 10 years in this case. From the constant rate the 1-year probability can then be calculated,

$$p_{1y} = 1 - e^{-rt} \qquad (3)$$

using the constant rate *r* and the time period of interest *t* which is one year. This assumes that the fracture risk is continuous over the 10 year period, which is a simplification.[170]

In the groups with a 10-year fracture risk of 30 % the 1-year probability of fracture is 3.5 %. In the groups with a 10-year fracture risk of 20 % the 1-year probability of fracture is 2.2 %. This probability includes fractures of the spine and the hip as stated in the DVO guideline. Unlike the FRAX 10-year risk, it does not include all major osteoporotic fractures.[171]

Table 5: Incidence of fractures by location and share of fractures of total fracture numbers by location.

Publication	**Population**	**Fracture type**	**Incidence (per 100 000)**	**Share of fractures**
Bäßgen et al 2013	Rostock (Data shown for women, age 70-74)	Hip fracture	198	13.1 %
		Vertebral fracture	269	17.8 %
		Other fracture	1048	69.3 %
Hadji et al. 2013	TK insurants (all sexes and ages)	Hip fracture		13.7 %
		Lumbar vertebral or pelvic fr.		15.5 %
		Wrist fracture		5.1 %
		Humerus fracture		11.7 %
		Other fractures		53.9 %

According to data from the city of Rostock (Germany) and the claims data of the Techniker Krankenkasse hip fractures and vertebral fractures occur at similar rates (table 5). The hip to vertebrae fracture ratio in the data from Rostock for women aged 70-74 is 42 to 58 and in the data from the Techniker Krankenkasse it is 47 to 53.[172] For the model a ratio of 45 to 55 was applied. Therefore the 1-year probability of hip fracture is 1.6 % and that of sustaining a vertebral fracture is 1.9 % if the underlying 10 year fracture risk is 30 %. If the 10-year fracture risk is 20 %, the 1-year probability of sustaining a hip fracture is 0.99 %

170 Briggs et al. 2011: 51
171 Dachverband Osteologie DVO e.V. 2014: 183; Kanis et al. 2011: 2396
172 Hadji et al. 2013; Bassgen et al. 2013

and that of sustaining a vertebral fracture is 1.2 %. The ratio of hip and vertebral fracture to all other fractures is 30 to 70. Therefore in the model the 1-year probability for sustaining "other fractures" was set at 8 % (10-year fracture risk of 30 %) and 5 % (10-year fracture risk of 20 %), respectively (see table 9, p.31).

Probability of osteoporosis treatment after fracture

The probability of transitioning to an osteoporosis medication state after a hip or vertebral fracture is dependent on whether a woman is treated following the S3-guideline or not. Of those hip or vertebral fracture patients treated according to the guideline all are subsequently treated with bisphosphonates (transition probability of 100 %), including those who had previously been treated with bisphosphonates as their 10-year fracture risk was 30 %. In the most extreme case, a patient frequently sustaining vertebral fractures during treatment would repeatedly receive up to three years of bisphosphonate treatment with at least a one year drug holiday (temporary treatment cessation) in between, as no treatment is modelled in the fracture state. This may be longer than patients are commonly treated, but still justifiable.[173] In the guideline it is stated that the optimal treatment duration with bisphosphonates is unknown, mainly due to most studies being short-term, but as long as risk is high treatment is warrented.[174]

For patients not assessed and treated on the basis of the S3-guideline the rate of diagnosis and treatment after fracture is low. In a study of German hospitals only 115 of 328 hospitals had a standardized procedure and only approximately half of these hospitals gave an antiresorptive and vitamin D and calcium supplements after a fracture, as specified by the DVO.[175] This amounts to approx. 17 % of fracture patients. Whether or not this treatment is then continued by the general physician or an orthopaedic specialist once the patient is back home is unknown.

In the Bone Evaluation Study based on data of the Techniker Krankenkasse 172 437 insurants sustained a fracture in the course of three years. Of these 1 837 were treated for osteoporosis without a recorded diagnosis of osteoporosis and 24 448 received treatment and had an osteoporosis diagnosis. This amounts to 15 % of all fracture patients receiving some form of osteoporosis treatment, however, this is including treatment with vitamin D.[176]

As the data on osteoporosis treatment after fracture stem from populations aged 50 years and older in the case of the Bone Evaluation Study and mainly 50 years and older in the hospital survey by Vogel, and treatment rates in general are lower for older women, it is probable that persons aged 70 years and above receive osteoporosis treatment after fracture even less often. As treatment additional to vitamin D is recommended again a probability

173 Faßbender, Pfeilschifter 2008: 15
174 Dachverband Osteologie DVO e.V. 2014: 247
175 Vogel et al. 2008: 874–876
176 Hadji et al. 2013: 53–54

of 10 % of being treated with bisphosphonates is assumed for the model for those surviving the cycle. This may still be a higher portion of fracture patients than is actually treated with osteoporosis medication.

Effect of treatment with bisphosphonates

Treatment with bisphosphonates reduces the occurrence of future fractures and reduces mortality. Several studies have observed that the treatment effect differs depending on composite used for treatment, treatment duration and fracture type.[177] As no specific treatment is modelled, applied values are based on values taken from two Cochrane reviews of common bisphosphonate treatments (see table 6).

Table 6: Relative risk reduction due to treatment with bisphosphonate by fracture site.

Publication	**Population**	**Study type**	**Treatment**	**Fracture**	**RRR[a]**
Wells et al. 2011	11 trials, 12 068 women	Cochrane review (Meta-analysis)	Alendronate 10mg	Hip fracture	40 %
				Vertebral fracture	45 %
				Non-vertebral fracture	16 %
Wells et al. 2010	7 trials, 14 049 women	Cochrane review (Meta-analysis)	Risedronate 5mg	Hip fracture	26 %
				Vertebral fracture	37 %
				Non-vertebral fracture	20 %

[a] *Reduced relative risk*

The effect of treatment is more evident for secondary prevention, however, due to the new paradigm of risk assessment, which has not yet been broadly implemented in studies, treatment effect in the high risk groups cannot be excluded. An effect of primary preventive intervention is only modelled in the subgroups with a 10-year fracture risk of 30 %. Hip fracture was found to be reduced by between 26 and 40 %.[178] For the model a reduction by 30 % was applied during treatment. The relative risk reduction for vertebral fractures was found to lie between 37 and 45 %. Therefore a reduction of 40 % was modelled for vertebral fractures during treatment and the following offset time. The model assumes a relative risk reduction of 20 % with respect to sustaining an “other fracture”. Treatment effects were modelled to decline linearly over three years, resulting in no effect in the fourth year after treatment has been stopped.

No effect of treatment was modelled for the subgroup of persons with a 10-year risk of 20 % who were over-treated, as the efficacy of bisphosphonates has not been proven in people with a T-score above -2.0.[179]

Studies indicate that medication with bisphosphonates after a fracture may reduce mortality as much as 28 %.[180] However, as follow-up of these studies was short and not all

177 Beaupre et al. 2011;Bondo et al. 2013; Boonen et al. 2010; Lindsay et al. 2013; Masud et al. 2009; Wells et al. 2010a, 2010b, 2011

178 Haentjens et al. 2003; Iwamoto et al. 2008

179 Bartl, Bartl 2015: 7

180 Lyles et al. 2007; Bondo et al. 2013; Black et al. 2007

found such a drastic reduction, only a 10 % reduction of mortality due to fracture is modelled. The effect persists for the duration of treatment and declines linearly thereafter for the next 3 years.

Probability of fracture after fracture

Sustaining an osteoporotic fracture is a risk factor for subsequent fractures.[181] As can be seen in table 7, the risk of future fracture following a vertebral fracture corresponds to the risk after a hip fracture, while the risk after a wrist fracture is lower, although still increased.[182] This was confirmed in a systematic review by Haentjens and colleagues.[183]

Table 7: Risk for women of sustaining a subsequent fracture according to prior fracture location.

Publication	**Population**	**Study type**	**Prior fracture**	**10y cumulative fracture risk of new fracture**
Hodsman et al. 2008	Manitoba, Canada	Database	Hip	24.9 %
			Vertebrae	25.7 %
			Wrist	14.2 %
			Humerus	23.7 %

Applying the previously mentioned formulas probabilities for sustaining a fracture for the Markov model were calculated from the study shown above. The risk of sustaining a fracture after an “other fracture” was derived to be 2 % after combining the data of wrist and humerus fracture from Hodsman et al.[184]. This would be less than the fracture probabilities calculated for both the 20 % and 30 % 10-year fracture risk populations. This is probably due to the younger population in the study which comprises women aged 45 years and above. In the model, therefore, the same probability values as if the fracture had not occurred were taken as the probability of a fracture after an “other fracture”. This is in line with the S3-guideline which only states an increased risk of fracture after a spine or hip fracture.[185]

Patients sustaining a hip or vertebral fracture are assumed to have a 10-year fracture risk of at least 30 %. Therefore for the subgroups with a previously lower 10-year fracture risk the risk of sustaining another fracture within the next year was 3.5 % (Spine: 1.9 %; hip: 1.6 %). For those already with a 10-year fracture risk of 30 % and more the 1-year probability of sustaining another fracture after sustaining a vertebral fracture was increased to 4.5 %. Therefore the probability of a further vertebral fracture is 2.5 % and while the 1-year probability is 2 % for hip fracture. The probabilities are corrected for the effects of medication for the “treatment after vertebral fracture” and “treatment offset after vertebral fracture” states (see previous section).

181 Kanis et al. 2004
182 Hodsman et al. 2008
183 Haentjens et al. 2003
184 Hodsman et al. 2008
185 Dachverband Osteologie DVO e.V. 2014: 183

In the Framingham study, a prospective cohort, 9.7 % of women with a hip fracture sustained another hip fracture within 5 years. This amounts to a 1-year probability of 1.9 %.[186] Data from the Manitoba Bone Density Program indicate a 1-year probability of 2.8 %.[187] A 1-year probability of 2 % was used in the model. Here also, the values are adapted for treatment effect if treatment is provided.

Probability of death

As probability of death increases with age time-dependency was included in the Markov model.[188] Essentially age-dependent mortality was possible from each state. The age-dependent mortality data for the generation born in 1945 was obtained from the German Federal Statistical Office.[189]

Short-term mortality effects of fractures

Fractures incur further probability of death. For hip fractures the mortality is especially increased in the first six to twelve months after fracture.[190] This was modelled as an increased probability of death directly from the hip fracture state. In current studies approximately between 15.8 % and 26.4 % of hip fracture patients died within the first year (see table 8). Due to the half cycle correction the average time from hip fracture to the next state is 6 months therefore the 1-year mortality value was chosen conservatively: a probability of 20 % of dying after a hip fracture was applied. The probability of dying after sustaining a subsequent hip fracture was modelled as 25 %.

Mortality data concerning vertebral fractures is sparse, diagnosis is infrequent and definitions and inclusion criteria of studies differ.[191] Based on the two studies at hand the probability of dying due to a vertebral fracture was set to 10 %.

186 Berry et al. 2007
187 Hodsman et al. 2008
188 Briggs, Sculpher 1998: 401
189 Statistisches Bundesamt 2015
190 Cooper et al. 1993: 1002; Center et al. 1999, 882; Teng et al. 2008
191 Teng et al. 2008

Table 8: 1-year mortality rates for different fracture locations.

Publication	Population	Study type	Fracture	1-year mortality
Bondo 2013	Denmark (women)	Health register	Hip	26.4 %
Brozek 2014	Austria	SHI claims data	Hip	20.2 %
Klop et al. 2014	Britain	Database (8% of total population)	Hip	22.0 %
Endres et al. 2006	Germany	Data from 242 participating acute care hospitals	Hip	19.2 %[a]
			Wrist	3.0 %[a]
Center et al. 1999	Dubbo, Australia (women)	Prospective cohort	Hip	19.7 %
			Vertebral	11.8 %
			Other major	15.1 %
Morin et al 2011	Manitoba, Canada (women)	Database	Hip	15.8 – 23.3 %
			Vertebral	5.9 – 20.3 %
			Wrist	1.8 – 5.7 %
			Humerus	5.3 – 10.2 %
Berry et al. 2007	Framingham, USA	Prospective cohort	Hip (1st)	15.9 %
			Hip (2nd)	24.1 %[b]

[a] *Mortality at 1.5 years. 90 % of deaths due to femur fracture occured in the first 12 months* [192]
[b] *Values only apply to women*

Apart from hip and vertebral fractures the most common osteoporotic fractures are wrist and arm fractures. These mainly constitute the state “other fracture” in the model. These wrist and arm fractures only lead to a minimally increased short term risk of death. Therefore the “other fracture”-specific mortality is set at 5 % in the model, based on the values reported for wrist fractures and allowing for the effect of other fracture types.[193] [194]

As the 1-year mortality after fractures also includes causes other than the fracture itself[195], the age-dependent mortality was omitted as a transition possibility from the fracture states.

Long-term mortality effects of fractures

Depending on fracture location fractures can also have long-term effects on mortality. No long-term studies on home-dwelling people pertaining to Germany were found. Studies from other countries have reported effects even 20 years after fracture.[196] For hip fractures the increased mortality mainly occurs in the first six to twelve months after fracture. After that the probability of dying is still higher than in the non-fracture population, but it is constant and only slightly increased.[197] Especially with old age competing risks of dying

192 Endres et al. 2006: 89
193 Ioannidis et al. 2009
194 Cooper et al. 1993
195 Center et al. 1999: 881
196 Vestergaard et al. 2007
197 Haentjens et al. 2010

take over. [198] Therefore in a meta-analysis Haentjens and colleagues calculated the relative hazard at the time of 15 years after hip fracture, excluding the deaths which occurred in the first year. The relative hazard of mortality after fracture is 1.73 times that of the general age and sex matched population.[199] This value was applied to the model. The long-term mortality after sustaining a second hip fracture was modelled with 20 % based on the data from the Framingham study.[200]

Table 9: Overview of the transition probabilities applied in the model.

Treatment allocation (decision tree)			**Treatment effect (if T-score ≤ -2.5)**	
Percent of female population with T-score ≤ -2.5		25 %	Hip fracture red.	30 %
Osteodensitometry (non-S3)		25 %	Vertebr. fracture red.	40 %
Treated for osteoporosis (non-S3)		10 %	Other fracture red.	20 %
Treatment after hip/vertebral fracture (non-S3)		10 %	Mortality red.	10 %
Risk of fractures	**10-year risk 20 %**		**10-year risk 30 %**	
First fracture	Other fracture	5.0 %	Other fracture	8.0 %
	Vertebral fracture	1.2 %	Vertebral fracture	1.9 %
	Hip fracture	0.9 %	Hip fracture	1.6 %
Subsequent fracture after other fracture	Other fracture	5.0 %	Other fracture	8.0 %
	Vertebral fracture	1.2 %	Vertebral fracture	1.9 %
	Hip fracture	0.9 %	Hip fracture	1.6 %
Subsequent fracture after vertebral fracture	Vertebral fracture	1.9 %	Vertebral fracture	2.5 %
	Hip fracture	1.6 %	Hip fracture	2.0 %
After hip fracture	2nd hip fracture	2.0 %	2nd hip fracture	2.0 %
Mortality	**Short-term mortality**		**Long-term mortality**	
Dependent on specific fracture location	Other fracture	5 %	Other fracture	0
	Vertebral fracture	10 %	Vertebral fracture	(10 %)[a]
	Hip fracture	20 %	Hip fracture	(73 %)[b]
	2nd hip fracture	25 %	2nd hip fracture	20 %

[a] *Factor multiplied with age dependent mortality. Transition probability for long-term mortality due to vertebral fracture ranges from 0.1 % (70y) to 3 % (100y) in addition to age dependent mortality*
[b] *Factor multiplied with age dependent mortality. Transition probability for long-term mortality due to hip fracture ranges from 0.8 % (70y) to 21.9 % (100y) in addition to age dependent mortality*

With vertebral fractures death is mainly due to resulting frailty and co-morbidities. The relative survival ratio at 5 years is slightly decreased in the study by Cooper et al. They also found the risk of death following vertebral fractures to remain relatively constant.[201]

198 Berry et al. 2010
199 Haentjens et al. 2010
200 Berry et al. 2007
201 Cooper et al. 1993

Morin et al. found that after the first year the age-adjusted relative risk of death was 1.1 following a vertebral fracture. Long-term mortality due to vertebral fracture was modelled as 10 % of the age dependent mortality. No long-term mortality due to “other fractures” was modelled. Figure 9 gives an overview of the transition probabilities applied in the model. Examples of the transition matrices are provided in the appendix.

4.2.2 Health State Utility Values

The quality-adjusted life-year is a measure which combines quality of life during a health state and the duration of this health state. This enables comparison of diseases or treatment effects. It was initially developed to support decision-makers in the allocation of funds.[202]

In order to calculate QALYs each health state in the model is assigned a value. Values are gained by asking either a sample of patients or the general population to value various health states by preference or desirability.[203] Methods commonly applied are standard gamble, time trade-off and visual analogue scale.[204] The visual analogue scale is less favoured as it is not choice based, and unlike the first two methods, does not generate utilities. However the utility values derived by standard gamble and time trade-off differ, under or overestimating utility of a state due to loss aversion and risk preference of the population interviewed.[205] The obtained values, from all of the methods, also mask the strong underlying heterogeneity of the individuals' preferences.[206] Concerning hip fracture the long-term health related quality of life is influenced by several factors such as age and level of activity before fracture.[207]

As the decision tree part of the model does not represent any passed time no utility values are assigned there. The health states of the Markov model, however, are each assigned a value indicating the quality of life of the state. Values range from 1 for full health to 0 for dead. The utilities of each cycle are summed up over time to calculate the QALYs for each of the scenarios.[208] This assumes that the period of time spent in a health state, as well as which health state precedes it, does not influence how it is weighted. This is a strong assumption as it has been shown that chronic patients either adapt to a health state thereby perceiving it as more tolerable or on the other hand the duration of the state may exacerbate the perceived restriction and burden of the health state.[209]

202 Weinstein et al. 2009: S5
203 Brazier et al. 2005
204 Weinstein et al. 2009: S7
205 Parkin, Devlin 2004; Bleichrodt 2002: 453; Abellán-Perpiñán et al. 2006
206 Roberts, Dolan 2004
207 Buecking et al. 2014: 477
208 Briggs, Sculpher 1998: 402; Sonnenberg, Beck 1993: 329f.
209 Weinstein et al. 2009: S8

Table 10: Utility values for health states in persons aged 70+ with osteoporosis.

Asymptomatic	Other fracture	Post-other fracture [a]	Vertebral fracture	Post-vertebral fracture[a]	Hip fracture	Post-hip fracture [a]	Dead
0.73	0.61	0.73	0.44	0.66	0.31	0.66	0

[a] *Including the post-fracture treatment as well as post-treatment offset states*

The utility values were taken from a meta-analysis of 62 studies including 142 477 patients by Si and colleagues.[210] Due to the cycle-length of one year the utility value could be directly applied to the states, giving the quality-adjusted life year (QALY). As people generally have a positive time preference – meaning they would rather experience benefits today than in the future, and would postpone the costs if possible – QALYs and cost of each year were discounted with the following formula:

$$C_0 = \frac{C_n}{(1+d)^n} \tag{4}$$

With C_n being the QALYs or cost of a cycle n, d is the discount rate and C_0 being the value of the later QALYs or cost at the present time.[211] A constant discount rate of 3% was applied, as is stipulated by the German Institute for Quality and Efficiency in Health Care (IQWiG).[212] The discounting of QALYs is disputed as time preference may already be included in time trade-off derived utilities.[213]

4.2.3 Cost

Costs were assigned from the perspective of the statutory health insurance which insures 88 % of the German population.[214] Depending on the availability of data indirect costs disbursed by the SHI were included additionally to the (average) direct costs of each health state in the model.[215] Cost occurring per year for each health state was derived from literature or reference listings of actual prices. Expenditures included in the model are visits to the physician, osteodensitometry with DXA, medication with bisphosphonates and treatment of fractures.

Costs are taken from 2015 prices or, if values stem from earlier years, are adjusted for inflation to amount to October 2015 Euros. Values are adapted to 2015 Euro based on the harmonised consumer price index (HVPI)[216] using the following formula:

$$value_{2015} = \frac{price_t * pricelevel_{2015}}{pricelevel_t} \tag{5}$$

210 Si et al. 2014
211 Drummond 2007: 73
212 Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen 2015: 95
213 Drummond 2007: 189f.
214 Bundeszentrale für politische Bildung 2013: 4
215 Philips et al. 2006: 359
216 Statistisches Bundesamt 2015b; Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen 2015: 95

The price of a specific year was multiplied with the harmonised consumer price index of 2015 and divided by the harmonised consumer price index of the respective year.

Osteodensitometry and Blood Work

Osteodensitometry is included only as part of the allocation in the decision tree. Inclusion in the Markov model would be preferable, but is not realisable as the interval between osteodensitometry examinations is dependent on the T-score in the S3-guideline and is even less predictable in the non-S3 subgroups.[217] Cost of osteodensitometry is given at € 16.54 in the Einheitlicher Bewertungsmaßstab[218] (EBM).[219] Müller and Gandjour state a cost of € 40.16 for osteodensitometry including blood work laboratory costs for 2010.[220] Therefore osteodensitometry and blood work are costed at € 43.09 for 2015. It is assumed that all patients treated according to the guideline undergo osteodensitometry and have their blood levels checked. No information is available as to how many patients not treated according to the guideline undergo bone density measurement. A press release by the patient association "Sozialverband VdK Deutschland e.V." states that many physicians still only offer osteodensitometry for out-of-pocket payment,[221] which likely reduces the number of patients getting the examination. The share of non-S3-guideline treated patients undergoing osteodensitometry covered by the SHI is therefore set to 25 %.

Consultations

Physician consultation occurs once in the decision tree for the whole cohort. In the Markov model four doctor-patient encounters are modelled for the first year of treatment (pre-fracture treatment as well as post-fracture treatment), and two encounters in the second and third year of treatment. In these two years cost of issuing a follow-up prescription is added.

Cost of a routine or check-up visit by a GP is given at € 16.13 for people aged 55-74 in the EBM.[222] This may be topped up by € 13.35 lump sum for the treatment of chronically ill persons, amounting to € 29.48.[223] If diagnosis is performed by an orthopaedic physician the lump sum for a consultation of a patient over the age of 60 is € 21.57 plus an additional € 3.18 once per case.[224] There is a possible lump sum add-on of € 17.26 for degenerative diseases of the spine.[225] Further accounting items may apply and the actual payout to the physician is dependent on the amount of services rendered and is calculated on the basis of a point system.[226] The identified costs for physician check-up are in the same range as those

217 Dachverband Osteologie DVO e.V. 2014: 240; Gourlay et al. 2012; Berry et al. 2013
218 This is the fee schedule for office-based physicians in Germany. It is translated as Uniform Assessment Standard by the National Association of Statutory Physicians.
219 Kassenärztliche Bundesvereinigung (KBV) 2015: accounting code: 34600 or 34601
220 Müller, Gandjour 2011: 265
221 Sozialverband VdK Deutschland e.V. 2014
222 Kassenärztliche Bundesvereinigung (KBV) 2015: accounting code: 03000
223 Kassenärztliche Bundesvereinigung (KBV) 2015: accounting code: 03220
224 Kassenärztliche Bundesvereinigung (KBV) 2015: accounting code: 18212 and 18220
225 Kassenärztliche Bundesvereinigung (KBV) 2015: accounting code: 18331
226 Kassenärztliche Bundesvereinigung (KBV) 2015

used by Müller and Gandjour for the year 2010.[227] For the model a cost of € 25 is applied per consultation. Cost for solely issuing a follow-up prescription is € 1.23 (EBM 01430).

Medication

Cost of medication was attached to the first three years of the Markov model for the groups receiving treatment, as well as for each of the post-fracture treatment states. The treatment prices (see table 11) were taken from the Rote Liste, which provides information on pharmaceuticals in Germany.[228] Each package size of every product available is listed with its unique identifier number: the Pharmazentralnummer (PZN). Cost of osteoporosis medication for one year ranges from just above € 200 to nearly € 7 500. With € 202.36 a year weekly treatment with alendronate (Alendromed, Fosavance or Tevaboe) was the cheapest and was therefore applied. It should be noted that, with the exception of Fosamax, treatment with bisphophonates, which is recommended as first line treatment,[229] generally lies in this price range.

Table 11: Cost of medication for 3 months.

Name	**Active agent**	**Regimen**	**Package size**	**Price**	**PZN**
Alendromed 70mg	alendronate	weekly	N3 – 12 pills	€ 50.59	01972892
Fosavance 70mg	alendronate	weekly	N3 – 12 pills	€ 50.59	05703143
Tevaboe 70mg	alendronate	weekly	N3 – 12 pills + 84 vit.D	€ 50.59	00770560
Actonel 75mg	risedronate	monthly	N3 – 6 pills	€ 59.60	07210060
Actonel 35mg	risedronate	weekly	N3 – 12 pills	€ 59.61	03390763
Actonel 5mg	risedronate	daily	N3 – 98 pills	€ 64.07	01888312
Fosamax 70mg	alendronate	weekly	N3 – 12 pills	€ 69.13	01453666
Fosamax 10mg	alendronate	daily	N3 – 112 pills	€ 89.44	07332691
Protelos 2g	strontium ranelate	daily	N3 – 84 sachets	€ 138.43	03702926
Evista 60mg	raloxifen	daily	N3 – 84 pills	€ 142.79	00027909
Optruma 60mg	raloxifen	daily	N3 – 84 pills	€ 142.79	04531680
Prolia 60mg	denosumab	every 6 months	N1 – 1 syringe	€ 311.90	06145082
Forsteo 20µg	teriparatide	daily	N3 – 3 injectors	€ 1856.73	05127722

Fractures

It was assumed that costs of fracture only arise in the year of the fracture. Long-term fracture costs such as nursing care are not included in the model.

Cost of a “forearm fracture” in the study by Müller & Gandjour (2011) was stated as € 1 066.28 for outpatient treatment and € 3 222.00 for inpatient treatment including rehabilitation.[230] Bleibler and colleagues applied a value of € 835 for outpatient treatment

227 Müller, Gandjour 2011: 265
228 Rote Liste Service 2015
229 Dachverband Osteologie DVO e.V. 2014: 192
230 Müller, Gandjour 2011: 265

and € 3 794 for inpatient treatment.[231] Since the state in the model is “other fracture”, which also includes a share of fractures besides wrist and forearm fractures which may be more expensive, the higher of each of the two values was picked and adjusted to 2015 values. The weighting of the occurrence of inpatient versus outpatient treatment was based on a study of the city of Rostock. 77 % of wrist fractures were treated during a hospital stay.[232]

Total health care cost of a vertebral fracture over the course of one year were found to be € 5 024 in a study of AOK insurants data.[233] Cost data stem from the years 2005 – 2010. Since the actual year of occurrence was not available, the values were adjusted to 2015 values based on the assumption that the stated cost is a 2010 value.

Hip fractures are the most expensive osteoporotic fractures. Direct cost of fracture treatment, consisting of inpatient treatment and rehabilitation in 2003, are estimated between € 9 731 and € 12 288.[234] In their model Gandjour and Weyler arrive at a 6-month health care cost for hip fracture of between € 14 074 and € 15 229 (2004). The values lie in the same range. Conservatively, the lower value of Gandjour and Weyler was adjusted and applied in the model as it also includes treatment cost following the surgery for hip fracture. An overview of all cost factors can be found in the table below.

Table 12: Cost of diagnosis and treatment of osteoporosis and osteoporotic fractures. Values applied per year, except DXA which occurs during group allocation (October 2015 values).

DXA	Physician	Medication	Other fracture	Vertebral fracture	Hip fracture
€ 43.09	€ 100.00 [a] € 52.46 [b]	€ 202.36	€ 3432.78	€ 5390.60	€ 16686.51

[a] *First year of treatment*
[b] *Second and third year of treatment*

Death

Cost of dying is not included, as no osteoporosis-specific cost data could be found. However, it should be kept in mind that patients dying in a hospital, for example after a fracture, will incur higher costs, than patients dying at home.[235] On the other hand, after age 65 (or 70, depending on study) increasing age seems to be associated with a reducing cost of dying.[236] Overall cost of dying seems to vary between diseases, but even more strongly within diseases. [237]

231 Bleibler et al. 2014: 289
232 Bassgen et al. 2013: 259
233 Lange et al. 2014: 2439
234 Häussler et al. 2007: 82
235 Briggs, Sculpher 1998: 403
236 Polder et al. 2006: 1723; Felder et al. 2000: 690; Breyer, Felder 2006: 180
237 Polder et al. 2006: 1723

4.3 Sensitivity Analysis

The model is based on assumptions and published data, both of which include uncertainty. Therefore a sensitivity analysis is recommendable in order to test which factors especially influence the model outcome and how strongly the outcomes may vary.[238] This may then even identify areas in which more research would be valuable. Sensitivity analyses are most commonly conducted on epidemiological rates and direct costs, but are also increasingly applied to compliance rates and test characteristics. [239] There still is disagreement as to how uncertainty should best be assessed.[240]

It is also important to differentiate between parameter uncertainty stemming from the quality of the data applied in the model and structural uncertainty based on the included aspects of e.g. disease and treatment possibilities.[241] If a model is very sensitive to a parameter with high uncertainty, this will render the outcomes uncertain. The sensitivity of the model toward specific parameters was examined by increasing and decreasing each of the values by 20 % and observing the extent of change in the output values.

The parameter uncertainty within the model was examined by applying the respective highest and lowest values found in the literature. For some of the parameters of the model a multitude of articles were found, displaying a wide range of results (as described in the previous chapter). The lowest and highest values were applied for the sensitivity analysis (see table 13). For values derived from only one source the confidence intervals were used.[242] In the absence of these alternatives the model values were increased and decreased by 20 % to accommodate uncertainty. These values are distinguishable by the brackets.[243]

As the estimated portion of women aged 70 who should be treated according to the S3-guideline of 2009[244] is larger than the values based solely on T-score[245], this estimate was applied as the higher value in the sensitivity analysis.

238 Briggs et al. 2012: 836
239 Agro et al. 1997: 82
240Philips et al. 2006: 355
241 Briggs et al. 2011: 83
242 Briggs, Sculpher 1995: 357
243 Briggs et al. 2012: 837f.
244 Sondergeld 2015: 33
245 Luhn 2012: 34

Table 13: Transition probabilities for the sensitivity analysis based on ranges given in literature. For values not found in literature a change of 20 % was applied (values in brackets).

		Base case value	Identified range from literature	
			Lowest value	Highest value
Percent of female population with a T-score ≤ -2.5 (age 70)		25 %	13.7 % [246]	28.5 % [247]
Portion of female population with osteoporosis according to S3-guideline 2009 (age 70)		See above T-score ≤ -2.5	-	33.8 %[248]
Treated for osteoporosis (non-S3)		10 %	[8.0 %]	32 % [249]
Treatment after hip or vertebral fracture (non-S3)		10 %	[8.0 %]	17 % [250]
Fractures				
10-year risk 20 %	Other fracture	5.0 %	[4.0 %]	[5.0 %]
	Vertebral fracture	1.2 %	1.27 % [a]	1.16 % [a]
	Hip fracture	0.99 %	0.92 % [b]	1.04 % [b]
10-year risk 30 %	Other fracture	8.0 %	[6.4 %]	[9.6 %]
	Vertebral fracture	1.9 %	2.03 % [a]	1.86 % [a]
	Hip fracture	1.6 %	1.47 % [b]	1.64 % [b]
Fracture after fracture				
After other fracture (prior 10-year fracture risk: 20%)	Other fracture	5.0 %	2.0 % [251]	10.1 % [c]
	Vertebral fracture	1.2 %	[0.96 %]	2.4 % [c]
	Hip fracture	0.9 %	[0.79 %]	2.1 % [c]
After other fracture (prior 10-year fracture risk: 30%)	Other fracture	8.0 %	2.0 % [252]	16.2 % [c]
	Vertebral fracture	1.9 %	[1.5 %]	3.8 % [c]
	Hip fracture	1.6 %	[1.28 %]	3.7 % [c]
After vertebral fracture (prior 10-year fracture risk: 20%)	Vertebral fracture	1.9 %	[1.5 %]	3.8 % [c]
	Hip fracture	1.6 %	[1.28 %]	3.7 % [c]
After vertebral fracture (prior 10-year fracture risk: 30%)	Vertebral fracture	2.5 %	[2.0 %]	5.1 % [c]
	Hip fracture	2.0 %	[1.6 %]	4.6 % [c]
After hip fracture	2nd hip fracture	2.0 %	1.9 % [253]	2.8 % [254]

246 Berkemeyer et al. 2009: 4,6
247 Luhn 2012: 34
248 Sondergeld 2015: 33
249 Hadji et al. 2013
250 Vogel et al. 2008: 874ff.
251 Hodsman et al. 2008
252 Hodsman et al. 2008
253 Berry et al. 2007
254 Hodsman et al. 2008

Table 13: Transition probabilities for the sensitivity analysis based on ranges given in literature. For values not found in literature a change of 20 % was applied (values in brackets) (continued).

Short-term mortality after fracture				
After other fracture		5.0 %	1.8 % [255]	10.2 % [256]
After vertebral fracture		10.0 %	5.9 % [257]	20.8 % [258]
After hip fracture		20.0 %	15.8 % [259]	26.4 % [260]
After 2nd Hip fracture		25.0 %	24.1 % [261]	[30.0 %]
Long-term mortality after fracture				
After other fracture		0		
After vertebral fracture (of age dependent mortality)		10 %	[8.0 %]	[1.2 %]
After hip fracture (of age dependent mortality [d)]		73 %	[58.4 %]	[87.6 %]
After 2nd Hip fracture		20 %	12.9 % [262]	[24.0 %]
Treatment effect (reduction of fractures & mortality by)				
T-score ≤ -2.5	Other fracture	20 %	16 % [263]	[24 %]
	Vertebral fracture	40 %	37 % [264]	45 % [265]
	Hip fracture	30 %	26 % [266]	40 % [267]
	Mortality	10 %	*0 %*[e] [268]	28 %[f] [269]
T-score > -2.5		0	-	-

[a] *Only ratio between hip and vertebrae fractures was varied, as overall risk is defined by S3-guideline. Ratio taken from Techniker Krankenkasse.[270] Higher levels of hip fracture applied in the sensitivity analysis with the upper values.*

[b] *Only ratio between hip and vertebrae fractures was varied, as overall risk is defined by S3-guideline. Ratio taken from City of Rostock.[271]*

[c] *Calculated on the basis of the meta-analysis by Kanis and colleagues[272] and corroborated.[273]*

[d] *Ranging from 1.9 % at age 70 to 51.9% at age 100.*

[e] *In persons below the age of 75 2.1 % of the 2 727 placebo recipients and 2.3 % of the 2 721 zoledronic acid recipients died. In persons over the age of 75 7.5 % of the 1 921 placebo recipients and 7.0 % of the zoledronic acid recipients died. The differences not being significant with p-values above 0.5. Therefore as a lower estimation no treatment effect on mortality was modelled.*

[f] *5 year follow-up, no discrimination of fracture related and age dependent mortality*

255 Morin et al. 2011
256 Morin et al. 2011
257 Morin et al. 2011
258 Morin et al. 2011
259 Morin et al. 2011
260 Bondo et al. 2013
261 Berry et al. 2007
262 Berry et al. 2007
263 Wells et al. 2011
264 Wells et al. 2010b
265 Wells et al. 2011
266 Wells et al. 2010b
267 Wells et al. 2011
268 Boonen et al. 2010
269 Lyles et al. 2007
270 Hadji et al. 2013
271 Bassgen et al. 2013
272 Kanis et al. 2004: 379
273 Haentjens et al. 2003: 1938

Table 14: Utility values for health states in persons aged 70+ with osteoporosis – model values and lower and upper confidence interval values applied for the sensitivity analysis.

Values	Asymp-tomatic	Other fracture	Post-other fracture [a]	Vertebral fracture	Post-vertebral fracture [a]	Hip fracture	Post-hip fracture [a]
Model	0.73	0.61	0.73	0.44	0.66	0.31	0.66
Lower CI	0.70	0.54	0.70	0.37	0.62	0.22	0.60
Upper CI	0.78	0.67	0.78	0.51	0.71	0.39	0.70

[a] *Including the post-fracture treatment as well as post-treatment offset states*

The applied health state utility values were taken from a meta-analysis and are varied in accordance with the upper and lower 95 % confidence intervals (see table 14). Where possible higher and lower cost estimates were included from published data, for example by taking a more costly bisphosphonate pharmaceutical product, and by adding long-term fracture cost to the post-fracture states (table 15). Values in brackets indicate that no data was available, in those cases values were varied by 10 % for the sensitivity analysis.

Table 15: Variation of cost applied in the sensitivity analysis. Except for DXA which only occurs in the decision tree, values are applied per year. (October 2015 values).

Values	DXA	Bisphosphonate treatment	Other fracture	Vertebral fracture	Hip fracture	Post-hip or vertebral fracture
Model	43.09 €	302.36 € [a] 254.82 € [b]	3 432.78 €	5 390.60 €	16 686.51 €	-
Lower	[38.78 €]	[272.12 €] [a] [229.34 €] [b]	2 897.84 € [c]	[4 851.54 €]	11 740.79 €[274]	-
Upper	[47.40 €]	401.48 € [a] 349.19 € [b]	[3 776.06 €]	[5 929.66 €]	18 055.91 €[275]	764.46 €

[a] *First year of treatment*
[b] *Second and third year of treatment*
[c] *77 % inpatient treatment and 23 % outpatient treatment* [276]

Treatment cost was reduced by 10 % to obtain the lower value. For the upper value cost of physician consultation was increased by 10 % and the cost of bisphosphonates was increased by assuming a prescription of Fosamax 10 mg instead of Alandromed 70 mg, Fosavance 70 mg or Tevaboe 70 mg. The cost was based on 3.3 packages of Fosamax 10 mg (112 pills) a year.

Expenses for analgesics were added based on the data from Häussler et al. stating that prescriptions of analgesics made up three times as much costs as did bisphosphonates in Germany.[277] These costs were applied to the post-hip fracture and post- vertebral fracture states. Other long term costs such as nursing care were not included. As no disease specific data were found for cost of dying, this cost was also not added in the sensitivity analysis.

274 Häussler et al. 2007: 82
275 Gandjour, Weyler 2006
276 Müller, Gandjour 2011: 265; Bleibler et al. 2014: 289
277 Häussler et al. 2007: 81

5 Results of the Model

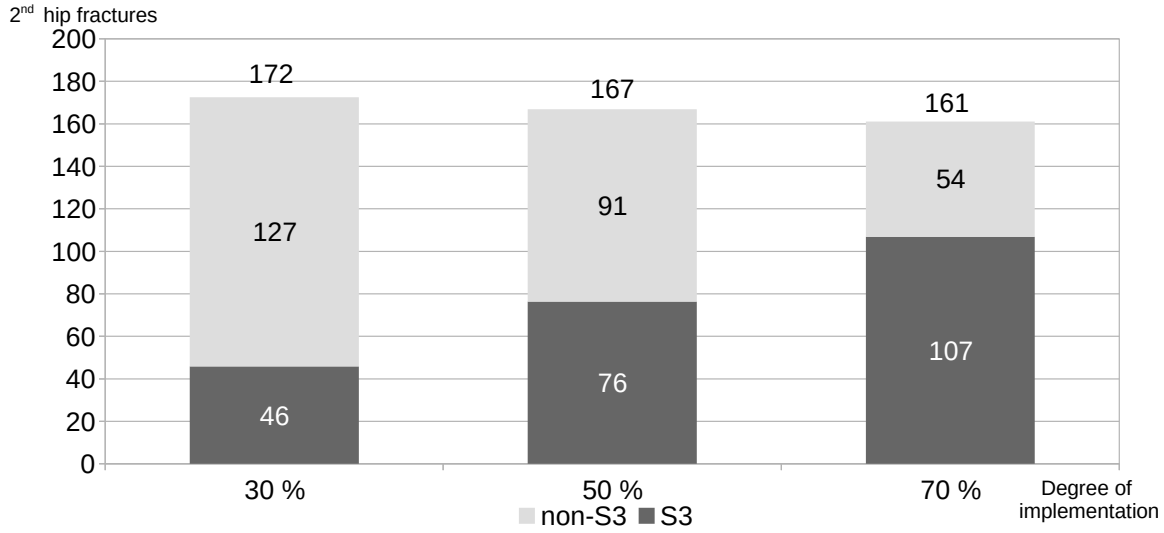
Three scenarios were modelled assuming 30 %, 50 % and 70 % of patients are treated according to the S3-guideline. The differences between the degrees of implementation are not very pronounced (for absolute numbers see table 16). Increasing the amount of patients treated according to the S3-guideline by 20 percentage points generally only leads to a change of less than 1 % in the outcome events, the exception being the occurrence of second hip fractures which changes by 3.41 % per implementation scenario.

Table 16: Occurrence of fracture events and fracture related deaths by degree of implementation of the S3-guideline on osteoporosis (Cohortsize: 10 000).

Degree of implementation	100-year-olds without fracture	Vertebral fractures	1st hip fractures	2nd hip fractures	Other fractures	Deaths due to fracture	Deaths overall
30 %	20	2 043	1 705	172	7 488	1 683	9 740
50 %	20	2 023	1 694	167	7 481	1 668	9 740
70 %	20	2 004	1 683	161	7 474	1 653	9 739

The distribution of second hip fractures according to degree of implementation can be seen below (figure 4). While the absolute numbers change, the percentage stays the same with 1.5 % of the population treated by the S3-guideline experiencing a second hip fracture compared to 1.8 % of the population not treated on the basis of the S3-guideline. Regarding the German female population aged 70 (31.12.2014) the difference of 0.3 % (between no implementation and full implementation) amounts to 1 311 women.[278]

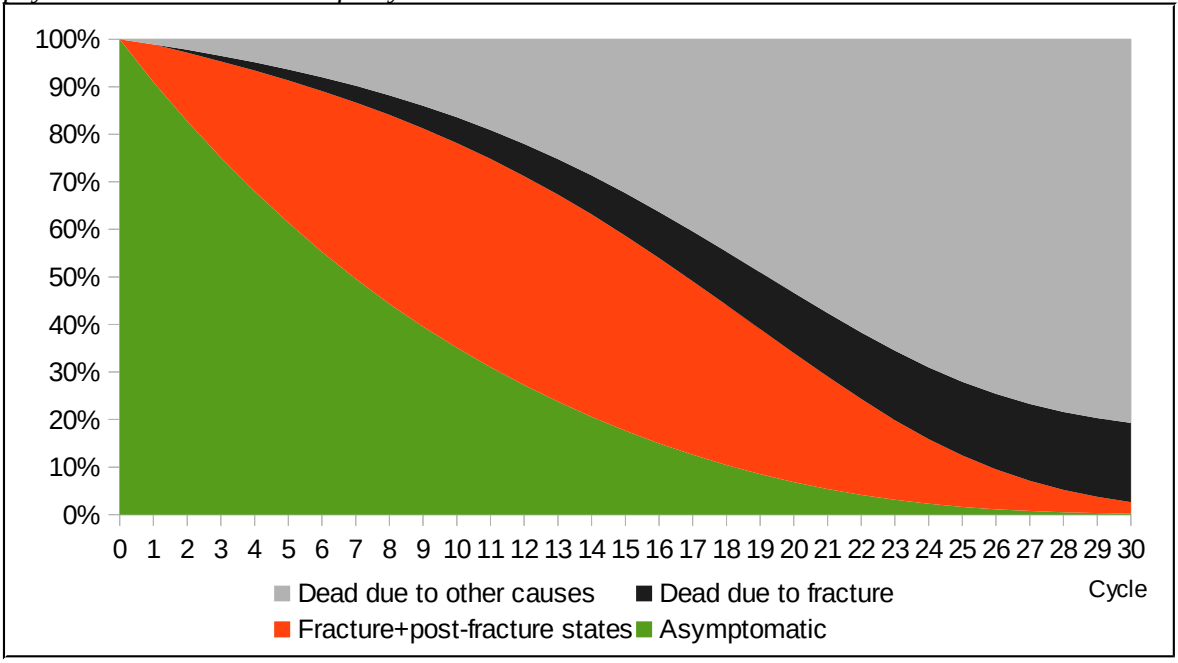
Figure 4: Number of 2nd hip fractures by degree of S3-guideline implementation.



278 Statistisches Bundesamt 2015a

The development of the cohort over the duration of 30 years is shown in figure 5. As the scenarios only differ marginally not all three are illustrated. The 50 % implementation scenario was used for the example.

Figure 5: Fracture events and mortality for an implementation of the S3-guideline by 50 % of physicians over the course of 30 years.



The amount of people fractured or having experienced at least one fracture increases over time, with the largest number of persons in fracture and post-fracture states in cycle 12. The number of people dying from fracture per cycle increases until the 17th cycle at which point just over half the cohort has died (1 045 due to fractures; 4 045 from other causes). In the 50 % implementation scenario 2.6 % of the cohort live to see their 101th birthday, of which only 7.8 % (20 persons) have not (yet) experienced a fracture since they were 70.

QALYs are an important outcome measure as they incorporate quality of life as well as life duration.[279] The QALYs and cost for each of the scenarios, based on a cohort size of 10 000 women with a starting age of 70 years, are shown below in table 17. In the model approximately 90 % of all cost (30 % implementation: 92.7 %; 50 % implementation 89.8 % implementation: 89.1 %) results from the treatment of fractures as opposed to the cost of medication.

The QALYs in model are accumulated over the course of 30 years combined for both of the treatment groups. From one scenario to the next (increase of degree of implementation by 20 percentage points) the QALYs increase by 0.11 % while the cost increases by 2.54 % (undiscounted: 0.12 % and 2.10 %).

279 Zethraeus et al. 2007 :11

Table 17: Costs and QALYs of different degrees of implementation of the S3-guideline on osteoporosis.

Degree of implementation	QALYs	Disc. QALYs	Cost	Discounted cost	Cost per QALY	Disc. cost per disc. QALY	Disc. cost per QALY
30 %	115 024	87 856	€ 72 438 977	€ 55 137 590	€ 629.77	€ 627.59	€ 479.18
50 %	115 160	87 950	€ 73 994 507	€ 56 571 810	€ 642.53	€ 643.22	€ 491.24
70 %	115 297	88 045	€ 75 550 037	€ 58 006 029	€ 655.26	€ 658.82	€ 503.10

Comparing the cost per QALY, with and without discounting, of the three scenarios, it becomes obvious that the costs and benefits of the S3-guideline treated group and the non-S3-guideline treated group occur at different time points. More costs occur early on due to diagnostic procedures and preventive treatment in the S3-guideline treated group, while in the non-S3-guideline treated group costs mainly occur later on due to fractures.

In the model an increase of implementation by 20 percentage points prevents 19 vertebral fractures, eleven hip fractures and six second hip fractures. The effect on other fractures is minimal (7 fractures prevented – approximately 0.1 % of all other fractures) since they mainly occur in persons with a lower risk and the preventive effect of bisphosphonate is lower. The treatment of these averted fractures would have cost € 410 120 (undiscounted, as time of occurrence not known). Regarding solely the diagnostic procedures (2 000 people) and treatment for the first three years (500 people with a fracture risk of 30 %) the increase of the implementation of the S3-guideline by 20 percentage points would incur an additional cost of € 467 540. It appears that the increase of implementation is close to an economic break even point, but cost of treatment after fractures (tertiary prevention) is not included, which in turn would lead to further cost and even less avoided subsequent fractures, making break even less likely. Overall, in a span of thirty years, the costs increase by approximately € 1 500 000 for an additional 20 percentage points of implementation.

In the table below (table 18) the distribution of the overall discounted QALYs and costs between the two groups are shown for treatment of 50 % of patients according to the S3-guideline. It can be seen that the QALYs and also, to a larger extent, the costs are higher for the S3-guideline treated groups.

Regarding the outcomes by 10-year fracture risk group it is evident, that the S3-guideline leads to higher QALY values both for the low risk patients with a 10-year fracture risk of 20 % as well as for the high risk patients (see table 17). For both groups the costs are also higher for the S3-guideline treated group. But regarding the difference in cost, the increase for the high risk group, with a 10-year fracture risk of 30 %, is less by a factor of 6 compared to the low risk group. (approx. € 500 000 versus € 3 million).

Table 18: Costs and QALYs incurred by the S3-guideline treated group and the not S3-guideline treated group (at a 50 % degree of implementation).

10-year fracture risk	QALYs		Costs		Cost per QALY	
	S3	Non-S3	S3	Non-S3	S3	Non-S3
Whole cohort (20 % + 30 %)	44 094	43 857	€ 30 078 679	€ 26 493 130	€ 682.15	€ 604.08
20 %[a]	33 233	33 169	€ 21 057 688	€ 17 966 799	€ 633.64	€ 541.66
30 %	10 861	10 687	€ 9 020 991	€ 8 526 331	€ 830.60	€ 797.84

[a] *The population with a 10-year fracture risk of 20 % makes up 75 % of the modelled population*

The average discounted cost per patient with a 10-year fracture risk of 20 % is € 5 615 for patients treated according to the guideline and € 4 791 for patients treated unsystematically. For patients with a 30 % 10-year risk of fracture the average cost is € 7 217 if treated according to the guideline and € 6 821 if not treated according to the guideline. On average a person with a 10-year fracture risk of 20 % will accumulate 8.85 QALYs (undiscounted: 11.59) after reaching age 70 if treated without the guideline and 8.86 QALYs (undiscounted: 11.62) if treated with the guideline. For persons with a 10-year fracture risk of 30 % the average QALYs accumulated are 8.55 (undiscounted: 11.15) for non-S3 treatment and 8.69 QALYs (undiscounted: 11.34) if treated following the guideline. In the 50 % implementation scenario the overall average cost-effectiveness ratio (ACER) is € 643.22 per QALY.

$$ACER = \frac{cost\ of\ programme}{effect\ of\ programme} \qquad (5)$$

In order to maximise the health gain from a given budget the various competing options need to be compared not each with no implementation, but always to the next best option. This requires that the options are mutually exclusive and independent of each other.[280] By dividing the difference in price by the difference in effectiveness unit (QALYs in this case) the options can be compared appropriately. The ICER is the average cost for achieving one additional effectiveness-unit.[281]

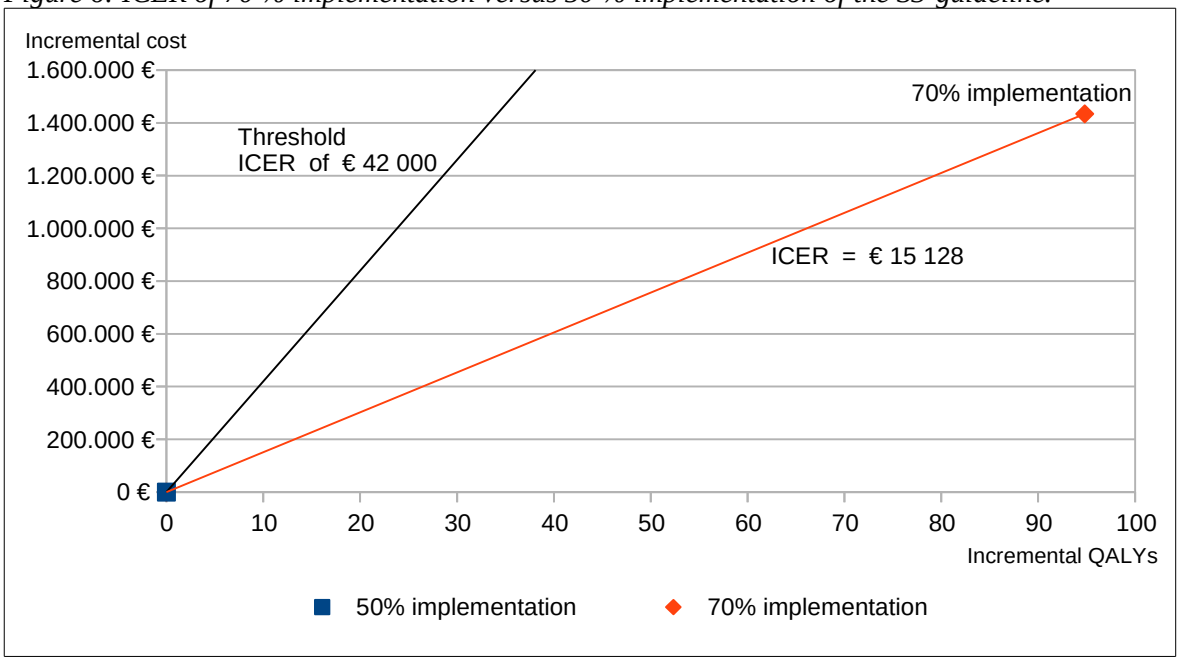
$$ICER = \frac{cost_{more\ effective\ programme} - cost_{next\ effective\ programme}}{effect_{more\ effective\ programme} - effect_{next\ effective\ programme}} = \frac{\Delta cost}{\Delta effect} \qquad (6)$$

The different degrees of implementation are mutually exclusive. If the degree of implementation were to be raised by 20 percentage points, say from 50 % to 70 %, this would incur an incremental cost of € 1 434 219.43 (€1 555 530.07 if not discounted) while gaining 95 QALYs (137 without discounting). The incremental cost effectiveness ratio (ICER) is € 15 128.37 per QALY (see figure 6). If neither cost nor QALYs are discounted the ICER decreases to € 11 382.96 per QALY. The ICER stays the same whether there is an

280 Karlsson, Johannesson 1996
281 Gafni, Birch 2006

increase from 50 % implementation to 70 % or to 100 % showing that there is no critical threshold after which proportionally more people profit from the intervention. If physical activity and knowledge transfer were included in the model, this may change.

Figure 6: ICER of 70 % implementation versus 50 % implementation of the S3-guideline.



Whether a given ICER is considered cost-effective ultimately depends on the payor. In health economics several methods are recommended: comparison to other treatments which are already funded, setting an overall budget and funding treatments beginning with the most favourable ICER until the funds are exhausted, or setting a threshold of maximum cost per effectiveness unit. The threshold value is termed lambda (λ).[282] If the health payor, such as the SHI, does not state a specific threshold an – albeit controversial and partly misappropriated – approach may be to apply a hypothetical threshold subject to the gross domestic product (GDP) of a country.[283] In 2002 the Commission on Macroeconomics and Health of the WHO estimated that one disease adjusted life year (DALY) averted can be valued at minimum one year of average per capita income.[284] This then transmuted to the understanding that if the ICER for one QALY gained is less than three times the annual per capita GDP, a treatment can be considered cost-effective, if it is less than the annual GDP, the product can be considered highly cost-effective.[285] The per capita GDP of Germany is approximately € 42 000[286], with this threshold (see figure 6) further implementation of the S3- guideline could be considered cost-effective.

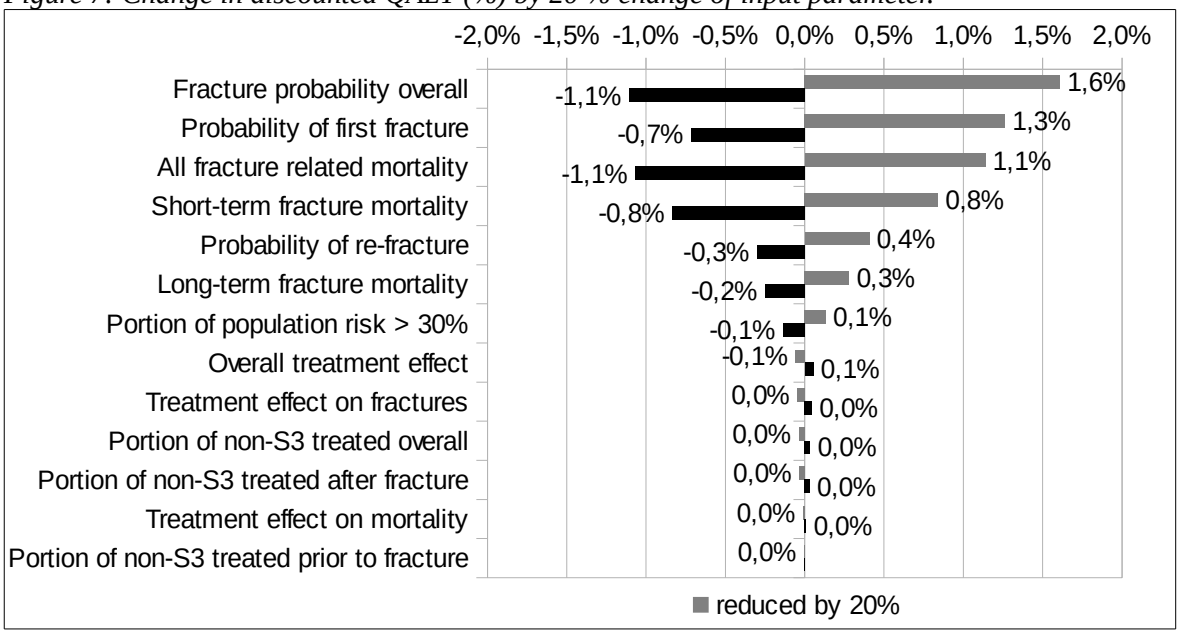
282 Gafni, Birch 2006
283 Marseille et al. 2015
284 Commission on Macroeconomics and Health, World Health Organization 2001: 103
285 Marseille et al. 2015: 118
286 Central Intelligence Agency 2016

6 Results of the Sensitivity Analysis

Due to the large number of variables in the model and their minimal impact on the results when varied within the set boundaries, only a condensed form of the sensitivity analysis is presented here. Besides varying the portion of the population with a 10-year fracture risk over 30 %, the portion of the patients receiving diagnostic procedures and/or treatment in the non-S3-guideline group, the following clusters of probabilities are varied: fracture probabilities, mortality rates and treatment effects.

The sensitivity of the model with respect to the input parameters was examined by increasing and decreasing the values by 20 %. The effect of this change on the overall QALYs (figure 7) and cost (figure 8) can be seen below.

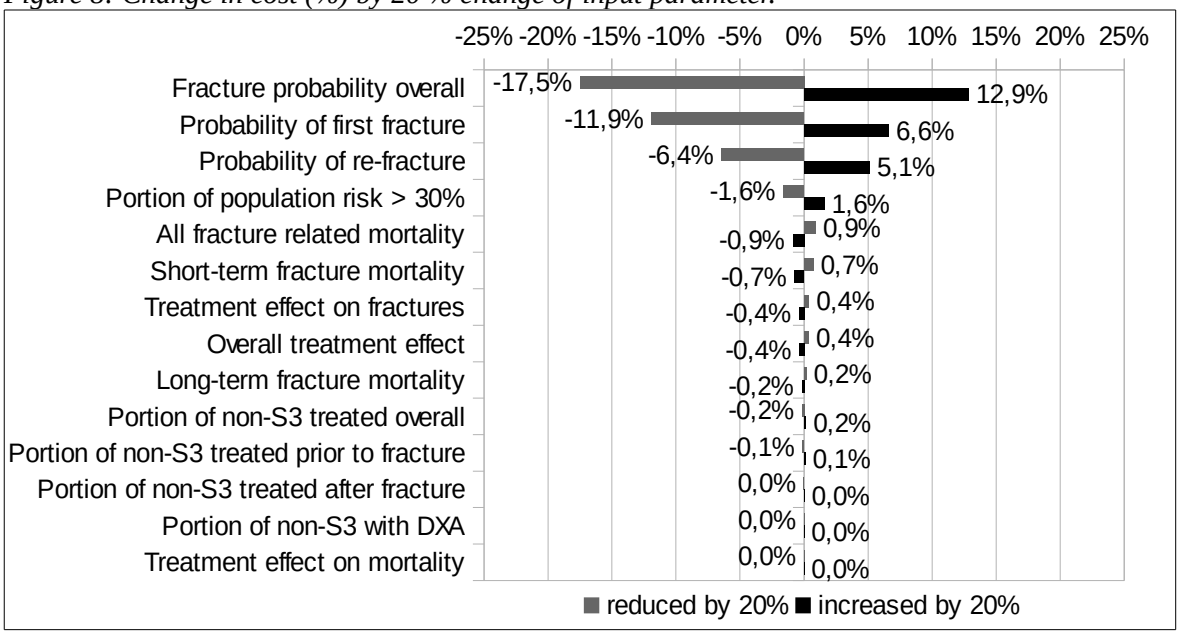
Figure 7: Change in discounted QALY (%) by 20 % change of input parameter.



Overall the number of QALYs does not vary very strongly. They are influenced by changes in the probability of fractures and in mortality rates. The effect of fractures is driven by the occurrence of the first fracture, as it has the strongest effect on the quality of life, while the effect of mortality is driven by the death within the first year of a fracture (short-term mortality).

Cost on the other hand is strongly driven by the probability of fracture, initial fracture as well as re-fracture. This can be explained by the omission of cost of death in the model. Therefore, if fracture related mortality rates are increased by 20 %, the cost is slightly reduced (-0.9 %) since dead people cannot sustain further cost-incurring fractures. The cost is also slightly influenced by the portion of the population at high risk of fracture.

Figure 8: Change in cost (%) by 20 % change of input parameter.



Varying the cost by 10 % leads to a change in total cost of 10 % as the total cost is a linear function over all costs and hence the 10 % can be factored out. The same applies to the QALY values. If only fracture-related costs are changed by 10 % and the treatment and diagnostic cost are kept steady the total cost changes by 9.0% reflecting the strong impact of fractures on the cost (89.8 % in the 50 % implementation scenario, see previous chapter).

The impact of uncertainty concerning the parameters themselves was examined by applying the highest and lowest values found in the literature. The uncertainty of fracture probabilities, mortality rates and treatment effect affects the overall QALYs and cost as can be seen in table 19. The difference in QALYs between the lowest values available and the upper values is 7 877 over the course of 30 years for a cohort of 10 000 women and a S3-guideline implementation degree of 50 % (30 % implementation: 8 005; 70 % implementation: 7 750). This indicates that the non-S3-guideline practice is more strongly affected by the parameters. This can be explained by the higher number of occurring fractures.

Combined the uncertainty concerning fracture probabilities, mortality rates and treatment effect has a strong impact on the cost. Cost after applying the upper values for the aforementioned parameters is approx. 140% of the cost when applying the lower values. With increasing degree of S3-guideline implementation the difference in cost due to the upper and lower values of the parameters declines from € 21 435 859 (30 % implementation) to € 19 894 230 (70 % implementation).

Table 19: QALYs and cost for the three scenarios. Parameters varied: fracture probabilities, mortality rates and inverse treatment effect.

Degree of implementation	QALYs			Cost		
	Lower values	Base case	Upper values	Lower values	Base case	Upper values
30 %	90 166	87 856	82 161	€ 47 466 622	€ 55 137 590	€ 68 902 481
50 %	90 269	87 950	82 392	€ 48 888 521	€ 56 571 810	€ 69 553 565
70 %	90 373	88 045	82 623	€ 50 310 420	€ 58 006 029	€ 70 204 650

Over the course of 30 years it is visible that the effect of parameter uncertainty regarding fracture probabilities, fracture related mortality rates and treatment effects (inverse) has a stronger effect on the number of QALYs than the degree of S3-guideline implementation (see figure 9). Figure 10 and figure 11 illustrate the impact of fracture probabilities, mortality rates and inverse treatment effect on the cost incurred. During the first six cycles the cost for a cycle differs by degree of implementation as well as due to the uncertainty in parameters. This is especially pronounced for the first three cycles and is due to the cost of prophylactic treatment with bisphosphonate. After the first six cycles the base case and upper as well as lower estimates of the scenarios converge. As with the QALYs the change in the fracture and mortality rates affects more change than the degree of implementation.

Figure 9: QALYs per cycle – base case as well as upper and lower values – for each of the three scenarios. Parameters varied: fracture probabilities, mortality rates and inverse treatment effect.

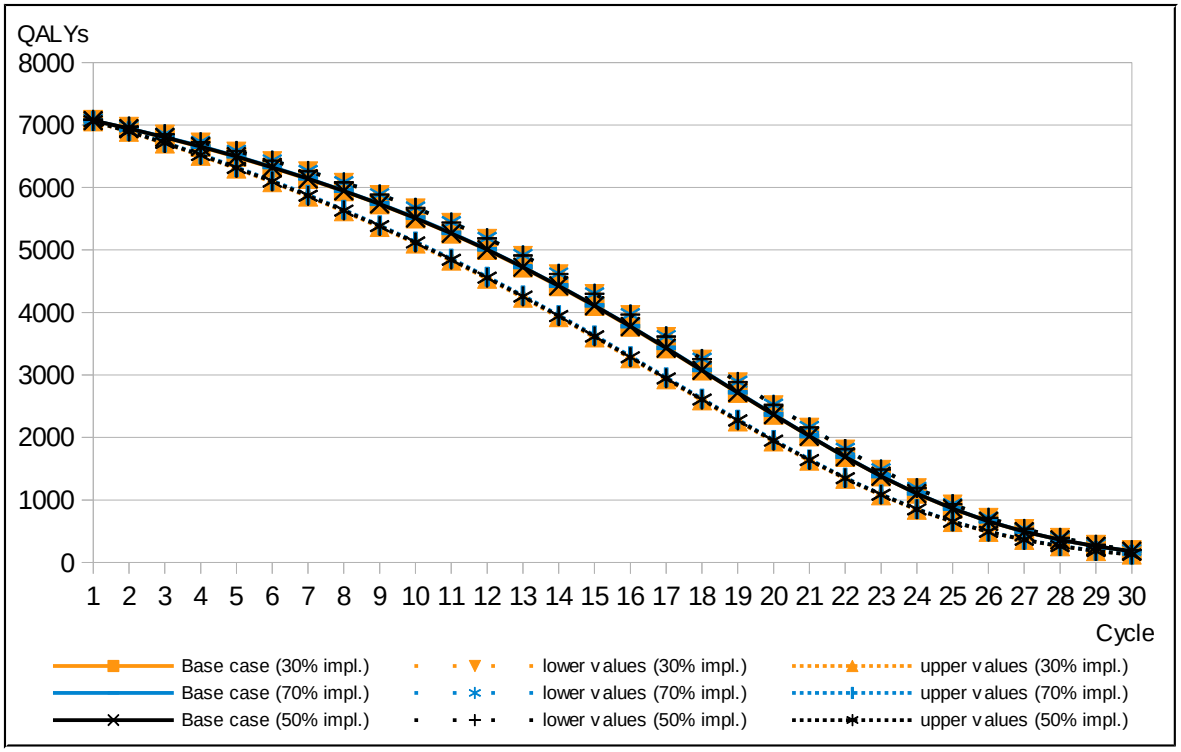


Figure 10: Cost per cycle – base case as well as upper and lower values – for each of the three scenarios. Parameters varied: fracture probabilities, mortality rates and inverse treatment effect.

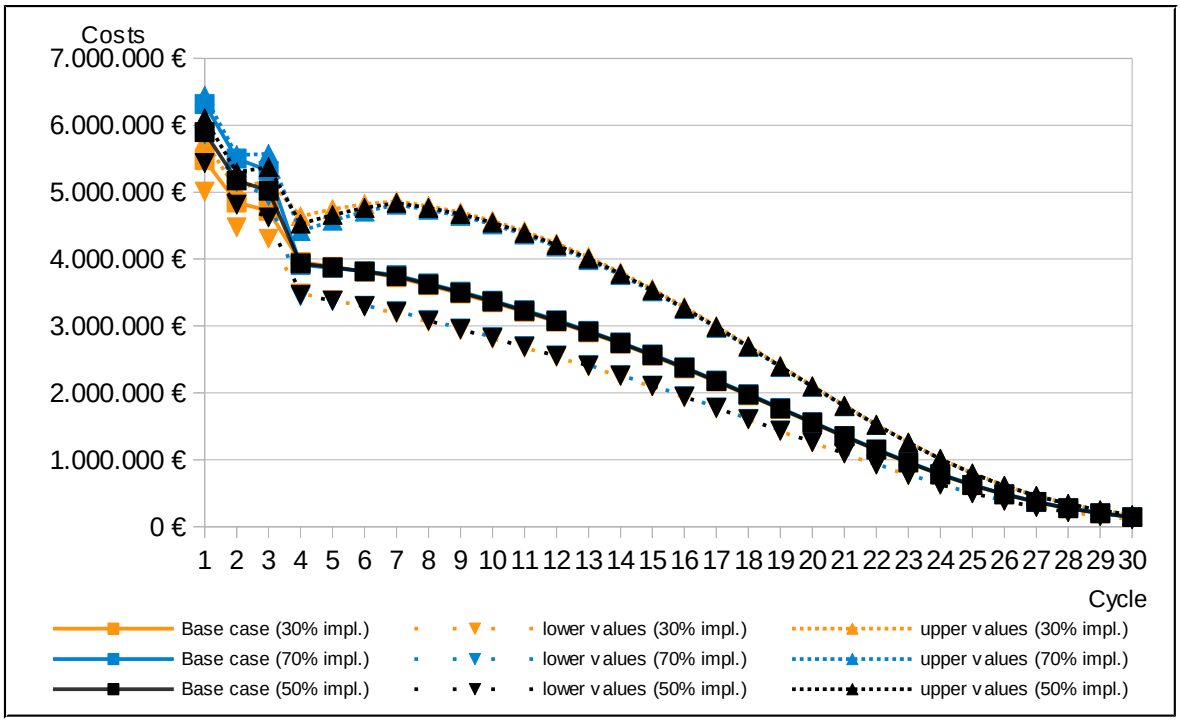
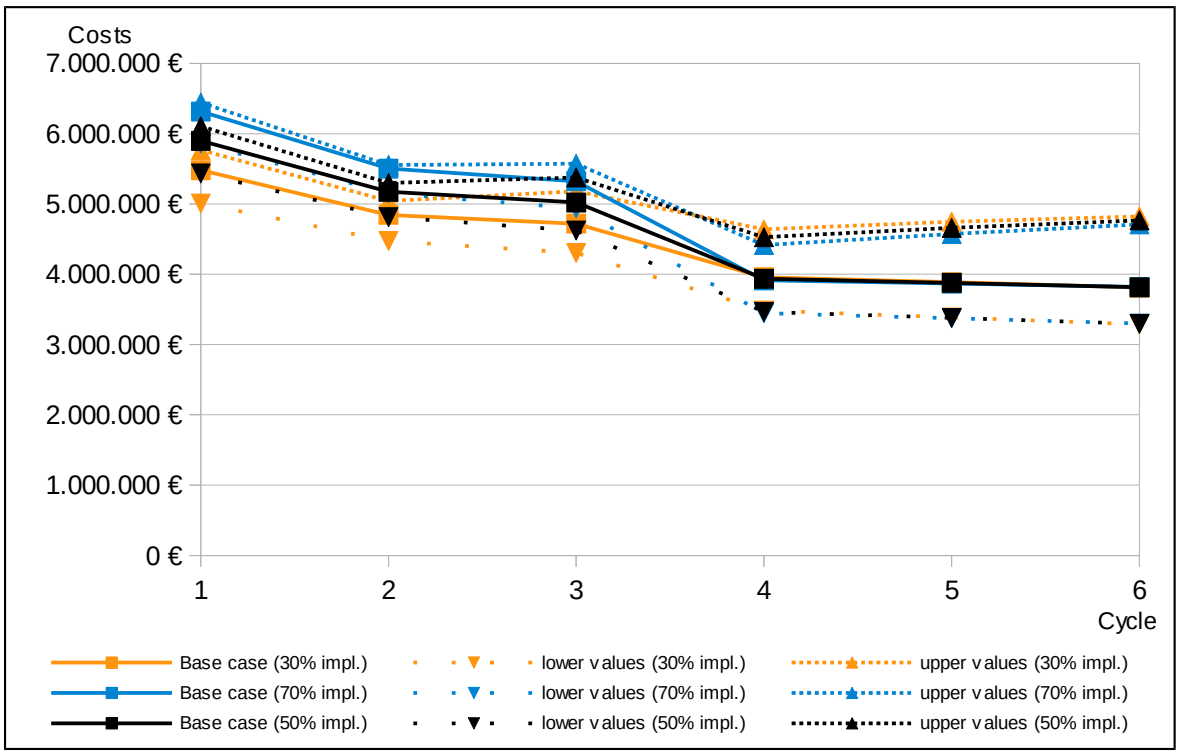


Figure 11: Cost for each of the first 6 cycles – base case as well as upper and lower values – for each of the three scenarios. Parameters varied: fracture probabilities, mortality rates and inverse treatment effect.



As general uncertainty exists regarding the prevalence of persons with a 10-year fracture risk of at least 30 %, stemming from varying data pertaining to T-scores and lack of data concerning the prevalence of other risk factors, changes in the cost-effectiveness ratios by prevalence and degree of implementation were examined.

It was found that the average cost per QALY increases with increasing prevalence and increases with increasing implementation. However regarding the increments of the increase, the table below shows that the increase increases with prevalence, but decreases with increasing implementation.

Table 20: Incremental increase of ACER for increase of prevalence (portion of persons with a 10-year fracture risk of 30 %) by 10 percentage points for different degrees of implementation.

Implementation \ Prevalence	0	10	20	30	40	50	60	70	80	90	100
0		24,84 €	25,01 €	25,18 €	25,35 €	25,52 €	25,70 €	25,87 €	26,05 €	26,23 €	26,41 €
10		24,30 €	24,46 €	24,62 €	24,78 €	24,94 €	25,10 €	25,27 €	25,44 €	25,60 €	25,77 €
20		23,76 €	23,91 €	24,06 €	24,21 €	24,36 €	24,51 €	24,66 €	24,82 €	24,98 €	25,13 €
30		23,22 €	23,36 €	23,49 €	23,63 €	23,77 €	23,92 €	24,06 €	24,20 €	24,35 €	24,49 €
40		22,67 €	22,80 €	22,93 €	23,06 €	23,19 €	23,32 €	23,45 €	23,59 €	23,72 €	23,86 €
50		22,12 €	22,24 €	22,36 €	22,48 €	22,60 €	22,72 €	22,85 €	22,97 €	23,09 €	23,22 €
60		21,57 €	21,68 €	21,79 €	21,90 €	22,01 €	22,13 €	22,24 €	22,35 €	22,47 €	22,58 €
70		21,02 €	21,12 €	21,22 €	21,32 €	21,43 €	21,53 €	21,63 €	21,74 €	21,84 €	21,95 €
80		20,47 €	20,56 €	20,65 €	20,74 €	20,84 €	20,93 €	21,03 €	21,12 €	21,22 €	21,31 €
90		19,91 €	19,99 €	20,08 €	20,16 €	20,25 €	20,33 €	20,42 €	20,51 €	20,59 €	20,68 €
100		19,35 €	19,42 €	19,50 €	19,58 €	19,66 €	19,73 €	19,81 €	19,89 €	19,97 €	20,05 €

Figure 12: ICER of 70 % versus 50 % implementation depending on prevalence of 30 % 10-year fracture risk in the population.

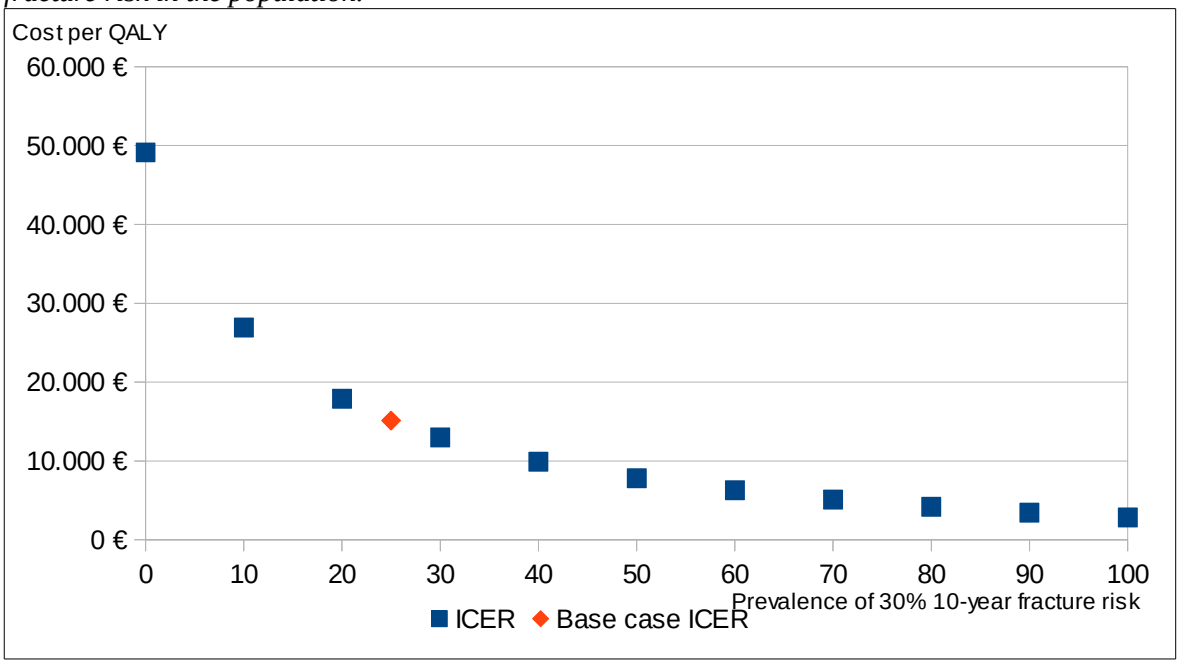
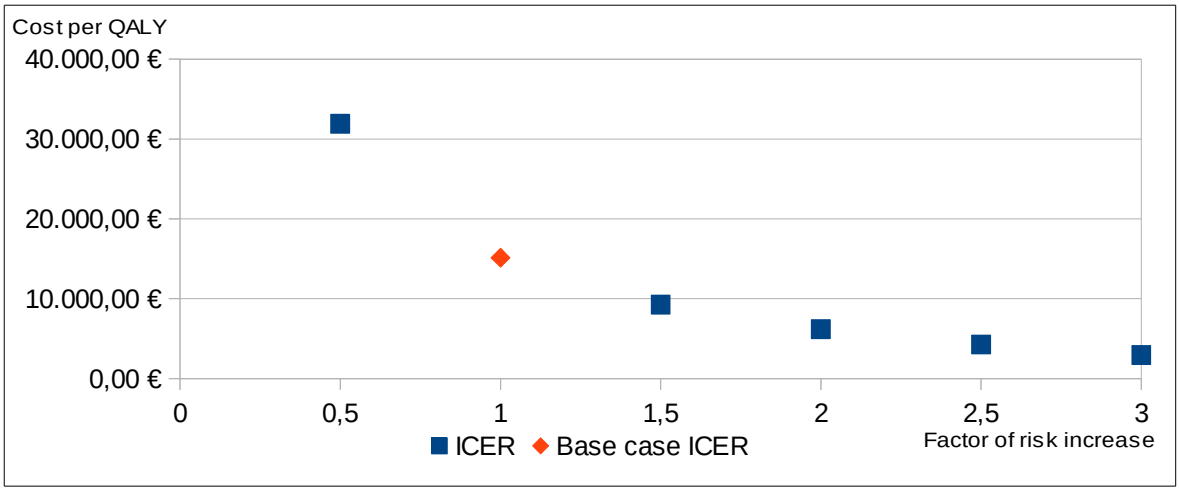


Figure 13: ICER of 70 % versus 50 % implementation depending on factor of fracture risk.



This development of the ratio can also be observed in the change of the ICER. The cost for one additional QALY decreases with increasing prevalence. Figure 12 shows the respective ICERs for an additional 20 % of the population being treated according to the S3-guideline dependent on the prevalence of a 10-year fracture risk of 30 %. Figure 13 shows a similar development regarding the change in ICER according to overall fracture risk. Each fracture risk was multiplied with a factor. For example with a factor of two the probability of an asymptomatic person (with a 10-year risk of fracture of 30 %) of sustaining a hip fracture increases from 1.6 % to 3.2 % per year. With increasing prevalence of high risk persons as well as with increasing fracture risk the programme becomes more cost-effective, as the screening cost per high risk person become less and more QALYs are gained by preventive treatment.

7 Discussion

The model is based on a cohort of women who have not previously been diagnosed with osteoporosis, who do not have any diseases influencing osteoporosis, such as breast cancer or inflammatory bowel disease, and who all visit their GP at age 70. The 10-year fracture risk is based only on T-score, not on other risk factors such as parental hip fracture, and simplifying only 10-year risk fractures of 20 % and 30 % are modelled.

Treatment according to the S3-guideline on osteoporosis results in fewer fractures and fewer fracture related deaths than unsystematic treatment. The S3-guideline procedure obtains more QALYs, but also even more cost. Changing the degree of implementation has a stronger percental impact on cost than on the occurrence of fractures.

Sensitivity analysis demonstrates that the model is influenced more strongly by changes in fracture probability than by the degree of implementation. This is explicable as an increase of the implementation by 20 percentage points affects only 500 people (10-year risk of fracture of 30 %) of a cohort of 10 000. Of those 500 persons 50 would have been treated

anyway. A 20 percentage point increase of implementation therefore only affects 4.5 % of the population. With a treatment effectiveness of 40 % at most, it is not surprising that the observed effects are small. Fracture rates on the other hand affect the whole cohort.

A higher degree of implementation of the guideline can nonetheless be seen as favourable, as under- and over-treatment are combated and with a cost of € 15 128 per additional QALY the ICER could be seen as acceptable. The ICER in the model is the same for an increase from 50 % implementation to 70 % implementation as from 70 % implementation to 90 % implementation. It could be assumed that on the one hand including lifestyle change as part of treatment, as well as knowledge transfer, may lead to a decreasing ICER with increasing implementation, as people might motivate each other, reinforcing the effect of the guideline. On the other hand cost for knowledge dissemination and acquisition amongst physicians was not included which could have a contrary effect, as effort and cost of reaching the remaining physicians would increase.

7.1 Merits of the Model

As advocated for by Consensus Conference on Guidelines on Economic Modelling in Health Technology Assessment the developed model is fully described and the data sources and deliberations have been made transparent. The time frame, population and treatments as well as the cost perspective have been stated, thereby allowing other researchers to reproduce the results. Also the uncertainty of the model was explored in a sensitivity analysis.[287] The model at hand also has the advantage of building upon a publicised reference model, which was developed in accordance with the mentioned consensus statement.[288]

The health states of a state transition model should be defined by the clinical classifications of the underlying disease,[289] as is the case for the developed model. However, whether a patient, treated based on the S3-guideline, is given treatment or not depends on the individual fracture risk which is inferred from an algorithm. This model bridges the gulf between the previous concept of osteoporosis, based firmly on T-scores and the new approach based on individual risk, which is still missing detailed clinical trials and epidemiological data such as population prevalence. With further research in the light of the new paradigm, statements will be able to be made for populations groups other than 70 year old women.

287 Consensus Conference on Guidelines on Economic Modelling in Health Technology Assessment 2000: 444
288 Zethraeus et al. 2007: 18f.
289 Philips et al. 2006: 359

Modelling is posed with the challenge of simplifying while still including all relevant effects and aspects of an issue. This is termed parsimony.[290] The model at hand may seem quite exhaustive, as it includes multiple fracture states, fracture risks dependent on previous site of fracture and age dependent mortality. This is due to the fine differences between S3-guideline and non-guideline treatment, which could otherwise not have been modelled. The complexity of the model is therefore warranted.

The inclusion of treatment inducement during the course of the model as advocated by Bala and Mauskopf is a novelty concerning models of osteoporosis treatment.[291] This enables the modelling of persons with a low risk of fracture being treated if their fracture risk increases, for example after sustaining a fracture, instead of being trapped in the no-treatment arm for the remainder of the model. This is especially important in models with a long time horizon.[292] For the sake of simplicity only two levels of 10-year fracture risk (20 % and 30 %) were modelled. The model also provides the possibility of including adherence levels for future investigation.

7.2 Limitations of the Model

Data from meta-analyses were applied where possible. However, data on the diagnosis and treatment practices of physicians not applying the S3-guideline were sparse. It could be possible that physicians not applying the guideline mainly have patients without osteoporosis or with a very low fracture risk. On the other hand it is also possible that they overlook the fracture risk of their patients, leading to under-treatment. At age 70 every person has a 10-year risk of fracture of at least 20 % and according to the guideline should receive vitamin D and where required also calcium, in regular treatment this is currently not the case.[293] Over-treatment is also a relevant aspect, although this would probably be of more concern with a younger cohort.[294]

Population
Possible deterioration of T-score with age was not included, but most of bone mineral density loss occurs during menopause,[295] therefore further bone mineral density loss is not as pronounced in this cohort. Although the increase of the subsequent fracture risk after sustaining a fracture may already include possible BMD loss.

290 Consensus Conference on Guidelines on Economic Modelling in Health Technology Assessment 2000: 444
291 Bala, Mauskopf 2006
292 O'Mahony et al. 2015
293 Acker 2013: 44
294 Häussler et al. 2007: 80
295 Cauley et al. 2013: 749; Tella, Gallagher 2014: 156

The model only included women, a choice which can be explained by the better data base and also the higher prevalence of osteoporosis amongst women. However, due to demographic change, men will increasingly be affected by osteoporosis and fractures.[296] And it should be kept in mind that for men fractures have an even stronger effect on health related quality of life and are fatal more often.[297]

The model cohort was also based on the assumption that the women did not have any comorbidities, having the 10-year fracture risk of 30 % only due to bone mineral density loss. This is of course a strong simplification as on average women in Germany aged 65-74 have 3.4 (men 2.9) co-morbidities and women in the age group 75+ have 3.8 (men 3.1).[298] Many of these conditions and their treatments can increase the fall risk and exacerbate osteoporosis. Especially the combination of medications, poly-pharmacy, is detrimental.[299] Another limitation is that only 10-year fracture risks of 20 % and 30 % were modelled, while it is possible for persons to have higher fracture risks. This leads to an underestimation of fractures and prevented fractures. Then again, the screening algorithm of DVO incorporated in the S3-guideline does not constitute a perfect test, so persons may be thought to have a 10-year fracture risk of 30 % when it is actually higher or lower.[300]

Additionally, the data on age dependent post-fracture mortality rates should be deemed uncertain, as most studies reported a relative risk increase for age groups. In the model the respective relative risks were applied to the age-specific mortality rate.

Physicians

The degree of implementation was modelled as directly affecting the amount of patients treated according to the S3-guideline. In reality, a physician will treat more than one patient and the guideline also allows for individual treatment decisions, which was not included here. Often treating osteoporosis patients leads to a sensitisation for the issue and possibly to use of the guideline, as the effort made by reading the guideline pays off in more situations.[301] Guideline implementation is facilitated in settings where guideline adoption by others becomes visible, as well as in training settings with younger physicians.[302] This is a strong impediment for implementation in GP practice.

Physicians who are not aware of the significance of osteoporosis on quality of life will be less inclined to making the effort of reading the guideline or treating the disease if diagnosed. Also they will often not detect the condition in their patients as they are not sensitized to the issue.[303] Possibly physicians providing better care may have an inflow of

296 Konnopka et al. 2009: 1121
297 Semel et al. 2010: 802f.
298 Fuchs et al. 2012: 577
299 Semel et al. 2010: 803
300 Mueller, Gandjour 2009
301 Chenot et al. 2007: 589
302 Weingart 2014
303 Chenot et al. 2007: 589

patients, which would impact the number of patients treated by the guideline even without increasing the number of physicians implementing it. Furthermore, cost and barriers for physicians could not be taken into consideration in the model, but should be included in future research on the topic.

Treatment Effect
The result may overestimate the primary preventive effect of bisphosphonates on fractures other than of the vertebrae.[304] This has two causes: On the one hand, few studies have targeted primary prevention, gaining insignificant results. On the other hand, data on primary prevention with bisphosphonates have been coupled to T-scores, further studies are necessary to examine the effectiveness of risk dependent primary prevention.

The S3-guideline on osteoporosis also recommends treatment with vitamin D and calcium, as well as lifestyle changes such as weight bearing exercise to increase bone strength. Fall prevention with exercises, modification of housing and treatment of vision impairments can also prevent fractures.[305] These factors are all not included in the model due to lack of data. This leads to an underestimation of the effects of the guideline.

Health State Utility Values
As the applied HSUV stem from a meta-analysis, they are not specific to the German population, although studies from Germany were included.[306] This might pose an issue as the restrictions experienced, such as lack of social participation, availability of help for daily tasks, due to a fracture may differ by country and would therefore impact the utility of the states.

Cost
The model does not include long-term nursing care cost which makes up a large amount of the burden of fractures on the society. It would be beneficial to incorporate this into the model, however, as it is unclear firstly to which extent the different fractures lead to long-term care needs and secondly which of the various forms of long-term care, such as neighbourly help, privately paid household help or professional nursing at a long-term care facility, are utilized and thirdly over which time period the various forms of long-term care would be provided. This aspect was left aside to not further increase the uncertainty of the model. It is essential that possible long-term care necessities are taken into consideration when contemplating the issue as such. It can be assumed that the S3-guideline is more cost-effective than shown in the model, as it prevents fractures, and therefore also their long-term consequences, compared to regular treatment.

The model was developed from the perspective of the SHI. While the SHI is responsible for bearing the lion's share of expenses, the individuals, their families and friends also take

304 Wells et al. 2011: 2010b
305 Karlsson et al. 2013; Giangregorio et al. 2013; Cameron et al. 2014; Tseng et al. 2012
306 Si et al. 2014

on costs for example for transport and medical supplies. Costs for society are also incurred by the non-productive time of fracture patients, although at age 70 and above, this will not apply as strongly as with younger patients who to a larger extent part of the workforce. However, in 2012/13 nearly one quarter of persons over the age of 65 participated in volunteer organisations spending two hours a day on average with those tasks,[307] which could also have a health improving effect as it strengthens the sense of coherence and enables social contacts.[308]

Osteoporosis often leads to fractures which necessitate support with daily activities for a limited period of time or in some cases for the rest of life. Care is provided either by professional organisations such as nursing services and nursing homes, or by families and friends assisting, nursing and contributing social support. The costs are partly borne by nursing-insurances.[309] Many family member carers cut down on gainful employment to support their relatives.[310] Also, less than half of family member carers rate their own health status as good or very good.[311] This can be seen as affirmation of the findings that caring for family members leads to strain for the individual, in turn leading to health issues, death and thereby also to societal cost.[312] A societal perspective would certainly be of interest; it was omitted here, due to lack of data.

Model Structure

On the structural level the omission of other fractures after vertebral fractures, and other fractures and vertebral fractures after hip fractures could be criticized. This was done, as the quality of life would have improved after such a fracture due to the memorylessness of the model. However, costs of less severe fractures are thereby not accounted for in the model. Also, individuals can only sustain two hip fractures and do not receive any tertiary preventive treatment after the second hip fracture.

The number of DXA examinations does not have an impact on the number of diagnoses and rehabilitation and long-term care are only partially implemented. A better representation of these states and complications would have led to an even more extensive model, since various combinations of aspects exist leading to many parallel tunnel states. This is a serious drawback of Markov models,[313] nevertheless, for a disease with a long time horizon and only limited computation power it is still the best choice. Due to the many variables included the impact of the individual aspect is rather small, but then again reality is multi-factorial. Lastly, it could also be criticized that the effect of osteoporosis and osteoporosis treatments on other diseases (indirect benefits) was not modelled, since

307 Statistisches Bundesamt 2015c: 33
308 Antonovsky, Franke 1997
309 Bundesministerium für Gesundheit 2015
310 Bestmann et al. 2014: 14f.
311 Bestmann et al. 2014: 15
312 Siddiqui et al. 2010: 40
313 Marsh et al. 2012: 5

associations exist and costs may not always be clearly divided, nor were the indirect medical costs of osteoporosis e.g. treatment of another disease which a person endured in the wake of a prevented fatal fracture, included.[314]

7.3 Integration of the Findings into the Current Research

Many economic models of osteoporosis screening and osteoporosis treatment have been developed. Two cohort-based Markov models are often applied, the model of Zethraeus et al.[315] and the model of Tosteson et al.[316]. The model of this thesis is based on the reference model proposed by Zethraeus et al.[317]. The main limitation of patients experiencing a hip fracture not being able to experience any further non-hip fractures was inherited. The elimination of this short-coming by establishing multiple vertebral, wrist, and "other" fracture states by Tosteson et al. was not workable within the scope of this thesis[318]. Contrary to the two models, however, an increased risk after a prior fracture is included in the model at hand.[319]

The model of Tosteson et al. was primarily worked as an example of challenges when modelling osteoporosis and does not include a cost per QALY value. Zethraeus et al. on the other hand found the treatment with alendronate to be cost-effective for the Swedish population at 260 000 Swedish kronor (SEK) per QALY compared to no treatment. Based on the currency table from the 25th of January 2007,[320] this amounts to approximately € 28 500 per QALY. As the model at hand does not compare a specific treatment to no treatment, but compares different degrees of implementation of a guideline no direct comparison can be made, especially since in the case of 0 % implementation a portion of the patients would nonetheless still receive treatment.

Müller, Gandjour and Weyler examined the German screen-and-treat strategy of the DVO S3-guideline of 2006. Compared to no intervention, which has an average cost-effectiveness ratio of € 12 121 per QALY in the study, screening and subsequent treatment with alendronate had an ICER of € 6 600 for the groups of females between 70 and 80 years of age with a 10-year fracture risk of more than 30 %.[321] When attempting to replicate the situation with the model of this thesis a lower ACER of € 801 per QALY (discounted: € 793 per QALY) for no screening and no treatment was found, and the ICER for complete implementation of screening and subsequent treatment was € 2 383 per

314 Grima et al. 2012; van Baal et al. 2013; van Baal et al. 2011; Mobley et al. 2006; Meadows et al. 2006
315 Zethraeus et al. 2007
316 Tosteson et al. 2001
317 Zethraeus et al. 2007
318 Tosteson et al. 2001: 850
319 Hiligsmann et al. 2009
320 XE 2016
321 Mueller et al. 2008: 527

QALY. However, it is not possible to screen only persons with a risk of ≥ 30 % as was modelled in the article. The ICER for the complete implementation of the screen-and-treat strategy as modelled in this thesis, compared to no screening and no treatment would be much higher at € 11 442 per QALY (discounted: € 15 216 per QALY). Despite this disadvantageous assumption the article has the distinct advantage that it also includes the sensitivity and specificity of the screening test, which was omitted in the thesis as no further data to corroborate the sensitivity and specificity of the test could be found.

In a later paper Müller and Gandjour examined the cost-effectiveness of secondary versus tertiary prevention of osteoporosis.[322] For osteoporosis programmes increasing bone strength in children and young adults is considered primary prevention,[323] treatment once bone loss starts is termed secondary prevention, while tertiary prevention is treatment after a fracture has already occurred. The strategy proposed by the DVO combines both secondary and tertiary prevention.[324] Müller and Gandjour found that implementing secondary and tertiary prevention instead of only tertiary prevention lead to a 2.4-fold increase of QALYs gained in the age-group 70-80 compared to no prevention.[325] However, in absolute numbers the QALYs gained by tertiary prevention compared to no prevention are 0.06 and the QALYs gained by secondary and tertiary prevention compared to only tertiary prevention are stated as 0.14 (0.21 compared to no prevention). For the age-group 70-80 the ICER of implementing the S3-guideline (secondary and tertiary prevention) compared to only tertiary prevention is given as € 8 670 per QALY. Replication of the comparison with the model of the thesis yields an ICER of € 17 175 per QALY, however, this does assume that all patients receive tertiary preventive treatment after a fracture, which is currently not the case in Germany.

Overall the values obtained by the model, when replicating the research questions of other studies, are of similar magnitude as values from the published studies. Additional data on long-term care and the inclusion of sensitivity and specificity would be desirable and the future effects on society, e.g. caused by demographic change need to be examined by other methods than a cohort simulation. The specific focus on a real world setting and the inclusion of “physician adherence” by way of degrees of implementation to the proposed intervention is a novelty. As predicted by Ollenschläger the implementation of guidelines does not inevitably lead to savings, since the rectification of previous under-treatment will incur costs.[326]

Treating older patients with osteoporosis requires time and the building of trust.[327] This may also be the best approach to increasing adherence to medication and initiating lifestyle

322 Müller, Gandjour 2011
323 Barondess 2008; Munch, Shapiro 2006
324 Müller, Gandjour 2011: 260
325 Müller, Gandjour 2011: 267
326 Ollenschläger et al. 2001: 481
327 Berlin Hallrup et al. 2009: 381f.

changes. Due to the interdisciplinary treatment of osteoporosis and the subsequent fractures, coordination of treatment is an important issue, which suggests the supervision of a patient's health by a GP. A survey amongst German GPs showed that the S3-guideline on osteoporosis was especially implemented by younger physicians, physicians with knowledge of the internet and who often times work in a group practice.[328] On this basis it could be assumed that the degree of implementation will increase in the years to come.

In this thesis a SHI perspective was taken, which does not account for the expenditures and efforts of physicians in staying up-to-date. Nor were issues such as professional self-determination covered. So, while it can be regarded as a matter of course that physicians keep up with current research, research into possible incentives and paths of dissemination may be beneficial. It is curious that treatment of some indicators, such as hypertension (high blood pressure), is common while osteoporosis, which has an equally predictive value for forecasting fractures, is undertreated.[329]

8 Conclusion

A higher degree of implementation results in slightly higher cost as well as an increase of overall QALYs due to less fractures occurring and less people dying subsequent to a fracture. With an ICER of approx. € 15 130 per QALY for an increase of 20 percentage points of the degree of implementation, a more wide-spread implementation can be considered (highly) cost-effective in accordance with the WHO GDP related threshold. The model and therefore also its results can be deemed pertinent.

The distinct advantage of the S3-guideline is the incorporation of a stepwise age- and risk-dependent screening approach which improves the treatment situation as fewer patients fall through the cracks. Even though a hypothetical increase of the degree of implementation from 50 % to 70 % leads to only 44 averted fractures (of which 20 are vertebral fractures and 17 are hip fractures) amongst 10 000 patients, every prevented fracture is of importance due to the high mortality rates and the high impact on the daily lives of the affected.

Since multi-morbidity is frequent amongst the elderly population it may be beneficial to develop joint guidelines for the most common diseases of this societal group, thereby also targeting the issue of poly-pharmacy and adverse effects. Nonetheless, the S3-guideline is an effective way of improving the treatment of osteoporosis by making it evidence-based and bringing the often times underestimated “silent” disease into focus. Since the implementation hinges on the understanding and acceptance of physicians and motivation of patients, further research into their perceptions and concerns may be beneficial to target obstacles preventing wide-spread implementation of the S3-guideline on osteoporosis.

328 Chenot et al. 2007: 586f.
329 Kanis 1994: 371; Kanis et al. 2013a: 27

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10 Appendix

Abreviations used in the Appendix:

Asymp	Asympomatic state (starting position)
Dead Age	Dead due to age dependent probability of dying
Dead Fr	Dead following a fracture event
HF	Hip fracture state
OF	Other fracture state
OffHF	Treatment offset state after hip fracture
	(Number gives the year of offset)
OffVF	Treatment offset state after vertebral fracture
	(Number gives the year of offset)
P-HF	Post-hip fracture state (no treatment)
P-OF	Post-other fracture state (no treatment)
P-VF	Post-vertebral fracture state (no treatment)
P-2ndHF	Post-second hip fracture state (no treatment)
T-HF	State with treatment after hip fracture
	(Number gives the year of treatment duration)
T-VF	State with treatment after vertebral fracture
	(Number gives the year of treatment duration)
VF	Vertebral fracture state
2ndHF	Second hip fracture state

Fields highlighted in grey contain age-dependent values. Values at age 70 are shown in the transition matrices.

Table 21: Transition matrix for a 70-year old woman with 10-year risk of 20 % treated according to the S3-guideline

Startingposition	Asymp	OF	P-OF	VF	T-VF1	T-VF2	T-VF3	OffVF1	OffVF2	OffVF3	P-VF	HF	T-HF1	T-HF2	T-HF3	OffHF1	OffHF2	OffHF3	P-HF	2ndHF	P-2ndHF	Dead Fr	Dead A
Asymp	0.917	0.050		0.012								0.010											0.011
OF			0.950																			0.050	0
Post-OF		0.050	0.917	0.012								0.010										0.000	0.011
VF					0.900						0.000											0.100	0
TreatVF1				0.011		0.965						0.011										0.001	0.011
TreatVF2				0.011			0.965					0.011										0.001	0.011
TreatVF3				0.011				0.965				0.011										0.001	0.011
OffVF1				0.013					0.962			0.012										0.001	0.011
OffVF2				0.015						0.959		0.014										0.001	0.011
OffVF3				0.017							0.956	0.015										0.001	0.011
Post-VF				0.019							0.953	0.016										0.001	0.011
HF													0.800						0.000			0.200	0
TreatHF1														0.968						0.014		0.007	0.011
TreatHF2															0.968					0.014		0.007	0.011
TreatHF3																0.968				0.014		0.007	0.011
OffHF1																	0.966			0.016		0.008	0.011
OffHF2																		0.964		0.017		0.008	0.011
OffHF3																			0.962	0.019		0.008	0.011
Post-HF																			0.961	0.020		0.008	0.011
2ndHF																					0.750	0.250	0
Post 2ndHF																					0.800	0.200	0
Dead Fr																						1	
Dead Age																							1

Table 22: Transition matrix for a 70-year old woman with 10-year risk of 30 % treated according to the S3-guideline.

Startingposition	Asymp	OF	P-OF	VF	T-VF1	T-VF2	T-VF3	OffVF1	OffVF2	OffVF3	P-VF	HF	T-HF1	T-HF2	T-HF3	OffHF1	OffHF2	OffHF3	P-HF	2ndHF	P-2nd HF	Dead Fl	Dead A
Asymp	0.874	0.080		0.019								0.016											0.011
OF			0.950																			0.050	0
Post-OF		0.080	0.874	0.019								0.016										0.000	0.011
VF					0.900						0.000											0.100	0
TreatVF1				0.015		0.959						0.014										0.001	0.011
TreatVF2				0.015			0.959					0.014										0.001	0.011
TreatVF3				0.015				0.959				0.014										0.001	0.011
OffVF1				0.018					0.955			0.016										0.001	0.011
OffVF2				0.020						0.951		0.017										0.001	0.011
OffVF3				0.023							0.947	0.019										0.001	0.011
Post-VF				0.025							0.943	0.020										0.001	0.011
HF													0.800						0.000			0.200	0
TreatHF1														0.968						0.014		0.007	0.011
TreatHF2															0.968					0.014		0.007	0.011
TreatHF3																0.968				0.014		0.007	0.011
OffHF1																	0.966			0.016		0.008	0.011
OffHF2																		0.964		0.017		0.008	0.011
OffHF3																			0.962	0.019		0.008	0.011
Post-HF																			0.961	0.020		0.008	0.011
2ndHF																					0.750	0.250	0
Post 2nd HF																					0.800	0.200	0
Dead Fr																						1	
Dead Age																							1

Table 23: Treatment effect applied during the first six years of the model (10-year fracture risk of 30 % treated S3, and 10-year fracture risk of 30 % not treated according to S3 guideline, but with initial treatment).

Effect of treatment prior to fracture (secondary prevention)	T1	T2	T3	Off1	Off2	Off3
on other fractures	0.800	0.800	0.800	0.850	0.900	0.950
on vertebral fractures	0.600	0.600	0.600	0.700	0.800	0.900
on hip fractures	0.700	0.700	0.700	0.775	0.850	0.925
on mortality	0.900	0.900	0.900	0.925	0.950	0.975

Table 24: Transition matrix for a 70-year old woman with 10-year risk of 20 %, not treated according to the S3-guideline (for both the initial treatment [but no treatment effect due to to high T-score] and no initial treatment subgroup).

Startingposition	Asymp	OF	P-OF	VF	T-VF1	T-VF2	T-VF3	OffVF1	OffVF2	OffVF3	P-VF	HF	T-HF1	T-HF2	T-HF3	OffHF1	OffHF2	OffHF3	P-HF	2ndHF	P-2ndHF	Dead Fr	Dead Age
Asymp	0.917	0.050		0.012								0.010											0.011
OF			0.950																			0.050	0
Post-OF		0.050	0.917	0.012								0.010										0.000	0.011
VF					0.090						0.810											0.100	0
TreatVF1				0.011		0.965						0.011										0.001	0.011
TreatVF2				0.011			0.965					0.011										0.001	0.011
TreatVF3				0.011				0.965				0.011										0.001	0.011
OffVF1				0.013					0.962			0.012										0.001	0.011
OffVF2				0.015						0.959		0.014										0.001	0.011
OffVF3				0.017							0.956	0.015										0.001	0.011
Post-VF				0.019							0.953	0.016										0.001	0.011
HF													0.080						0.720			0.200	0
TreatHF1														0.968						0.014		0.007	0.011
TreatHF2															0.968					0.014		0.007	0.011
TreatHF3																0.968				0.014		0.007	0.011
OffHF1																	0.966			0.016		0.008	0.011
OffHF2																		0.964		0.017		0.008	0.011
OffHF3																			0.962	0.019		0.008	0.011
Post-HF																			0.961	0.020		0.008	0.011
2ndHF																					0.750	0.250	0
Post 2ndHF																					0.800	0.200	0
Dead Fr																						1	
Dead Age																							1

Table 25: Transition matrix for a 70-year old woman with 10-year risk of 30 %, not treated according to the S3-guideline (for both the initial treatment [see table 23] and no initial treatment subgroup).

Startingposition	Asymp	OF	P-OF	VF	T-VF1	T-VF2	T-VF3	OffVF1	OffVF2	OffVF3	P-VF	HF	T-HF1	T-HF2	T-HF3	OffHF1	OffHF2	OffHF3	P-HF	2ndHF	P-2 nd HF	Dead Fr	Dead A
Asymp	0.874	0.080		0.019								0.016											0.011
OF			0.950																			0.050	0
Post-OF		0.080	0.874	0.019								0.016										0.000	0.011
VF					0.090						0.810											0.100	0
TreatVF1				0.015		0.959						0.014										0.001	0.011
TreatVF2				0.015			0.959					0.014										0.001	0.011
TreatVF3				0.015				0.959				0.014										0.001	0.011
OffVF1				0.018					0.955			0.016										0.001	0.011
OffVF2				0.020						0.951		0.017										0.001	0.011
OffVF3				0.023							0.947	0.019										0.001	0.011
Post-VF				0.025							0.943	0.020										0.001	0.011
HF													0.080						0.720			0.200	0
TreatHF1														0.968						0.014		0.007	0.011
TreatHF2															0.968					0.014		0.007	0.011
TreatHF3																0.968				0.014		0.007	0.011
OffHF1																	0.966			0.016		0.008	0.011
OffHF2																		0.964		0.017		0.008	0.011
OffHF3																			0.962	0.019		0.008	0.011
Post-HF																			0.961	0.020		0.008	0.011
2ndHF																					0.750	0.250	0
Post 2nd HF																					0.800	0.200	0
Dead Fr																						1	
Dead Age																							1

Table 26: Distribution of the S3-guideline treated portion of the cohort with a 10-year fracture risk of 20 % over 30 cycles (for 50 % implementation).

State at the end of cycle	Asymp	OF	P-OF	VF	T-VF1	T-VF2	T-VF3	OffVF1	OffVF2	OffVF3	P-VF	HF	T-HF1	T-HF2	T-HF3	OffHF1	OffHF2	OffHF3	P-HF	2ndHF	P-2ndHF	Dead FI	Dead A
0	3750																						
1	3439	188		45								37											42
2	3149	172	178	41	41							34	30									21	85
3	2879	166	326	40	37	39						33	27	29								41	132
4	2627	160	456	39	36	36	37					33	27	26	27					1		61	183
5	2393	154	567	38	35	35	34	36				32	26	26	25	26				1	1	81	240
6	2174	148	662	37	34	34	33	33	34			31	25	25	24	24	25			1	2	101	302
7	1970	142	740	36	33	33	32	32	31	32		30	25	24	24	23	23	24		2	2	121	370
8	1780	136	804	35	33	32	31	31	30	29	30	29	24	23	23	22	22	21	22	2	3	141	446
9	1601	129	852	34	32	31	30	30	29	28	56	28	23	23	22	21	21	20	41	3	4	162	530
10	1435	123	886	33	31	30	29	28	28	27	78	27	23	22	21	20	20	19	56	3	5	184	622
11	1279	116	906	32	30	29	28	27	26	26	98	26	22	21	20	19	19	18	70	3	6	206	723
12	1133	109	913	30	28	28	27	26	25	25	113	25	21	20	19	18	18	17	80	3	7	229	835
13	997	102	907	29	27	26	25	25	24	23	126	24	20	19	18	17	17	16	87	3	8	252	956
14	870	95	889	27	26	25	24	23	23	22	135	23	19	18	17	16	16	15	91	3	9	277	1088
15	752	88	859	26	24	24	23	22	21	20	140	21	18	17	16	15	14	14	92	3	10	302	1229
16	643	81	818	24	23	22	21	20	20	19	142	20	17	16	15	14	13	12	90	3	10	327	1379
17	544	73	768	22	21	20	20	19	18	17	141	18	16	14	13	12	12	11	86	3	11	353	1536
18	454	66	710	20	20	19	18	17	16	16	136	17	15	13	12	11	10	10	79	3	11	378	1699
19	373	58	646	18	18	17	16	15	15	14	129	15	13	12	11	10	9	8	71	3	11	404	1864
20	301	51	578	16	16	15	14	14	13	12	119	13	12	10	9	8	8	7	61	2	11	428	2030
21	239	44	506	14	14	13	13	12	11	11	107	12	11	9	8	7	6	6	51	2	10	451	2192
22	185	37	434	12	13	12	11	10	10	9	94	10	9	8	7	6	5	5	40	2	10	473	2350
23	140	31	363	10	11	10	9	9	8	8	80	8	8	7	5	5	4	4	31	1	9	493	2498
24	103	25	296	8	9	8	8	7	7	6	66	7	7	5	4	4	3	3	22	1	8	510	2633
25	74	20	236	7	7	7	6	6	5	5	53	6	6	4	3	3	2	2	15	1	8	525	2750
26	52	16	185	5	6	5	5	5	4	4	41	4	4	3	3	2	2	1	10	1	7	537	2849
27	35	12	141	4	5	4	4	4	3	3	31	3	3	3	2	2	1	1	6		6	547	2930
28	23	9	105	3	4	3	3	3	2	2	23	3	3	2	1	1	1	1	4		5	554	2995
29	15	6	76	2	3	2	2	2	2	2	17	2	2	1	1	1	1		2		4	560	3046
30	9	5	54	2	2	2	2	1	1	1	11	1	1	1	1				1		4	564	3086
Totals		2561		689								574								53			

Table 27: Distribution of the S3-guideline treated portion of the cohort with a 10-year fracture risk of 30 % over 30 cycles (for 50 % implementation).

State at the end of cycle	Asymp	OF	P-OF	VF	T-VF1	T-VF2	T-VF3	OffVF1	OffVF2	OffVF3	P-VF	HF	T-HF1	T-HF2	T-HF3	OffHF1	OffHF2	OffHF3	P-HF	2ndHF	P-2ndHF	Dead Fı	Dead A
0	1250																						
1	1128	80		14								14											14
2	1016	72	76	13	13							13	11									7	28
3	914	70	138	13	12	12						12	10	11								14	43
4	814	72	189	14	11	11	12					13	10	10	11							21	60
5	718	72	235	16	13	11	11	11				14	11	10	10	10						29	79
6	627	72	274	17	14	12	10	10	11			15	11	10	9	9	10			1	1	38	99
7	541	72	305	18	15	13	12	10	10	10		15	12	11	10	9	9	9		1	1	47	121
8	465	68	331	17	16	14	13	11	9	9	9	15	12	11	10	9	8	8	9	1	1	57	145
9	399	64	348	17	16	15	14	12	10	9	17	14	12	11	10	10	9	8	16	1	2	67	172
10	340	60	357	16	15	15	14	13	11	10	23	13	11	11	11	10	9	8	22	1	2	77	202
11	288	56	360	15	14	14	14	13	12	10	30	13	11	10	10	10	9	8	27	1	3	88	234
12	243	52	356	14	14	13	13	13	12	11	37	12	10	10	10	9	9	8	32	1	3	98	269
13	203	48	347	14	13	13	12	12	11	11	43	11	10	9	9	9	8	8	36	2	4	109	308
14	169	44	334	13	12	12	11	11	11	10	49	11	9	9	8	8	8	7	39	2	4	120	350
15	139	40	316	12	12	11	11	10	10	10	52	10	9	8	8	7	7	7	41	2	4	132	395
16	113	36	295	11	11	10	10	9	9	9	54	9	8	7	7	7	6	6	40	2	5	143	442
17	90	33	271	10	10	9	9	9	8	8	54	8	7	7	6	6	6	5	39	1	5	155	492
18	71	29	245	9	9	9	8	8	8	7	53	8	7	6	6	5	5	5	36	1	5	167	543
19	56	25	219	8	8	8	7	7	7	6	51	7	6	6	5	5	4	4	33	1	5	178	595
20	43	22	191	7	7	7	7	6	6	6	47	6	6	5	4	4	4	3	28	1	5	189	646
21	32	19	164	6	7	6	6	5	5	5	42	5	5	4	4	3	3	3	23	1	5	200	697
22	23	16	138	5	6	5	5	5	4	4	37	4	4	4	3	3	2	2	19	1	5	210	746
23	17	13	113	4	5	4	4	4	4	3	31	4	4	3	2	2	2	2	14	1	4	219	792
24	11	10	91	4	4	4	3	3	3	3	26	3	3	2	2	2	1	1	10	1	4	226	833
25	8	8	71	3	3	3	3	2	2	2	21	2	2	2	2	1	1	1	7		3	233	868
26	5	6	54	2	3	2	2	2	2	2	16	2	2	1	1	1	1	1	5		3	238	898
27	3	5	41	2	2	2	2	2	1	1	12	1	2	1	1	1	1		3		3	242	923
28	2	4	30	1	2	1	1	1	1	1	9	1	1	1	1				2		2	246	942
29	1	3	21	1	1	1	1	1	1	1	6	1	1	1					1		2	248	957
30	1	2	15	1	1	1	1	1	1		4	1	1						1		2	250	969
Totals		1171		298								259								23			

Table 28: Distribution of the not S3-guideline treated portion of the cohort with a 10-year fracture risk of 20 %, not receiving initial bisphosphonate treatment, over 30 cycles (for 50 % implementation).

State at the end of cycle	Asymp	OF	P-OF	VF	T-VF1	T-VF2	T-VF3	OffVF1	OffVF2	OffVF3	P-VF	HF	T-HF1	T-HF2	T-HF3	OffHF1	OffHF2	OffHF3	P-HF	2ndHF	P-2ndHF	Dead FI	Dead A
0	3375																						
1	3095	169		41								33											38
2	2834	155	160	37	4						33	31	3						24			19	76
3	2591	150	294	37	3	4					61	30	2	3					45	1		37	118
4	2365	144	410	36	3	3	3				88	30	2	2	2				65	1		55	165
5	2154	139	511	35	3	3	3	3			112	29	2	2	2	2			83	1	1	73	216
6	1957	133	596	34	3	3	3	3	3		134	28	2	2	2	2	2		99	2	2	91	272
7	1773	128	666	33	3	3	3	3	3	3	154	28	2	2	2	2	2	2	114	2	3	110	333
8	1602	122	723	32	3	3	3	3	3	3	174	27	2	2	2	2	2	2	129	2	4	129	401
9	1441	116	767	31	3	3	3	3	3	3	191	26	2	2	2	2	2	2	141	3	5	149	476
10	1291	110	797	30	3	3	3	3	3	2	206	25	2	2	2	2	2	2	151	3	6	169	559
11	1151	104	815	29	3	3	3	3	2	2	217	24	2	2	2	2	2	2	158	3	7	189	650
12	1019	98	822	28	3	3	2	2	2	2	225	23	2	2	2	2	2	2	162	3	8	211	750
13	897	92	816	27	3	2	2	2	2	2	230	22	2	2	2	2	2	1	163	3	9	233	859
14	783	86	800	25	2	2	2	2	2	2	231	21	2	2	2	1	1	1	161	3	10	255	977
15	677	79	773	24	2	2	2	2	2	2	229	20	2	2	1	1	1	1	157	3	10	279	1104
16	579	72	736	22	2	2	2	2	2	2	224	18	2	1	1	1	1	1	149	3	11	302	1238
17	490	66	692	20	2	2	2	2	2	2	215	17	1	1	1	1	1	1	139	3	11	326	1379
18	408	59	639	18	2	2	2	2	2	1	203	15	1	1	1	1	1	1	126	3	11	350	1525
19	336	52	582	17	2	2	1	1	1	1	188	14	1	1	1	1	1	1	112	3	11	373	1673
20	271	46	520	15	1	1	1	1	1	1	171	12	1	1	1	1	1	1	97	2	11	396	1821
21	215	40	455	13	1	1	1	1	1	1	153	11	1	1	1	1	1	1	82	2	10	417	1967
22	166	34	390	11	1	1	1	1	1	1	133	9	1	1	1	1			66	2	10	437	2107
23	126	28	326	9	1	1	1	1	1	1	112	8	1	1					52	1	9	455	2240
24	92	23	267	8	1	1	1	1	1	1	93	6	1						39	1	8	471	2360
25	66	18	213	6	1	1	1	1			75	5	1						29	1	8	485	2465
26	46	14	166	5	1	1					59	4							21	1	7	496	2553
27	32	11	127	4							45	3							15		6	505	2626
28	21	8	94	3							33	2							10		5	512	2684
29	14	6	68	2							24	2							7		4	517	2729
30	9	4	48	1							17	1							4		3	521	2764
Totals		2305		633								524								55			

Table 29: Distribution of the not S3-guideline treated portion of the cohort with a 10-year fracture risk of 20 %, receiving initial bisphosphonate treatment (over-treatment), over 30 cycles (for 50 % implementation).

State at the end of cycle	Asymp	OF	P-OF	VF	T-VF1	T-VF2	T-VF3	OffVF1	OffVF2	OffVF3	P-VF	HF	T-HF1	T-HF2	T-HF3	OffHF1	OffHF2	OffHF3	P-HF	2ndHF	P-2ndHF	Dead Fi	Dead A
0	375																						
1	344	19		5								4											4
2	315	17	18	4							4	3							3			2	8
3	288	17	33	4							7	3							5			4	13
4	263	16	46	4							10	3							7			6	18
5	239	15	57	4							12	3							9			8	24
6	217	15	66	4							15	3							11			10	30
7	197	14	74	4							17	3							13			12	37
8	178	14	80	4							19	3							14			14	45
9	160	13	85	3							21	3							16		1	17	53
10	143	12	89	3							23	3							17		1	19	62
11	128	12	91	3							24	3							18		1	21	72
12	113	11	91	3							25	3							18		1	23	83
13	100	10	91	3							26	2							18		1	26	95
14	87	10	89	3							26	2							18		1	28	109
15	75	9	86	3							25	2							17		1	31	123
16	64	8	82	2							25	2							17		1	34	138
17	54	7	77	2							24	2							15		1	36	153
18	45	7	71	2							23	2							14		1	39	169
19	37	6	65	2							21	2							12		1	41	186
20	30	5	58	2							19	1							11		1	44	202
21	24	4	51	1							17	1							9		1	46	219
22	18	4	43	1							15	1							7		1	49	234
23	14	3	36	1							12	1							6		1	51	249
24	10	3	30	1							10	1							4		1	52	262
25	7	2	24	1							8	1							3		1	54	274
26	5	2	18	1							7								2		1	55	284
27	4	1	14								5								2		1	56	292
28	2	1	10								4								1		1	57	298
29	2	1	8								3								1			57	303
30	1		5								2											58	307
Totals		256		70								58								6			

Table 30: Distribution of the not S3-guideline treated portion of the cohort with a 10-year fracture risk of 30 %, not receiving initial bisphosphonate treatment (under-treatment), over 30 cycles (for 50 % implementation).

State at the end of cycle	Asymp	OF	P-OF	VF	T-VF1	T-VF2	T-VF3	OffVF1	OffVF2	OffVF3	P-VF	HF	T-HF1	T-HF2	T-HF3	OffHF1	OffHF2	OffHF3	P-HF	2ndHF	P-2ndHF	Dead FI	Dead A
0	1125																						
1	983	90		21								18											13
2	858	79	86	19	2						17	16	1						13			10	25
3	747	75	149	18	2	2					31	15	1	1					24			19	38
4	650	72	201	18	2	2	2				44	15	1	1	1				34	1		28	53
5	564	68	243	17	2	2	2	2			56	15	1	1	1	1			43	1	1	38	69
6	488	65	275	17	2	2	1	1	2		66	14	1	1	1	1	1		51	1	1	47	87
7	421	61	299	16	2	1	1	1	1	1	75	14	1	1	1	1	1	1	58	1	1	56	107
8	362	58	315	16	1	1	1	1	1	1	84	13	1	1	1	1	1	1	66	1	2	65	128
9	310	54	324	15	1	1	1	1	1	1	92	13	1	1	1	1	1	1	71	1	3	75	152
10	265	51	328	15	1	1	1	1	1	1	98	12	1	1	1	1	1	1	76	2	3	85	178
11	225	47	327	14	1	1	1	1	1	1	102	12	1	1	1	1	1	1	79	2	4	95	207
12	189	44	320	13	1	1	1	1	1	1	105	11	1	1	1	1	1	1	81	2	4	105	238
13	158	41	310	12	1	1	1	1	1	1	107	10	1	1	1	1	1	1	81	2	5	115	273
14	131	37	296	12	1	1	1	1	1	1	106	10	1	1	1	1	1	1	80	2	5	126	310
15	108	34	279	11	1	1	1	1	1	1	104	9	1	1	1	1	1	1	77	2	5	137	349
16	88	31	259	10	1	1	1	1	1	1	101	8	1	1	1	1	1	1	73	2	5	148	391
17	70	28	237	9	1	1	1	1	1	1	96	8	1	1	1	1	1		67	2	6	159	435
18	56	25	214	8	1	1	1	1	1	1	90	7	1	1	1				61	1	6	170	480
19	43	22	190	7	1	1	1	1	1	1	83	6	1						54	1	5	181	525
20	33	19	166	7	1	1	1	1	1	1	75	5							46	1	5	192	570
21	25	16	142	6	1	1	1				66	5							39	1	5	202	615
22	18	13	119	5	1						57	4							31	1	5	211	657
23	13	11	97	4							48	3							24	1	4	219	697
24	9	9	78	3							39	3							18	1	4	226	732
25	6	7	61	3							31	2							13		4	232	763
26	4	5	47	2							24	2							9		3	237	789
27	3	4	35	2							18	1							6		3	241	810
28	2	3	26	1							14	1							4		2	244	827
29	1	2	18	1							10	1							3		2	247	840
30	1	2	13	1							7	1							2		2	248	850
Totals		1072		303								253								27			

Table 31: Distribution of the not S3-guideline treated portion of the cohort with a 10-year fracture risk of 30 %, receiving initial bisphosphonate treatment, over 30 cycles (for 50 % implementation).

State at the end of cycle	Asymp	OF	P-OF	VF	T-VF1	T-VF2	T-VF3	OffVF1	OffVF2	OffVF3	P-VF	HF	T-HF1	T-HF2	T-HF3	OffHF1	OffHF2	OffHF3	P-HF	2ndHF	P-2ndHF	Dead FI	Dead A
0	125																						
1	113	8		1								1											1
2	102	7	8	1							1	1							1			1	3
3	91	7	14	1							2	1							2			1	4
4	81	7	19	1							3	1							3			2	6
5	72	7	24	2							4	1							4			3	8
6	63	7	27	2							5	1							4			4	10
7	54	7	31	2							6	2							5			5	12
8	47	7	33	2							7	1							6			6	15
9	40	6	35	2							8	1							7			7	17
10	34	6	36	2							9	1							7			8	20
11	29	6	36	2							10	1							8			9	23
12	24	5	36	1							10	1							8			10	27
13	20	5	35	1							10	1							8			11	31
14	17	4	33	1							11	1							8			12	35
15	14	4	32	1							11	1							8		1	14	39
16	11	4	29	1							10	1							8		1	15	44
17	9	3	27	1							10	1							7		1	16	49
18	7	3	25	1							9	1							7		1	17	54
19	6	3	22	1							9	1							6		1	18	59
20	4	2	19	1							8	1							5		1	19	64
21	3	2	16	1							7	1							4		1	21	69
22	2	2	14	1							6								3		1	22	74
23	2	1	11								5								3			22	79
24	1	1	9								4								2			23	83
25	1	1	7								3								1			24	86
26	1	1	5								3								1			24	89
27			4								2								1			25	92
28			3								1											25	94
29			2								1											25	95
30			1								1											26	96
Totals		117		31								26								3			

Table 32: Cost occurring per cycle (discounted) in € 1000 by health state for S3-guideline treated group with a 10-year fracture risk of 20 %.

State at the end of cycle	Asymp	OF	P-OF	VF	T-VF1	T-VF2	T-VF3	OffVF1	OffVF2	OffVF3	P-VF	HF	T-HF1	T-HF2	T-HF3	OffHF1	OffHF2	OffHF3	P-HF	2ndHF	P-2ndHF	Dead Fr	Dead A
decision tree	255																						
0	567																						
1	1009	625		236								601											
2	756	556		210	12							535	8										
3	671	523		199	10	9						510	8	7						6			
4		489		188	10	8	8					483	7	6	6					12			
5		456		178	9	8	8					457	7	6	6					16			
6		426		168	9	7	7					432	6	5	5					21			
7		396		158	8	7	7					408	6	5	5					25			
8		367		149	8	6	6					385	6	5	5					29			
9		340		141	7	6	6					363	5	4	4					32			
10		313		132	7	6	6					340	5	4	4					35			
11		288		123	6	5	5					318	5	4	4					37			
12		263		114	6	5	5					295	4	4	3					38			
13		239		106	6	5	4					273	4	3	3					38			
14		216		97	5	4	4					251	4	3	3					37			
15		194		88	5	4	4					228	4	3	3					36			
16		172		80	4	3	3					206	3	2	2					34			
17		152		71	4	3	3					185	3	2	2					32			
18		132		63	3	3	3					163	3	2	2					29			
19		114		55	3	2	2					143	2	2	2					25			
20		97		48	3	2	2					123	2	1	1					22			
21		81		40	2	2	2					105	2	1	1					18			
22		67		34	2	2	1					87	1	1	1					15			
23		54		27	2	1	1					71	1	1	1					12			
24		42		22	1	1	1					57	1	1	1					9			
25		33		17	1	1	1					44	1	1						7			
26		25		13	1	1	1					34	1							5			
27		18		10	1							25								3			
28		13		7								18								2			
29		9		5								13								1			
30		6		3								9								1			
Totals	3259	6706		2783	136	102	91					7163	101	74	64					578			

Overall total 21058

Table 33: Cost occurring per cycle (discounted) in € 1000 by health state for S3-guideline treated group with a 10-year fracture risk of 30 %.

State at the end of cycle	Asymp	OF	P-OF	VF	T-VF1	T-VF2	T-VF3	OffVF1	OffVF2	OffVF3	P-VF	HF	T-HF1	T-HF2	T-HF3	OffHF1	OffHF2	OffHF3	P-HF	2ndHF	P-2ndHF	Dead Fr	Dead A
decision tree	85																						
0	189																						
1	331	267		75								227											
2	244	234		65	4							199	3										
3	213	220		62	3	3						190	3	3						2			
4		218		69	3	3	3					198	3	2	2					4			
5		214		73	3	2	2					203	3	2	2					6			
6		208		77	4	3	2					206	3	2	2					8			
7		201		79	4	3	2					207	3	2	2					10			
8		183		73	4	3	3					192	3	2	2					12			
9		168		69	4	3	3					179	3	2	2					14			
10		153		64	3	3	3					167	3	2	2					15			
11		138		59	3	3	2					154	2	2	2					16			
12		125		54	3	2	2					142	2	2	2					17			
13		112		50	3	2	2					130	2	2	2					17			
14		100		46	2	2	2					119	2	1	1					17			
15		89		41	2	2	2					108	2	1	1					17			
16		78		37	2	2	2					97	2	1	1					16			
17		68		33	2	1	1					86	1	1	1					15			
18		58		29	2	1	1					75	1	1	1					13			
19		50		25	1	1	1					65	1	1	1					12			
20		42		22	1	1	1					56	1	1	1					10			
21		35		18	1	1	1					47	1	1	1					9			
22		28		15	1	1	1					39	1							7			
23		22		12	1	1	1					32	1							5			
24		18		10	1							25								4			
25		13		8								20								3			
26		10		6								15								2			
27		7		4								11								1			
28		5		3								8								1			
29		4		2								6								1			
30		3		2								4											
Totals	1062	3068		1181	58	43	38					3208	45	33	29					255			

Overall total 9021

Table 34: Cost occurring per cycle (discounted) in € 1000 by health state for not S3-guideline treated group with a 10-year fracture risk of 20 %, not receiving initial bisphosphonate treatment.

State at the end of cycle	Asymp	OF	P-OF	VF	T-VF1	T-VF2	T-VF3	OffVF1	OffVF2	OffVF3	P-VF	HF	T-HF1	T-HF2	T-HF3	OffHF1	OffHF2	OffHF3	P-HF	2ndHF	P-2ndHF	Dead Fı	Dead A
decision tree	121																						
0																							
1		562		212								541											
2		501		189	1							482	1										
3		470		181	1	1						461	1	1						8			
4		440		172	1	1	1					439	1	1	1					14			
5		411		163	1	1	1					417	1	1						20			
6		383		155	1	1	1					396	1							25			
7		356		146	1	1	1					374	1							29			
8		331		138	1	1	1					353	1							33			
9		306		130	1	1	1					333								35			
10		282		122	1	1	1					312								37			
11		259		114	1							291								38			
12		237		106	1							271								39			
13		215		98	1							250								39			
14		194		89								230								38			
15		174		82								209								36			
16		155		74								189								34			
17		137		66								169								31			
18		119		58								150								28			
19		103		51								131								25			
20		87		44								113								22			
21		73		37								96								18			
22		60		31								80								15			
23		48		25								65								12			
24		38		20								52								9			
25		29		16								41								7			
26		22		12								31								5			
27		16		9								23								3			
28		12		7								17								2			
29		8		5								12								1			
30		6		3								8								1			
Totals	121	6036		2552	12	9	8					6535	9	7	6					604			

Overall total 15900

Table 35: Cost occurring per cycle (discounted) in € 1000 by health state for not S3-guideline treated group with a 10-year fracture risk of 20 %, receiving initial bisphosphonate treatment (over-treatment).

State at the end of cycle	Asymp	OF	P-OF	VF	T-VF1	T-VF2	T-VF3	OffVF1	OffVF2	OffVF3	P-VF	HF	T-HF1	T-HF2	T-HF3	OffHF1	OffHF2	OffHF3	P-HF	2ndHF	P-2ndHF	Dead FI	Dead A
decision tree	13																						
0	57																						
1	101	62		24								60											
2	76	56		21								54											
3	67	52		20								51								1			
4		49		19								49								2			
5		46		18								46								2			
6		43		17								44								3			
7		40		16								42								3			
8		37		15								39								4			
9		34		14								37								4			
10		31		14								35								4			
11		29		13								32								4			
12		26		12								30								4			
13		24		11								28								4			
14		22		10								26								4			
15		19		9								23								4			
16		17		8								21								4			
17		15		7								19								3			
18		13		6								17								3			
19		11		6								15								3			
20		10		5								13								2			
21		8		4								11								2			
22		7		3								9								2			
23		5		3								7								1			
24		4		2								6								1			
25		3		2								5								1			
26		2		1								3								1			
27		2		1								3											
28		1		1								2											
29		1		1								1											
30		1										1											
Totals	314	671		284	1	1	1					726	1	1	1					67			

Overall total 2067

Table 36: Cost occurring per cycle (discounted) in € 1000 by health state for not S3-guideline treated group with a 10-year fracture risk of 30 %, not receiving initial bisphosphonate treatment (under-treatment).

State at the end of cycle	Asymp	OF	P-OF	VF	T-VF1	T-VF2	T-VF3	OffVF1	OffVF2	OffVF3	P-VF	HF	T-HF1	T-HF2	T-HF3	OffHF1	OffHF2	OffHF3	P-HF	2ndHF	P-2ndHF	Dead Fı	Dead A
decision tree	40																						
0																							
1		300		112								292											
2		254		95	1							247											
3		237		91								236								4			
4		219		86								223								8			
5		202		81								210								10			
6		186		76								197								13			
7		170		71								185								15			
8		156		67								173								17			
9		143		62								162								18			
10		130		58								150								19			
11		118		54								139								19			
12		106		50								128								20			
13		95		46								118								19			
14		85		42								107								19			
15		75		38								97								18			
16		66		34								87								17			
17		58		30								77								15			
18		50		26								68								14			
19		42		23								59								12			
20		35		20								50								10			
21		29		17								42								9			
22		24		14								35								7			
23		19		11								28								5			
24		15		9								23								4			
25		11		7								17								3			
26		9		5								13								2			
27		6		4								10								1			
28		4		3								7								1			
29		3		2								5								1			
30		2		1								3											
Totals	40	2850		1232	6	5	4					3192	4	3	3					301			

Overall total 7639

Table 37: Cost occurring per cycle (discounted) in € 1000 by health state for not S3-guideline treated group with a 10-year fracture risk of 30 %, receiving initial bisphosphonate treatment.

State at the end of cycle	Asymp	OF	P-OF	VF	T-VF1	T-VF2	T-VF3	OffVF1	OffVF2	OffVF3	P-VF	HF	T-HF1	T-HF2	T-HF3	OffHF1	OffHF2	OffHF3	P-HF	2ndHF	P-2ndHF	Dead Fi	Dead A
decision tree	4																						
0	19																						
1	33	27		7								23											
2	24	23		7								20											
3	21	22		6								19											
4		22		7								20											
5		21		7								20								1			
6		21		8								21								1			
7		20		8								21								1			
8		18		8								20								2			
9		17		7								18								2			
10		15		7								17								2			
11		14		6								16								2			
12		12		6								15								2			
13		11		5								13								2			
14		10		5								12								2			
15		9		4								11								2			
16		8		4								10								2			
17		7		3								9								2			
18		6		3								8								1			
19		5		3								7								1			
20		4		2								6								1			
21		3		2								5								1			
22		3		2								4								1			
23		2		1								3								1			
24		2		1								3											
25		1		1								2											
26		1		1								2											
27		1										1											
28		1										1											
29												1											
30																							
Totals	102	307		121	1							325								29			

Overall total 887

Table 38: QALYs (discounted) per cycle and health state for S3-guideline treated group with 10-year fracture risk of 20 %.

State at the end of cycle	Asymp	OF	P-OF	VF	T-VF1	T-VF2	T-VF3	OffVF1	OffVF2	OffVF3	P-VF	HF	T-HF1	T-HF2	T-HF3	OffHF1	OffHF2	OffHF3	P-HF	2ndHF	P-2ndHF	Dead Fi	Dead A
decision tree																							
0 (half cycle)	1369																						
1	2437	111		19								11											
2	2167	99	123	17	25							10	18										
3	1923	93	218	16	22	24						9	16	17									
4	1704	87	296	15	21	21	24					9	16	15	16								
5	1507	81	357	15	20	20	22	20				8	15	15	14	15							
6	1329	76	405	14	19	19	20	18	19			8	14	14	13	13	14				1		
7	1170	70	439	13	18	18	19	17	17	17		8	13	13	13	12	12	13			1		
8	1026	65	463	12	17	17	18	16	16	15	16	7	13	12	12	12	11	11	12	1	2		
9	896	60	477	11	16	16	17	15	15	14	28	7	12	11	11	11	11	10	21	1	2		
10	779	56	481	11	15	15	16	14	14	13	39	6	11	11	10	10	10	10	28	1	3		
11	674	51	478	10	14	14	15	13	13	12	47	6	10	10	10	9	9	9	33	1	3		
12	580	47	467	9	13	13	14	12	12	11	53	5	10	9	9	9	8	8	37	1	3		
13	495	42	451	9	12	12	13	11	11	10	57	5	9	9	8	8	8	7	39	1	4		
14	420	38	429	8	11	11	12	10	10	10	59	5	8	8	7	7	7	6	40	1	4		
15	352	34	402	7	10	10	11	9	9	9	59	4	8	7	7	6	6	6	39	1	4		
16	293	31	372	7	9	9	10	8	8	8	59	4	7	6	6	6	5	5	37	1	4		
17	240	27	339	6	9	8	9	7	7	7	56	3	6	6	5	5	5	4	34	1	4		
18	195	24	305	5	8	7	8	7	6	6	53	3	6	5	5	4	4	4	31	1	4		
19	155	20	269	5	7	6	7	6	6	5	49	3	5	4	4	4	3	3	27		4		
20	122	17	233	4	6	6	6	5	5	5	44	2	4	4	3	3	3	3	22		4		
21	94	14	199	3	5	5	5	4	4	4	38	2	4	3	3	3	2	2	18		4		
22	70	12	165	3	4	4	4	4	3	3	32	2	3	3	2	2	2	2	14		3		
23	52	10	134	2	4	3	3	3	3	3	27	1	3	2	2	2	1	1	10		3		
24	37	8	106	2	3	3	3	2	2	2	21	1	2	2	1	1	1	1	7		3		
25	26	6	82	1	2	2	2	2	2	2	17	1	2	1	1	1	1	1	5		2		
26	17	4	62	1	2	2	2	1	1	1	13	1	1	1	1	1	1		3		2		
27	12	3	46	1	1	1	1	1	1	1	9		1	1	1				2		2		
28	7	2	33	1	1	1	1	1	1	1	7		1	1					1		1		
29	5	2	24		1	1	1	1			5		1						1		1		
30	3	1	16		1						3										1		
Totals	20155	1192	7873	227	297	265	260	208	183	159	788	133	220	191	166	144	124	106	460	11	71		

Overall total 33233

Table 39: QALYs (discounted) per cycle and health state for S3-guideline treated group with 10-year fracture risk of 30 %.

State at the end of cycle	Asymp	OF	P-OF	VF	T-VF1	T-VF2	T-VF3	OffVF1	OffVF2	OffVF3	P-VF	HF	T-HF1	T-HF2	T-HF3	OffHF1	OffHF2	OffHF3	P-HF	2ndHF	P-2nd HF	Dead Fi	Dead A
decision tree																							
0 (half cycle)	456																						
1	799	47		6								4											
2	699	42	53	5	8							4	7										
3	611	39	92	5	7	7						4	6	7									
4	528	39	123	6	7	7	8					4	6	6	6								
5	452	38	148	6	7	6	7	6				4	6	6	5	6							
6	383	37	167	6	8	7	6	6	6			4	6	6	5	5	5						
7	321	36	181	6	8	7	7	5	5	5		4	6	6	5	5	5	5					
8	268	33	191	6	8	8	7	6	5	5	5	4	6	6	5	5	4	4	4		1		
9	223	30	195	6	8	8	8	6	5	4	9	3	6	6	5	5	4	4	8		1		
10	185	27	194	5	7	7	8	6	5	5	12	3	6	5	5	5	4	4	11		1		
11	152	25	190	5	7	7	7	6	6	5	14	3	5	5	5	5	4	4	13		1		
12	124	22	182	4	6	6	7	6	6	5	17	3	5	5	4	4	4	4	15		1		
13	101	20	173	4	6	6	6	5	5	5	19	2	4	4	4	4	4	4	16		2		
14	81	18	161	4	5	5	6	5	5	5	21	2	4	4	4	3	3	3	17		2		
15	65	16	148	3	5	5	5	4	4	4	22	2	4	3	3	3	3	3	17		2		
16	51	14	134	3	4	4	4	4	4	4	22	2	3	3	3	3	3	2	17		2		
17	40	12	120	3	4	4	4	3	3	3	22	2	3	3	3	2	2	2	16		2		
18	31	10	105	2	4	3	4	3	3	3	21	1	3	2	2	2	2	2	14		2		
19	23	9	91	2	3	3	3	3	3	2	19	1	2	2	2	2	2	1	12		2		
20	17	7	77	2	3	3	3	2	2	2	17	1	2	2	2	1	1	1	10		2		
21	13	6	64	1	2	2	2	2	2	2	15	1	2	1	1	1	1	1	8		2		
22	9	5	53	1	2	2	2	2	1	1	13	1	1	1	1	1	1	1	6		2		
23	6	4	42	1	2	1	2	1	1	1	10	1	1	1	1	1	1	1	5		1		
24	4	3	33	1	1	1	1	1	1	1	8		1	1	1	1			3		1		
25	3	2	25	1	1	1	1	1	1	1	6		1	1					2		1		
26	2	2	18		1	1	1	1	1	1	5		1						1		1		
27	1	1	13		1	1	1				4								1		1		
28	1	1	10								3								1		1		
29		1	7								2										1		
30			4								1												
Totals	5650	545	2993	96	127	111	108	86	74	64	287	60	99	86	74	64	55	47	198	5	31		

Overall total 10861

Table 40: QALYs (discounted) per cycle and health state for not S3-guideline treated group with 10-year fracture risk of 20 %, not receiving initial bisphosphonate treatment.

State at the end of cycle	Asymp	OF	P-OF	VF	T-VF1	T-VF2	T-VF3	OffVF1	OffVF2	OffVF3	P-VF	HF	T-HF1	T-HF2	T-HF3	OffHF1	OffHF2	OffHF3	P-HF	2ndHF	P-2ndHF	Dead Fi	Dead A
decision tree																							
0 (half cycle)	1232																						
1	2193	100		17								10											
2	1950	89	110	15	2						20	9	2						15				
3	1731	84	196	15	2	2					37	9	1	2					27				
4	1534	78	266	14	2	2	2				51	8	1	1	1				38				
5	1356	73	322	13	2	2	2	2			64	8	1	1	1	1			47		1		
6	1196	68	364	13	2	2	2	2	2		74	7	1	1	1	1	1		55		1		
7	1053	63	396	12	2	2	2	2	2	2	83	7	1	1	1	1	1	1	61	1	2		
8	923	59	417	11	2	2	2	1	1	1	91	7	1	1	1	1	1	1	67	1	2		
9	806	54	429	11	1	1	2	1	1	1	97	6	1	1	1	1	1	1	71	1	3		
10	701	50	433	10	1	1	1	1	1	1	101	6	1	1	1	1	1	1	74	1	3		
11	607	46	430	9	1	1	1	1	1	1	103	5	1	1	1	1	1	1	75	1	3		
12	522	42	421	9	1	1	1	1	1	1	104	5	1	1	1	1	1	1	75	1	4		
13	446	38	406	8	1	1	1	1	1	1	103	5	1	1	1	1	1	1	73	1	4		
14	378	35	386	7	1	1	1	1	1	1	101	4	1	1	1	1	1	1	70	1	4		
15	317	31	362	7	1	1	1	1	1	1	97	4	1	1	1	1	1	1	66	1	4		
16	263	28	335	6	1	1	1	1	1	1	92	4	1	1	1	1			61	1	4		
17	216	24	305	5	1	1	1	1	1	1	86	3	1	1					55	1	4		
18	175	21	274	5	1	1	1	1	1	1	79	3	1						49	1	4		
19	140	18	242	4	1	1	1	1	1		71	2							42		4		
20	110	15	210	4	1	1	1				63	2							36		4		
21	84	13	179	3							54	2							29		4		
22	63	11	149	3							46	1							23		3		
23	46	9	121	2							38	1							17		3		
24	33	7	96	2							30	1							13		3		
25	23	5	74	1							23	1							9		2		
26	16	4	56	1							18	1							6		2		
27	10	3	42	1							13								4		2		
28	7	2	30	1							10								3		1		
29	4	1	21								7								2		1		
30	3	1	14								5								1		1		
Totals	18140	1073	7086	208	27	24	24	19	17	15	1760	121	20	17	15	13	11	10	1167	11	75		

Overall total 29853

Table 41: QALYs (discounted) per cycle and health state for not S3-guideline treated group with 10-year fracture risk of 20 %, receiving initial bisphosphonate treatment (over-treatment).

State at the end of cycle	Asymp	OF	P-OF	VF	T-VF1	T-VF2	T-VF3	OffVF1	OffVF2	OffVF3	P-VF	HF	T-HF1	T-HF2	T-HF3	OffHF1	OffHF2	OffHF3	P-HF	2ndHF	P-2ndHF	Dead Fı	Dead A
decision tree																							
0 (half cycle)	137																						
1	244	11		2								1											
2	217	10	12	2							2	1							2				
3	192	9	22	2							4	1							3				
4	170	9	30	2							6	1							4				
5	151	8	36	1							7	1							5				
6	133	8	40	1							8	1							6				
7	117	7	44	1							9	1							7				
8	103	7	46	1							10	1							7				
9	90	6	48	1							11	1							8				
10	78	6	48	1							11	1							8				
11	67	5	48	1							11	1							8				
12	58	5	47	1							12	1							8				
13	50	4	45	1							11	1							8				
14	42	4	43	1							11								8				
15	35	3	40	1							11								7				
16	29	3	37	1							10								7				
17	24	3	34	1							10								6				
18	19	2	30	1							9								5				
19	16	2	27								8								5				
20	12	2	23								7								4				
21	9	1	20								6								3				
22	7	1	17								5								3				
23	5	1	13								4								2				
24	4	1	11								3								1				
25	3	1	8								3								1				
26	2		6								2								1				
27	1		5								1												
28	1		3								1												
29			2								1												
30			2								1												
Totals	2016	119	787	23	3	3	3	2	2	2	196	13	2	2	2	1	1	1	130	1	8		

Overall total 3317

Table 42: QALYs (discounted) per cycle and health state for not S3-guideline treated group with 10-year fracture risk of 30 %, not receiving initial bisphosphonate treatment (under-treatment).

State at the end of cycle	Asymp	OF	P-OF	VF	T-VF1	T-VF2	T-VF3	OffVF1	OffVF2	OffVF3	P-VF	HF	T-HF1	T-HF2	T-HF3	OffHF1	OffHF2	OffHF3	P-HF	2ndHF	P-2ndHF	Dead Fı	Dead A
decision tree																							
0 (half cycle)	411																						
1	697	53		9								5											
2	590	45	59	8	1						11	5	1						8				
3	499	42	100	7	1	1					19	4	1	1					14				
4	421	39	131	7	1	1	1				26	4	1	1	1				20				
5	355	36	153	7	1	1	1	1			32	4	1	1	1	1			24				
6	298	33	168	6	1	1	1	1	1		37	4	1	1	1	1	1		28		1		
7	250	30	177	6	1	1	1	1	1	1	40	3	1	1	1	1	1	1	31		1		
8	209	28	181	5	1	1	1	1	1	1	44	3	1	1	1	1	1	1	34		1		
9	174	25	182	5	1	1	1	1	1	1	47	3	1	1	1				36		1		
10	144	23	178	5	1	1	1	1	1	1	48	3							37		2		
11	118	21	172	4	1	1	1	1	1	1	49	3							38		2		
12	97	19	164	4	1	1	1	1	1		49	2							37		2		
13	79	17	154	4	1	1	1				48	2							36		2		
14	63	15	143	3			1				46	2							35		2		
15	51	13	131	3							44	2							33		2		
16	40	12	118	3							42	2							30		2		
17	31	10	105	2							38	1							27		2		
18	24	9	92	2							35	1							24		2		
19	18	8	79	2							31	1							20		2		
20	13	6	67	2							27	1							17		2		
21	10	5	56	1							23	1							14		2		
22	7	4	45	1							20	1							11		2		
23	5	3	36	1							16	1							8		1		
24	3	3	28	1							13								6		1		
25	2	2	21	1							10								4		1		
26	1	2	16								7								3		1		
27	1	1	11								5								2		1		
28	1	1	8								4								1		1		
29		1	6								3								1		1		
30			4								2												
Totals	4612	506	2783	101	13	12	11	9	8	7	815	59	10	9	7	6	6	5	581	6	37		

Overall total 9603

Table 43: QALYs (discounted) per cycle and health state for not S3-guideline treated group with 10-year fracture risk of 30 %, receiving initial bisphosphonate treatment.

State at the end of cycle	Asymp	OF	P-OF	VF	T-VF1	T-VF2	T-VF3	OffVF1	OffVF2	OffVF3	P-VF	HF	T-HF1	T-HF2	T-HF3	OffHF1	OffHF2	OffHF3	P-HF	2ndHF	P-2ndHF	Dead Fı	Dead A
decision tree																							
0 (half cycle)	46																						
1	80	5		1																			
2	70	4	5	1							1								1				
3	61	4	9	1							1								1				
4	53	4	12	1							2								2				
5	45	4	15	1							2								2				
6	38	4	17	1							3								2				
7	32	4	18	1							3								3				
8	27	3	19	1							4								3				
9	22	3	19	1							4								3				
10	18	3	19	1							4								4				
11	15	2	19								5								4				
12	12	2	18								5								4				
13	10	2	17								5								4				
14	8	2	16								5								4				
15	6	2	15								4								3				
16	5	1	13								4								3				
17	4	1	12								4								3				
18	3	1	11								4								3				
19	2	1	9								3								2				
20	2	1	8								3								2				
21	1	1	6								2								1				
22	1		5								2								1				
23	1		4								2								1				
24			3								1								1				
25			2								1												
26			2								1												
27			1								1												
28			1																				
29			1																				
30																							
Totals	565	55	299	10	1	1	1	1	1	1	77	6	1	1	1	1	1		57	1	4		

Overall total 1083

Declaration of Independent Work

I hereby declare that I wrote this thesis without any assistance and used only the aids listed. Any material taken from other works, either as a quote or idea, has been indicated under 'references’.

Bad Bevensen, 9.2.2016