Osteoporosis, (bone) fractures and fracture liaison services

OSTEOPOROSIS, (BONE) FRACTURES AND FRACTURE LIAISON SERVICES:

Health-related quality of life, clinical and economic outcomes

NANNAN LI

Doctoral thesis

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CONTENTS

LIST OF ABBREVIATIONS

ABL	Abaloparatide
ADT	Androgen deprivation therapy
ALN	Alendronate
AFF	Atypical femoral fracture
AOM	Anti-osteoporosis medication
ASBMR	American Society of Bone and Mineral Research
BCT	Biomechanical computed tomography
BMD	Bone mineral density
BMI	Body mass index
BPF	Best Practice Framework
CBS	Centraal Bureau voor de Statistiek
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CTF	Capture the Fracture
CUA	Cost-utility analysis
CV	Clinical vertebral fracture
DALYs	Disability adjusted life years
DCE	Discrete choice experiment
DOES	Dubbo Osteoporosis Epidemiology Study
DXA	Dual X-ray Absorptiometry
EQ-VAS	EuroQol visual analog scale
EQ-VT	EuroQoL Group's Valuation Technology
ES	Effect size
ESCEO	European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases
EULAR	European Alliance of Associations for Rheumatology
FFN	Fragility Fracture Network
FLS	Fracture liaison service
GIOP	Glucocorticoid-induced osteoporosis
HCP	Health care professional
HRQoL	Health-related quality of life
HSUV	Health state utility value
ICC	Intra-class correlation coefficient
ICD-10	International Statistical Classification of Diseases and Related Health Problems 10th Revision

ICER	Incremental cost effectiveness ratio
ICUR	Incremental cost-utility ratio
ICUROS	International Costs and Utilities Related to Osteoporotic fractures Study
IOF	International Osteoporosis Foundation
ITT	Intention-to- treat
MAUI	Multi-attribute utility instrument
MCS	Mental Component Score
MI	Multiple imputation
MOF	Major osteoporotic fracture
MPR	Medication Possession Ratio
MTF	Minimal trauma fracture
NHIA	National health insurance administration
NHNV	Non-hip non-vertebral fracture
NHS EED	National Health Service Economic Evaluation Database
NNT	Number needed to treat
NOGG	National Osteoporosis Guideline Group
NSFC	National Natural Science Foundation of China
ONJ	Osteonecrosis of the jaw
PCP	Primary care physician
PCS	Physical Component Score
PDC	Proportion of Days Covered
PICO	Population, Intervention, Comparator, Outcome
PMO	Postmenopausal osteoporosis
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PTH	Parathyroid hormone
PVF	Prevalent vertebral fracture
QALYs	Quality-adjusted life years
QoL	Quality of life
SCOPE	Scorecard for Osteoporosis in Europe
SERMs	Selective estrogen receptor modulators
SRM	Standardized response mean
TPTD	Teriparatide
TTO	Time trade-off
VFA	Vertebral fracture assessment
VF&O	Dutch Osteoporosis Nurses Association
WHO	World Health Organization
ZiN	Zorginstituut Nederland

CHAPTER 1

General Introduction

1 THE EPIDEMIOLOGY OF OSTEOPOROSIS AND FRACTURES

Osteoporosis is a progressive systematic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue (porous bone), with a consequent increase in bone fragility and susceptibility to fracture [1]. In 1994, the World Health Organization (WHO) has defined osteoporosis as a bone mineral density (BMD) more than 2.5 standard deviations (SD) below the young normal mean (T-score ≤ -2.5) [2]. Despite the widespread acceptance of the BMD T-score, a definition based solely on BMD does not encompass all risk factors [3], and the predictive value of densitometric techniques also differs between sites and technologies. For these reasons, it is preferable to transform densitometric values into absolute risks [4]. Recently there has therefore been a move towards assessing an individual's absolute risk of osteoporotic fractures using risk calculators (algorithms); the majority of guidelines internationally use FRAX® as the measure of fracture risk over 10 years [5].

Osteoporosis is the most common bone (non-communicable) disease in humans, representing a major public health problem. It is more common in Caucasians, women, and older people [6]. Worldwide, due to the aging of the population and the changing lifestyle habits, the prevalence of osteoporosis has risen significantly. It has been estimated that more than 200 million people are suffering from osteoporosis, and that 1 in 3 women and 1 in 5 men over the age of 50 years will experience osteoporotic fractures in their lifetime according to statistics by the International Osteoporosis Foundation (IOF) [7]. As reported by the SCOPE (Scorecard for Osteoporosis in Europe) 2021 study [8], the prevalence of osteoporosis in the total Dutch population was estimated at 4.9%, slightly lower than the EU27+2 average of 5.6%. In patients aged 50 years and older, 20.8% of women and 6.3% of men were estimated to have osteoporosis in 2019.

Osteoporosis and its related fractures are associated with significant morbidity, reduction in health-related quality of life (HRQoL), increased subsequent fracture and mortality risk as well as considerable medical expenses. Worldwide, it was estimated that osteoporosis caused more than 8.9 million osteoporotic fractures annually in population aged 50 years and older, resulting in an osteoporosis fracture every 3 seconds [7,9]. In the Netherlands, the number of new fragility fractures was estimated at 99,600 in 2019 [8], corresponding to 273 fractures per day and 11 fractures per hour. The number of osteoporotic fractures is projected to be 136,821 in 2034, with the percentage increase of 37.4% over 15-year interval. Fractures often precede a cascade of declining mobility, physical activity, muscle

strength, and further causes impaired QoL. It was reported that hip fractures account for more disability adjusted life years (DALYs) than many other chronic non-communicable diseases such as cancer of the stomach, ovaries or cervix [9]. Both hip and vertebral fractures are also associated with serious disability and excess mortality in both sexes. Around 740,000 deaths per year are associated with hip fracture [9]. Women who have sustained a hip fracture have indeed a 10-20% higher mortality than would be expected for their age [10]. Besides, In women over 45 years, osteoporotic fractures also account for more hospital days than many other diseases, including diabetes, myocardial infarction and breast cancer [11]. Unsurprisingly, the economic cost of fracture is considerable. The SCOPE 2021 study reported that the total direct cost (consisting of direct cost of incident fractures, long-term disability costs, assessment and treatment costs) in the EU27+2 (excluding the value of quality-adjusted life-year lost) amounted to €56.9 billion in 2019 [8]. The cost of osteoporotic fractures in the Netherlands accounted for approximately 1.8% of healthcare spending (i.e., €1.4 billion out of €75.0 billion in 2019), which is significantly lower than the EU27+2 average of 3.5%.

Multiple factors are known to increase the risk of sustaining a fragility fracture, among them, a prior fracture is a well-documented major risk factor for a subsequent fracture. On average, the risk of future fracture is doubled in the presence of a prior fracture [12,13]. However, this risk is not constant over time, being highest immediately after the initial fracture and then decreasing over time but never going back to level pre-fracture [13]. Recently, the time elapsed since sustaining a prior fracture is recognized as an important factor influencing subsequent fracture risk, and the concept of "imminent fracture risk" defined as a markedly elevated risk of fracture within the next 12-24 months, has been emphasized [14]. A Dutch study [15] reported that the relative risk of subsequent fracture ranged from 5.3 within 1 year to 1.4 within 6-10 years after the first fracture in postmenopausal women older than 50 years, and this risk remained higher compared with the whole study population (postmenopausal women aged 50 to 80 years) during the follow-up period. These epidemiological data support the effort to initiate treatment strategies (interventions) for patients with osteoporosis and/or related fractures, and to reduce their risk of having subsequent fractures, mortality and impaired QoL.

1 CURRENT THERAPIES FOR OSTEOPOROSIS (FRACTURE PREVENTION) AND CARE GAPS

Advances in drug development for the treatment of osteoporosis over the last three decades have led to effective therapies for fracture prevention [16]. Pharmacological treatments for fracture prevention are typically classified as anabolic (bone forming) or anti-resorptive. Anti-resorptive drugs which modulate fracture risk by inhibiting bone resorption are the most commonly used therapies for fracture prevention, including five principal classes of agents: bisphosphonates, estrogens, selective estrogen receptor modulators (SERMs), calcitonin, and monoclonal antibodies such as denosumab [17]. Of these classes, until recently bisphosphonates (oral alendronate, risedronate, ibandronate, and intravenous pamidronate and zoledronate) are recommended as the first-line therapeutic option for the prevention of fracture in postmenopausal women and men aged 50 years and older.

Anabolic therapies represents another class for osteoporosis treatment, characterized by an increase bone formation by promoting osteoblast activity. Teriparatide as a recombinant human parathyroid hormone (PTH) analog is the first and most well-known anabolic agent approved by US Food and Drug Administration (FDA) in late 2002, and shortly followed by approval by European Medicines Agency (EMA) in 2003. Extensive clinical trials have demonstrated evidence of fracture reduction with the use of teriparatide. Abaloparatide achieved FDA approval in 2017 for the treatment of postmenopausal women with osteoporosis at high risk for fracture; however, it was initially rejected by EMA in 2018 based on concerns regarding the effectiveness at preventing non-vertebral fractures in postmenopausal women as well as the safety concern regarding increases in heart rate and palpitations [18], and eventually approved by EMA in 2022 for treatment of osteoporosis in postmenopausal women at increased risk of fracture [19]. Romosozumab, a humanised anti-sclerostin monoclonal antibody, is the latest anabolic therapy mostly reserved for patients with severe osteoporosis. It was initially rejected by the FDA before securing an approval for the treatment of osteoporosis in 2019 and later on in the same year the approval from EMA was gained, with continuous monitoring of its safety through the real-world data [3].

In recent years, the term ‘sequential treatment’ has been gaining importance in the management of patients with osteoporosis. However, the choice of which medication to prescribe and in what order has become more complicated. Several recent studies reported that the greatest gains in bone mass can be achieved with the initial use of an anabolic agent followed by an anti-resorptive drug whereas the initial use of a bisphosphonate may diminish the efficacy of subsequent anabolic

therapy [20]. The sequential therapy is still of great interest for future studies.

Despite the wide availability of these effective pharmacologic interventions for osteoporosis and bone fractures, a substantial proportion of patients with osteoporosis, at high risk of fractures or even with a recent fragility fracture, remain undiagnosed and/or untreated. This treatment gap is more pronounced in men than in women, and worsened in recent years [21]. The magnitude of the treatment gap is reported to be highly variable throughout Europe, ranging between 25% and 95% [22]. In the Netherlands, although the Dutch guidelines (2011, 2022) recommends in patients older than 50 years with a history of fracture to perform a dual X-ray Absorptiometry (DXA) to identify osteoporosis as well as vertebral fracture assessment (VFA) to identify subclinical vertebral fractures (VFs) [23,24]. However, DXA (with or without VFA) was performed in only 26% (out of 120,000) of such high risk patients according to Centraal Bureau voor de Statistiek (CBS) data in 2016 [25,26]. As reported by a retrospective study, the treatment gap in the Dutch population was estimated to vary from 60% to 72% [27], falling within the Eurpean range. There are many potential causes for the substantial treatment gap. The main reasons are phycician's and patient's awareness of the condition (as osteoporosis is a silent disease) and perception of benefit/risk balance, i.e. commonly the decision made by a patient to initiate treatment for osteoporosis or engage in healthy lifestyle behaviours depends on patient's understanding of his/her fracture risk, benefits and risks of taking action or not, and the barriers to implement an action plan [3]. The perception of individual risk that doctors communicate to them depends on patient's understanding of medical information (health literacy) [28]. If patients have poor health literacy and cannot recognize their vulnerability to fracture, they might not initiate the medication treatment.

In addition to poor initiation, medication adherence is also suboptimal. The WHO defined adherence in 2001 as "the degree to which the person's behaviour corresponds with the agreed recommendations from a health care provider [29]". In 2012, a collaboration of European research groups suggested the ABC taxonomy consisting of (a) initiation, (b) implementation and (c) discontinuation for describing and defining adherence to medications [30]. Poor adherence and persistence (defined as the length of time up to discontinuation) to osteoporotic medication remains a major problem increasing the treatment gap. Despite the fact that bisphosphonates are the first line of treatment for osteoporosis, about 20–30% of patients do not initiate a treatment after a prescription for oral bisphosphonates [31] even when there is no cost to the patient of the medication. In the Dutch population, 1-year persistence (no gap in refills for > 6 months) for all available oral osteoporosis medications was estimated at 43%; most stoppers did not restart

or switch during an additional 18-month follow-up [32]. In Dutch patients with a recent fracture aged 50 years and older, the persistence rate of alendronate was reported as 75%, 61%, and 45% after 1, 3, and 5 years, respectively [33].

In addition, there are other reasons which contribute to the large care gap for osteoporosis, including concerns regarding rare but serious side effects such as atypical femoral fractures and osteonecrosis of the jaw, which have been overemphasized and disseminated by the social media. Besides, compared to other chronic disease such as cancer, heart disease, and diabetes, there is apparent global shortfall in policies addressing bone health [3].

All the above evidence reveals the huge care gap in patients with osteoporosis, at high risk of fractures, or sustaining a recent fracture and supports the effort to develop interventions to improve fracture risk communication and medication adherence, and to improve secondary fracture prevention by introducing/ implementing post-fracture care program, such as fracture liaison service (FLS), for patients with a recent fracture. Recently, a considerable amount of data also highlights the importance of well-build risk communication from clinicians to patients using adequate support tools [34] (e.g., shared decision-making).

FRACTURE LIAISON SERVICE (FLS)

As patients with a recent fracture have a higher risk of subsequent fractures, various post-fracture care programs have been implemented to improve secondary fracture prevention and to close the care gap. The FLS as one of post-fracture care programs is nowadays widely advocated as the most appropriate and effective approach to cover all aspects of secondary fracture prevention, including patient identification, education, risk evaluation, treatment, and long-term monitoring. Worldwide, the first FLS was initiated by McLellan and colleagues in 1999, the success of their program for the evaluation and management of patients with osteoporotic fracture was reported in 2003 [35]. In 2012, the IOF started a global initiative called "Capture the Fracture®" [36] to facilitate the implementation of Post-Fracture Care (PFC) Coordination Program, such as FLS, for secondary fracture prevention. From the year 2012 onwards, the FLS initiatives have been gradually internationally endorsed by other scientific societies, including the American Society of Bone and Mineral Research ASBMR) in 2012 [37], the European Alliance of Associations for Rheumatology (EULAR) in 2017 [38], and the multidisciplinary Fragility Fracture Network (FFN) in 2018 [39].

A standard FLS is built upon four pillars [40], the first pillar consists of a bone leader, a coordinator, a multidisciplinary team and a business plan to run an FLS [37,38,41]. The bone leader, a specialist in metabolic bone diseases, plays a role of organizing a multidisciplinary team in consultation with the orthopaedic surgeons. A dedicated coordinator, often a well-educated nurse, acts as the link between the patient and the multidisciplinary team, the osteoporosis and falls prevention services, and the primary care physician (general practitioner GP) to ensure that all patients presenting with fragility fractures to the locality or institution receive fracture risk assessment and treatment where appropriate. The second pillar refers to the identification and invitation of all eligible patients with a recent fracture to the FLS. Commonly patients can be identified at the emergency department, at the orthogeriatric care unit, during hospitalization, at the plaster consultation, and at post-treatment stage after fracture healing [40]. Invitation can be sent through consultation, information letter, telephone call and e-mail. The third pillar consisted of orthogeriatric care, providing specialist geriatric care to patients with a recent hip fracture and to frail elderly with a recent major fracture. The fourth pillar refers to communication with the GP and long-term follow up of attended patients.

Until March 2023, 822 FLSs (registered in CTF) have been implemented in 54 countries worldwide. Compared to Europe and the US, the implementation and practice of FLS in Asia-Pacific region is still insufficient. In the Netherlands, the first FLS-related initiatives and outcomes were reported from Groningen in 2004 and from Maastricht in 2007 [42,43]. To optimize FLS initiatives and facilitate the communication between health care professionals, a formal national network (Dutch Osteoporosis Nurses Association VF&O) [44] was launched in 2008, and a nationwide quality assessment and the FLS five-step approach (case finding, risk evaluation, differential diagnosis, therapy, follow-up) has been proposed by van den Bergh et al. [45] in 2012 to strive for standardized FLS care in Dutch hospitals. With emphasizing the importance of initiating a FLS in hospitals by several Dutch scientific committees, there are 90 FLSs and 95 osteoporosis nurses registered in the database of VF&O as reported by a study published in 2015 [46].

With the increasing implementation of FLS worldwide, the Best Practice Framework (BPF) serves as the measurement tool to rationally evaluate the quality/performance (FLS) in their health care system in the context of globally-endorsed standards. FLS attendance as an important marker of FLS quality has been gradually recognized, however, the attendance rate was reported to be suboptimal and varies between FLSs, ranging from 20% to 86% [47], on average 25% attendance was estimated for FLSs in the Netherlands.

In recent years, extensive studies have conducted to investigate the outcomes of patients with a recent fracture managed through FLS programs; most papers focused on the impact of FLS on DXA testing and treatment initiation, only limited information was available on subsequent fractures and mortality. A previous review [48] including studies reporting the impact of FLS on subsequent fractures up to 2016 concluded that the observed reduction in subsequent fracture risk after the introduction of a FLS was flawed and should be evaluated in better-designed studies. Especially the follow-up duration and the comparability of groups with or without FLS care (selection bias (non-attenders in the FLS group were not accounted for) leads to prognostic dissimilarity between groups) were the main methodological issues.

ECONOMIC EVALUATIONS

Commonly clinical trials measure clinical outcomes to determine the efficacy of health care interventions. If financial resources are unlimited, the most effective option can be reimbursed in real-world care. However, given the tension between healthcare budget constraint and almost unlimited increase of healthcare needs/cost, the economic evaluation as a comparative analysis by comparing costs and benefits between health intervention and comparators therefore plays an important role to reveal whether the intervention represents good value for money. In other words, is the intervention cost effective compared to comparators? In addition to the introduction and diffusion of new technologies, there is an increased use of economic evidence in decisions about the reimbursement and pricing of health technologies. For market access, cost-effectiveness (value for money) is regarded as the 4th hurdle (in addition to efficacy, safety, quality), the initiative of using cost-effectiveness analysis in decision-making was first introduced by Australian Pharmaceutical Benefit Scheme, followed by Ontario (Canada), Nice (UK) and the rest of Europe. In the Netherlands, National Healthcare Institute (ZiN) appraises 3 criteria for reimbursement in basic healthcare package: therapeutic value, budget impact, and cost-effectiveness. ZiN provides advice for minister of Health, and the Minister then makes decision about reimbursement.

There are two main methods to conduct an economic evaluation: trial-based economic evaluation and model-based economic evaluation. A trial-based economic evaluation refers to an economic evaluation conducted alongside randomized controlled trials (RCTs) where all the costs and effects data are measured in the same subjects with high validity. Such method provides an early opportunity to produce reliable estimates of cost effectiveness at low marginal cost, and access to

individual patient data such as types and quantities of medications/services and length of hospital stays. However, RCTs do not always provide a sufficient basis for economic evaluations used to inform regulatory and reimbursement decisions given limitations such as truncated time horizons, lack of external validity, limited comparators (single trial might not compare against the 'best alternative' that is implemented in clinical care), restricted generalizability to different settings or countries, and the failure to incorporate all relevant evidence from other trials, meta-analyses, and observational studies [49]. In this circumstance, decision analytical modelling provides an alternative framework for economic evaluation, namely model-based economic evaluation.

Decision analytical modelling applies mathematical techniques to synthesize all available information regarding health care process to predict and compare the health outcome and cost consequences of different options, and to inform decision-making about resource allocation. A model-based economic evaluation allows systematic combination of evidence from variety of sources, extrapolation of effectiveness from preferably real-world evidence, comparison against the best alternative as used in clinical practice, and generalization results to other settings or patient groups. In the field of osteoporosis, a recently published guideline [50] for the conduct and reporting of economic evaluations by the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) and the US branch of the International Osteoporosis Foundation (IOF) also recommends a model-based economic evaluation using mathematical techniques to capture the long-term consequences of interventions in terms of costs and outcomes. However, the results of a decision analytical model are subject to the impact of variability, uncertainty, and heterogeneity. Sensitivity analysis and model validation are therefore important to make decision makers confident about the estimates of cost effectiveness [49].

Cost-effectiveness analysis (CEA) and cost-utility analysis (CUA) are the most common form of economic evaluation. CUA is often considered as a particular case of CEA which is even preferred as the same outcome (quality-adjusted life years QALYs) can be used for all diseases and all interventions, and therefore could be useful for decision-making. The results of CEA (CUA) express as incremental cost effectiveness ratio (ICER), which equals to the additional cost per extra unit of effectiveness from the comparator treatment (ICER = (CA-CB) / (EA-EB) = $\Delta C/\Delta E$). The lower the ICER, the more cost-effective the intervention. And the intervention can be adopted if the ICER is smaller than country-specific willingness-to-pay (WTP) threshold (i.e., the maximum amount of money that society is willing to pay for a gain in effectiveness). In the Netherlands, the cost-effectiveness threshold

value depends on disease severity, ranging from €20,000 to €80,000 per QALY gained [51].

To graphically display the results of economic evaluations, the cost-effectiveness plane is used to visually represent the differences in costs and effects between treatment options in two dimensions. Effects are usually plotted on the x-axis and costs on the y-axis. Commonly 'current practice' is plotted at the origin, therefore the x and y values represent incremental effectiveness and incremental costs versus current practice. More than two points can be represented on the plane, with the line connecting cost-effective alternatives being called the cost-effectiveness frontier. In addition, the cost-effectiveness acceptability curve (CEAC) as another intuitive graphical method is commonly used in a probabilistic sensitivity analysis (PSA) to summarize the impact of parameter uncertainty on cost-effectiveness estimations and further to help decision-makers understand the uncertainty when making a decision to approve or reject a new heath technology. The graph plots a range of WTP thresholds on the horizontal axis against the probability that the intervention will be cost-effective at that threshold on the vertical axis.

With regard to health state utility value (HSUV), which is a specific type of QoL assessment reflecting the strength of preference for a given health state. A specific application of HSUV is to calculate QALYs. HSUVs can be estimated in a variety of ways including direct and indirect methods. The most common direct utility elicitation techniques are standard gamble (SG) and time trade-off (TTO). However, these choice task based techniques are complicated and time-consuming. Consequently, the indirect utility elicitation instruments consisting of a generic muti-domain QoL questionnaire and corresponding utility algorithm or set of weights (tariffs) are increasingly applied to obtain HSUVs in recent years. The EuroQol 5-dimension (EQ-5D) and the Short Form 6-dimension (SF-6D) are the most dominant instruments, especially given the increasing availability of societal country-specific health utilities. The use of generic indirect utilities in CUA is supported by country-specific guidelines for economic evaluations, however, instruments differ in descriptive content and valuation method to derive the scoring algorithms, potentially leading to different estimates for the person's same "health state". This can further lead to different estimations of incremental cost-utility ratio (ICUR). Under this circumstance, healthcare decisions could potentially be compromised when researchers or decision-makers are not aware of differences in HSUVs obtained by different instruments. On that line, it is important to be informed on the specific psychometric properties (construct validity, known-group validity, and responsiveness/longitudinal validity) to understand the interchangeability of these instruments.

In the field of osteoporosis, extensive studies have been conducted to estimate QoL consequences for patients with a prior fracture, such as the International Costs and Utilities Related to Osteoporotic fractures Study (ICUROS) [52], suggesting patients with hip, vertebral, or distal forearm fractures incur substantial loss in QoL. However, very few studies have been conducted to investigate HRQoL in patients a recent fracture attending the FLS, especially the course of HSUV in the long term. In addition, the psychometric properties of EQ-5D and SF-6D have been compared in multiple studies in patients with different diseases and different conclusions were made regarding the interchangeability of the questionnaires. However, to our knowledge, longitudinal data on the sensitivity of HSUVs (longitudinal validity) are sparse in the literature, especially in the field of fractures, and no studies included patients presenting at an FLS.

THE CURRENT ECONOMIC EVIDENCE OF FLS AND INTERVENTIONS FOR OSTEOPOROSIS

With the wide implementation of FLS throughout the world, economic evaluations have also been increasingly performed to assess the potential health economic benefits of introducing/implementing FLS in country-specific hospital settings. The current economic evidence of FLS was summarized in a systematic review [53] (published in 2018), indicating FLS is a cost-effective or even a cost- saving secondary fracture prevention strategy in general. However, some recent studies indicated that the intensity and quality of implementation of FLSs vary between hospitals and countries (e.g., time horizon, model structure) [54,55], effectiveness data obtained in studies with different levels of quality, patient identification and selection differed markedly among FLSs in terms of proportions of inpatients and outpatients, age, the inclusion of women and/or men, and fracture site (any fracture or only patients with an nonvertebral fracture) [56], potentially leading to different clinical and economic outcomes. Further differences between countries in terms of fracture incidence, costs and QALYs limit the transferability of cost-effectiveness and suggests the importance to conduct national cost-effectiveness of FLS.

Cost-effectiveness is not only relevant for the FLS as a whole, but also for the increasing number of pharmacological treatments for fracture prevention that are being developed. Hiligsmann et al. [57] summarized 39 economic evaluations on drugs for postmenopausal osteoporosis published between January 2008 and December 2013, reporting active osteoporotic drugs were generally cost effective in postmenopausal women aged over 60–65 years with low bone mass, especially those with prior vertebral fractures. In view of the heterogeneity in fracture risk,

comparators, country setting, model structure, and incorporation of medication adherence, and given the lack of head-to-head comparisons, it is not yet possible to make clear recommendations between drugs in terms of cost effectiveness. Recently, with the availability of new agents (such as abaloparatide, romosozumab) and treatment strategies (sequential therapy) for osteoporosis, some new economic evaluations have been performed, however no overview of the recent literature of cost-effectiveness analyses of drugs in postmenopausal osteoporosis have been conducted.

As osteoporosis is commonly recognized as a women disease and is often overlooked in men, most economic evaluations have been performed for postmenopausal women. In recent years, with the increased awareness of treating osteoporosis in men, as well as some active agents (denosumab and teriparatide) have been licensed for men use, economic evaluations have also been increasingly conducted to assess the cost-effectiveness of these interventions in men. To our knowledge, no overview of these cost-effectiveness analyses in men is however available yet.

OBJECTIVES AND OUTLINE OF THIS DISSERTATION

Given the increasing burden of osteoporosis and fractures, as well as the wide implementation of FLS for secondary fracture prevention and the importance of economic evaluations when prioritizing health interventions and informing decision-making, this dissertation aims to summarize current evidence relevant to osteoporosis management and to study the clinical and economic outcomes of FLS. Two main parts can be found; each part includes several sub-studies (see Figure 1).

Part I focuses on summarizing the large amount of literature of two aspects relevant in osteoporosis management, i.e. 1) economic evaluations in both women and men with osteoporosis; 2) medication adherence and complexities of fracture risk communication. In **Chapter 2** updates a previous review of cost-effectiveness of drugs for osteoporosis in women. **Chapter 3** summarizes information on the cost-effectiveness of treating men with osteoporosis, reveals the origin of model input data and compares the cost-effectiveness results between men and women. Then, in **Chapter 4** studies the current status of patient adherence to osteoporosis medications, the determinants and consequences of non-adherence. Recommendations and tools for effective communication between healthcare professionals and patients regarding general health risk and risk of fracture are also summarized.

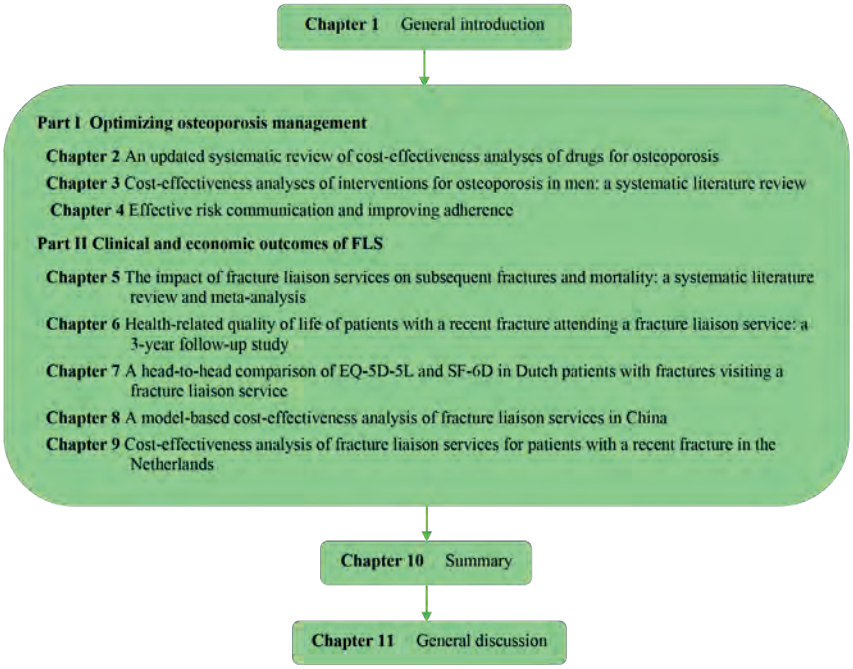

Figure 1. Outline of the thesis

Part II addresses the clinical and economic outcomes of FLS by revealing the clinical effectiveness of FLS, estimating long-term HRQoL, explores the interchangeability of different instruments in estimation of HSUVs in patients with a recent fracture presenting at an FLS and the cost-effectiveness of FLS in both the Netherlands and China. First, with an increasing number of studies that have assessed the clinical outcomes of FLS, **Chapter 5** summarizes the current evidence by conducting a systematic review and meta-analysis to investigate the impact of FLS on subsequent fractures and mortality. Using a large Dutch database of 500 patients, **Chapter 6** assesses the 3-year HSUV (as measured by EQ-5D-5L and SF-6D) in patients with a recent fracture presenting at an FLS, and explores factors associated with HSUV. Furthermore, **Chapter 7** compares the psychometric properties (construct validity, known-group validity, and responsiveness) of EQ-5D-5L and SF-6D based on the same database to assess the interchangeability of these two instruments in prospective Dutch patients with a recent fracture presenting at an FLS. Then, considering no economic evaluations have yet been conducted in the Netherlands and China to explore the economic benefits of FLS, **Chapter 8** assesses the potential economic benefits of the FLS from the Chinese healthcare perspective with a lifetime horizon, and **Chapter 9** presents the cost-effectiveness of FLS in patients with a recent fracture from the Dutch societal perspective using real-world data.

REFERENCES

1. Bouillon R, Burckhardt P, Christiansen C. Consensus Development Conference : Prophylaxis and. *Am J Med*. 1991;90:107-110. http://www.sciencedirect.com/science/article/pii/000293439190512V
2. WHO technical report series. *Screening for Postmenopausal Osteoporosis*.; 1994.
3. Elaine Dennison. *Osteoporosis Treatment: A Clinical Overview*.; 2021.
4. Kanis JA, Johnell O, Oden A, Dawson A, De Laet C, Jonsson B. Ten year probabilities of osteoporotic fractures according to BMD and diagnostic thresholds. *Osteoporos Int*. 2001;12(12):989-995. doi:10.1007/s001980170006
5. Kanis JA, Johnell O, Oden A, Johansson H, McCloskey E. FRAX™ and the assessment of fracture probability in men and women from the UK. *Osteoporos Int*. 2008;19(4):385-397. doi:10.1007/s00198-007-0543-5
6. Sozen T, Ozisik L, Calik Basaran N. An overview and management of osteoporosis. *Eur J Rheumatol*. 2017;4(1):46-56. doi:10.5152/eurjrheum.2016.048
7. International Osteoporosis Foundation. Fragility fractures-EPIDEMIOLOGY. https://www.osteoporosis.foundation/health-professionals/fragility-fractures/epidemiology
8. Kanis JA, Norton N, Harvey NC, et al. SCOPE 2021: a new scorecard for osteoporosis in Europe. *Arch Osteoporos*. 2021;16(1). doi:10.1007/s11657-020-00871-9
9. Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. *Osteoporos Int*. 2006;17(12):1726-1733. doi:10.1007/s00198-006-0172-4
10. Ross PD, SANTORA A, YATES AJ. Epidemiology and Consequences of Osteoporotic Fractures. *Aging Skelet*. 1999;359:339-347. doi:10.1016/b978-012098655-2/50031-4
11. O'Neill TW, Felsenbergp D, Varlow J, et al. The prevalence of vertebral deformity in european men and women: The European vertebral osteoporosis study. *J Bone Miner Res*. 1996;11(7):1010-1018. doi:10.1002/jbmr.5650110719
12. Klotzbuecher CM, Ross PD, Landsman PB, Abbott TA, Berger M. Patients with prior fractures have an increased risk of future fractures: A summary of the literature and statistical synthesis. *J Bone Miner Res*. 2000;15(4):721-739. doi:10.1359/jbmr.2000.15.4.721
13. Van Geel TACM, Huntjens KMB, Van Den Bergh JPW, Dinant GJ, Geusens PP. Timing of subsequent fractures after an initial fracture. *Curr Osteoporos Rep*. 2010;8(3):118-122. doi:10.1007/s11914-010-0023-2
14. Banefelt J, Åkesson KE, Spångéus A, et al. Risk of imminent fracture following a previous fracture in a Swedish database study. *Osteoporos Int*. 2019;30(3):601-609. doi:10.1007/s00198-019-04852-8
15. Van Geel TACM, Van Helden S, Geusens PP, Winkens B, Dinant GJ. Clinical subsequent fractures cluster in time after first fractures. *Ann Rheum Dis*. 2009;68(1):99-102. doi:10.1136/ard.2008.092775
16. Ayub N, Faraj M, Ghatan S, Reijers JAA, Napoli N, Oei L. The treatment gap in osteoporosis. *J Clin Med*. 2021;10(13):1-13. doi:10.3390/jcm10133002
17. Chen JS, Sambrook PN. Antiresorptive therapies for osteoporosis: A clinical overview. *Nat Rev Endocrinol*. 2012;8(2):81-91. doi:10.1038/nrendo.2011.146
18. Agency EM. Eladynos, abaloparatide. Published 2018. https://www.ema.europa.eu/en/medicines/%0Ahuman/EPAR/eladynos.
19. Agency EM. *Eladynos, Abaloparatide*. Vol 1.; 2018. https://www.ema.europa.eu/en/

medicines/%0Ahuman/EPAR/eladynos.

20. Leder BZ. Optimizing Sequential and Combined Anabolic and Antiresorptive Osteoporosis Therapy. 2018;2(2):62-68. doi:10.1002/jbm4.10041
21. Skjødt MK, Khalid S, Ernst M, et al. Secular trends in the initiation of therapy in secondary fracture prevention in Europe: a multi-national cohort study including data from Denmark, Catalonia, and the United Kingdom. *Osteoporos Int*. 2020;31(8):1535-1544. doi:10.1007/s00198-020-05358-4
22. Solomon DH, Johnston SS, Boytsov NN, Mcmorrow D, Lane JM, Krohn KD. Osteoporosis Medication Use After Hip Fracture in U . S . Patients Between 2002 and 2011. 2014;29(9):1929-1937. doi:10.1002/jbmr.2301
23. Dutch Institute for Healthcare Improvement CBO (2011) Richtlijn Osteoporose en Fractuurpreventie. www.diliguide.nl/document/1015/file/pdf/
24. Lems WF, Geusens P. Osteoporose en fractuurpreventie. *Leerb Reumatol en Klin Immunol*. Published online 2013:215-226. doi:10.1007/978-90-313-9894-2_20
25. https://www.zorginstituutnederland.nl/.
26. https://opendata.cbs.nl/statline/#/CBS/nl/navigatieScherm/zoeken?searchKeywords =osteoporose.
27. Dunnewind T, Dvortsin EP, Smeets HM, et al. Economic Consequences and Potentially Preventable Costs Related to Osteoporosis in the Netherlands. *Value Heal*. 2017;20(6):762-768. doi:10.1016/j.jval.2017.02.006
28. Liu C, Wang D, Liu C, et al. What is the meaning of health literacy? A systematic review and qualitative synthesis. *Fam Med Community Heal*. 2020;8(2):1-8. doi:10.1136/fmch-2020-000351
29. Dobbels F, Van Damme-Lombaert R, Vanhaecke J, De Geest S. Growing pains: Non-adherence with the immunosuppressive regimen in adolescent transplant recipients. *Pediatr Transplant*. 2005;9(3):381-390. doi:10.1111/j.1399-3046.2005.00356.x
30. Vrijens B, De Geest S, Hughes DA, et al. A new taxonomy for describing and defining adherence to medications. *Br J Clin Pharmacol*. 2012;73(5):691-705. doi:10.1111/j.1365-2125.2012.04167.x
31. Reynolds K, Muntner P, Cheetham TC, et al. Primary non-adherence to bisphosphonates in an integrated healthcare setting. *Osteoporos Int*. 2013;24(9):2509-2517. doi:10.1007/s00198-013-2326-5
32. Netelenbos JC, Geusens PP, Ypma G, Buijs SJE. Adherence and profile of non-persistence in patients treated for osteoporosis-a large-scale, long-term retrospective study in the Netherlands. *Osteoporos Int*. 2011;22(5):1537-1546. doi:10.1007/s00198-010-1372-5
33. Klop C, Welsing PMJ, Elders PJM, et al. Long-term persistence with anti-osteoporosis drugs after fracture. *Osteoporos Int*. 2015;26(6):1831-1840. doi:10.1007/s00198-015-3084-3
34. Beaudart C, Hiligsmann M, Li N, Lewiecki EM, Silverman S. Effective communication regarding risk of fracture for individuals at risk of fragility fracture: a scoping review. *Osteoporos Int*. 2022;33(1):13-26. doi:10.1007/s00198-021-06151-7
35. McLellan AR, Gallacher SJ, Fraser M, McQuillian C. The fracture liaison service: Success of a program for the evaluation and management of patients with osteoporotic fracture. *Osteoporos Int*. 2003;14(12):1028-1034. doi:10.1007/s00198-003-1507-z
36. www.capturethefracture.org.
37. Eisman JA, Bogoch ER, Dell R, et al. Making the first fracture the last fracture: ASBMR task force report on

secondary fracture prevention. *J Bone Miner Res*. 2012;27(10):2039-2046. doi:10.1002/jbmr.1698

38. Lems WF, Dreinhöfer KE, Bischoff-Ferrari H, et al. EULAR/EFORT recommendations for management of patients older than 50 years with a fragility fracture and prevention of subsequent fractures. *Ann Rheum Dis*. 2017;76(5):802-810. doi:10.1136/annrheumdis-2016-210289
39. Dreinhöfer KE, Mitchell PJ, Bégué T, et al. A global call to action to improve the care of people with fragility fractures. *Injury*. 2018;49(8):1393-1397. doi:10.1016/j.injury.2018.06.032
40. Geusens P, Bours SPG, Wyers CE, van den Bergh JP. Fracture liaison programs. *Best Pract Res Clin Rheumatol*. 2019;33(2):278-289. doi:10.1016/j.berh.2019.03.016
41. Majumdar SR, Beaupre LA, Harley CH, et al. Use of a Case Manager to Improve Osteoporosis Treatment After Hip Fracture. *Arch Intern Med*. 2007;167(19):2110. doi:10.1001/archinte.167.19.2110
42. Hegeman JH, Oskam J, van der Palen J, ten Duis HJ, Vierhout PAM. The distal radial fracture in elderly women and the bone mineral density of the lumbar spine and hip. *J Hand Surg Am*. 2004;29(5):473-476. doi:10.1016/j.jhsb.2004.05.002
43. Van Helden S, Cauberg E, Geusens P, Winkes B, Van Der Weijden T, Brink P. The fracture and osteoporosis outpatient clinic: An effective strategy for improving implementation of an osteoporosis guideline. *J Eval Clin Pract*. 2007;13(5):801-805. doi:10.1111/j.1365-2753.2007.00784.x
44. No Title. https://osteoporoseverpleegkundige.nl/
45. Van Den Bergh JP, Van Geel TA, Geusens PP. Osteoporosis, frailty and fracture: Implications for case finding and therapy. *Nat Rev Rheumatol*. 2012;8(3):163-172. doi:10.1038/nrrheum.2011.217
46. van den Berg P, Schweitzer DH, van Haard PMM, van den Bergh JP, Geusens PP. Meeting international standards of secondary fracture prevention: a survey on Fracture Liaison Services in the Netherlands. *Osteoporos Int*. 2015;26(9):2257-2263. doi:10.1007/s00198-015-3117-y
47. Li N, Hiligsmann M, Boonen A, et al. The impact of fracture liaison services on subsequent fractures and mortality: a systematic literature review and meta-analysis. *Osteoporos Int*. Published online 2021. doi:10.1007/s00198-021-05911-9
48. Soiza RL, Donaldson AIC, Myint PK. Fracture liaison services: do they reduce fracture rates? *Ther Adv Vaccines*. 2018;9(6):259-261.
49. Petrou S, Gray A. Economic evaluation alongside randomised controlled trials: Design, conduct, analysis, and reporting. *Bmj*. 2011;342(7806):1-6. doi:10.1136/bmj.d1548
50. Hiligsmann M, Reginster J, Tosteson ANA, et al. Recommendations for the conduct of economic evaluations in osteoporosis : outcomes of an experts ' consensus meeting organized by the European Society for Clinical and Economic Aspects of Osteoporosis , Osteoarthritis and Musculoskeletal Diseases (ESCEO . Published online 2019:45-57.
51. Status D. Guideline for economic evaluations in healthcare. Published online 2016.
52. Svedbom A, Borgström F, Hernlund E, et al. Quality of life after hip, vertebral, and distal forearm fragility fractures measured using the EQ-5D-3L, EQ-VAS, and time-trade-off: results from the ICUROS. *Qual Life Res*. 2018;27(3):707-716. doi:10.1007/s11136-017-1748-5
53. Wu CH, Kao IJ, Hung WC, et al. Economic impact and cost-effectiveness of fracture liaison services: a systematic review of the literature. *Osteoporos Int*. 2018;29(6):1227-1242. doi:10.1007/s00198-018-4411-2

54. Ganda K, Puech M, Chen JS, et al. Models of care for the secondary prevention of osteoporotic fractures: A systematic review and meta-analysis. *Osteoporos Int*. 2013;24(2):393-406. doi:10.1007/s00198-012-2090-y
55. Wu C, Chen C, Chen P, et al. Identifying characteristics of an effective fracture liaison service : systematic literature review. Published online 2018:1023-1047.
56. Vranken L, Wyers CE, van den Bergh JPW, Geusens PPMM. The Phenotype of Patients with a Recent Fracture: A Literature Survey of the Fracture Liaison Service. *Calcif Tissue Int*. 2017;101(3):248-258. doi:10.1007/s00223-017-0284-1
57. Hiligsmann M, Evers SM, Ben Sedrine W, et al. A Systematic Review of Cost-Effectiveness Analyses of Drugs for Postmenopausal Osteoporosis. *Pharmacoeconomics*. 2015;33(3):205-224. doi:10.1007/s40273-014-0231-1
58. Huntjens KMB, Van Geel TCM, Geusens PP, et al. Impact of guideline implementation by a fracture nurse on subsequent fractures and mortality in patients presenting with non-vertebral fractures. *Injury*. 2011;42(SUPPL. 4):S39-S43. doi:10.1016/S0020-1383(11)70011-0
59. Amphansap T, Stitkitti N, Dumrongwanich P. Evaluation of Police General Hospital's Fracture Liaison Service (PGH's FLS): The first study of a Fracture Liaison Service in Thailand. *Osteoporos Sarcopenia*. 2016;2(4):238-243. doi:10.1016/j.afos.2016.09.002
60. Axelsson KF, Jacobsson R, Lund D, Lorentzon M. Effectiveness of a minimal resource fracture liaison service. *Osteoporos Int*. 2016;27(11):3165-3175. doi:10.1007/s00198-016-3643-2
61. Hawley S, Kassim Javaid M, Prieto-Alhambra D, et al. Clinical effectiveness of orthogeriatric and fracture liaison service models of care for hip fracture patients: Population-based longitudinal study. *Age Ageing*. 2016;45(2):236-242. doi:10.1093/ageing/afv204
62. Bachour F, Rizkallah M, Sebaaly A, et al. Fracture liaison service: report on the first successful experience from the Middle East. *Arch Osteoporos*. 2017;12(1):4-9. doi:10.1007/s11657-017-0372-x
63. Davidson E, Seal A, Doyle Z, Fielding K, McGirr J. Prevention of osteoporotic refractures in regional Australia. *Aust J Rural Health*. 2017;25(6):362-368. doi:10.1111/ajr.12355
64. Singh S, Whitehurst DG, Funnell L, et al. Breaking the cycle of recurrent fracture: implementing the first fracture liaison service (FLS) in British Columbia, Canada. *Arch Osteoporos*. 2019;14(1). doi:10.1007/s11657-019-0662-6
65. Wasfie T, Jackson A, Brock C, Galovska S, McCullough JR, Burgess JA. Does a fracture liaison service program minimize recurrent fragility fractures in the elderly with osteoporotic vertebral compression fractures? *Am J Surg*. 2019;217(3):557-560. doi:10.1016/j.amjsurg.2018.09.027
66. González-Quevedo D, Bautista-Enrique D, Pérez-del-Río V, Bravo-Bardají M, García-de-Quevedo D, Tamimi I. Fracture liaison service and mortality in elderly hip fracture patients: a prospective cohort study. *Osteoporos Int*. 2020;31(1):77-84. doi:10.1007/s00198-019-05153-w
67. Shin YH, Hong WK, Kim J, Gong HS. Osteoporosis care after distal radius fracture reduces subsequent hip or spine fractures: a 4-year longitudinal study. *Osteoporos Int*. 2020;31(8):1471-1476. doi:10.1007/s00198-020-05410-3
68. Huntjens KMB, Van Geel TACM, Van Den Bergh JPW, et al. Fracture liaison service: Impact on subsequent nonvertebral fracture incidence and mortality. *J Bone Jt Surg - Ser A*. 2014;96(4):1-8. doi:10.2106/

JBJS.L.00223

69. Nakayama A, Major G, Holliday E, Attia J, Bogduk N. Evidence of effectiveness of a fracture liaison service to reduce the re-fracture rate. *Osteoporos Int*. 2016;27(3):873-879. doi:10.1007/s00198-015-3443-0
70. Inderjeeth CA, Raymond WD, Briggs AM, Geelhoed E, Oldham D, Mountain D. Implementation of the Western Australian Osteoporosis Model of Care: a fracture liaison service utilising emergency department information systems to identify patients with fragility fracture to improve current practice and reduce re-fracture rates: a 12-. *Osteoporos Int*. 2018;29(8):1759-1770. doi:10.1007/s00198-018-4526-5
71. Axelsson KF, Johansson H, Lundh D, Möller M, Lorentzon M. Association Between Recurrent Fracture Risk and Implementation of Fracture Liaison Services in Four Swedish Hospitals: A Cohort Study. *J Bone Miner Res*. 2020;35(7):1216-1223. doi:10.1002/jbmr.3990
72. Ruggiero C, Zampi E, Rinonapoli G, et al. Fracture prevention service to bridge the osteoporosis care gap. *Clin Interv Aging*. 2015;10:1035-1042. doi:10.2147/CIA.S76695
73. Henderson CY, Shanahan E, Butler A, et al. Dedicated orthogeriatric service reduces hip fracture mortality. *Ir J Med Sci*. 2017;186(1):179-184. doi:10.1007/s11845-016-1453-3
74. Wang L, Yu W, Yin X, et al. Prevalence of Osteoporosis and Fracture in China: The China Osteoporosis Prevalence Study. *JAMA Netw Open*. 2021;4(8):1-12. doi:10.1001/jamanetworkopen.2021.21106
75. Xu L, Jan S, Chen M, Si L. Sociodemographic and health system factors associated with variations in hospitalization costs for fractures in adults aged 45 years and over : a cross - sectional study of provincial health accounts in Jiangsu Province , China. *Arch Osteoporos*. Published online 2021:1-9. doi:10.1007/s11657-021-01009-1
76. Crespo C, Monleon A, Díaz W, Ríos M. Comparative efficiency research (COMER): Meta-analysis of cost-effectiveness studies. *BMC Med Res Methodol*. 2014;14(1):1-9. doi:10.1186/1471-2288-14-139
77. Bagepally BS, Chaikledkaew U, Chaiyakunapruk N, Attia J, Thakkinstian A. Meta-analysis of economic evaluation studies: data harmonisation and methodological issues. *BMC Health Serv Res*. 2022;22(1):1-10. doi:10.1186/s12913-022-07595-1
78. Veettil SK, Syeed MS, Noviyan R, Thakkinstian A, Chaiyakunapruk N. Does meta-analysis of economic evaluations have the potential to play a role in healthcare decision-making in the United States? *J Med Econ*. 2022;25(1):750-754. doi:10.1080/13696998.2022.2083347
79. Husereau D, Drummond M, Augustovski F, et al. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) Statement: Updated Reporting Guidance for Health Economic Evaluations. *Appl Health Econ Health Policy*. 2022;20(2):213-221. doi:10.1007/s40258-021-00704-x
80. Hiligsmann M, Reginster JY, Tosteson ANA, et al. Recommendations for the conduct of economic evaluations in osteoporosis: outcomes of an experts' consensus meeting organized by the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) and. *Osteoporos Int*. 2019;30(1):45-57. doi:10.1007/s00198-018-4744-x


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CHAPTER 2

An Updated Systematic Review of Cost-Effectiveness Analyses of Drugs for Osteoporosis

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ABSTRACT

Background Considering the heavy economic burden of osteoporotic fractures, the limits of healthcare resources, and the recent availability of new anti-osteoporosis drugs, there is continuing interest in economic evaluation studies of osteoporosis management strategies.

Objectives This study aims to (1) systematically review recent economic evaluations of drugs for osteoporosis and (2) to apply an osteoporosis-specific guideline to critically appraise them.

Methods A literature search was undertaken using PubMed, EMBASE, National Health Service Economic Evaluation database, and the Cost-Effectiveness Analysis Registry to identify original articles containing economic evaluations of anti-osteoporosis drugs, published between 1 July, 2013 and 31 December, 2019. A recent European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases-International Osteoporosis Foundation (ESCEO-IOF) guideline for the conduct and reporting of economic evaluations in osteoporosis was used to assess the quality of included articles.

Results The database search retrieved 3860 records, of which 27 studies fulfilled the inclusion criteria. These studies were conducted in 15 countries; 12 active drugs were assessed, including various traditional pharmacological treatments such as bisphosphonates, raloxifene, strontium ranelate, denosumab, and teriparatide, and new agents such as abaloparatide, romosozumab, and gastro-resistant risedronate. Eight out of 12 studies that compared traditional oral bisphosphonates to other active interventions (denosumab, zoledronic acid, gastro-resistant risedronate, and teriparatide) suggested that the other active agents were generally cost-effective or dominant. Additionally, the cost-effectiveness of sequential therapy has recently been assessed and indications are that it can lead to extra health benefits (larger gains in quality-adjusted life-year). The key drivers of cost effectiveness included baseline fracture risk, drug effect on the risk of fractures, drug cost, and medication adherence/persistence. The current average score for quality assessment was 17 out of 25 (range 2–15); room for improvement was observed for most studies, which could potentially be explained by the fact that most studies were published prior to the osteoporosis-specific guideline. Greater adherence to guideline recommendations was expected for future studies. The quality of reporting was also suboptimal, especially with regard to treatment side effects, treatment effect after discontinuation, and medication adherence.

Conclusions This updated review provides an overview of recently published cost-effectiveness analyses. In comparison with a previous review, recent economic evaluations of anti-osteoporosis drugs were conducted in more countries and included more active drugs and sequential therapy as interventions/comparators. The updated economic evidence could help decision makers prioritize health interventions and the unmet/unreported quality issues indicated by the osteoporosis-specific guideline could be useful in improving the transparency, quality, and comparability of future economic evaluations in osteoporosis.

Key Points for Decision Makers

- In comparison with oral bisphosphonates (including generic forms), other active interventions (such as denosumab, zoledronic acid, gastro-resistant risedronate, or teriparatide) were generally cost effective or dominant.
- Sequential therapy has the potential to generate extra health benefits and to be cost effective in comparison with monotherapy, although more clinical and economic data are needed.
- Although several studies partially followed the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases-International Osteoporosis Foundation guideline, quality was largely insufficient for most articles. Our study highlighted that insufficiently implemented and/or reported recommendations should be included in future studies; this could be useful in improving the transparency, quality, and comparability of economic evaluations in osteoporosis.

INTRODUCTION

Osteoporosis is a skeletal disease associated with a significant health and economic burden, which has become an increasing global health problem considering the aging population characterized by multi-morbidity. The morbidity and mortality imposed by osteoporotic fractures along with the negative impact on patients' quality of life are important clinical considerations [1]. Worldwide, osteoporosis causes more than 8.9 million fractures annually, resulting in an osteoporotic fracture every 3 s [2]. In the European Union, 22 million women and 5.5 million men had osteoporosis in 2010 [3]. As a result of changes in population demography, the annual number of fragility fractures was expected to rise from 3.5 million in 2010 to 4.5 million in 2025, corresponding to an increase of 28% [4]. In the USA, over 1.5 million fractures per year were attributable to osteoporosis, resulting in direct healthcare costs of 12–18 billion US dollars [5]. Improving osteoporosis care and reducing spiraling fracture-related costs pose worldwide challenges.

Health economic evaluations have become increasingly important to support the setting of priorities in healthcare and to help decision makers allocate healthcare resources efficiently in the context of limited healthcare resources, the ongoing aging of the population, and the heavy economic burden of osteoporotic fractures, as well as the recent availability of new agents for osteoporosis management (e.g., abaloparatide, romosozumab, gastro-resistant risedronate). In 2015, a study systematically reviewed all economic evaluations of anti-osteoporosis drugs published up to 31 June, 2013 and suggested that anti-osteoporosis drugs were generally cost effective in comparison with no treatment in postmenopausal women aged over 60–65 years with low bone mass, especially those with prior vertebral fractures. However, given the heterogeneity of fracture risk, comparators, country setting, model structure, and incorporation of medication adherence, as well as the lack of head-to-head comparisons, it remained challenging to make comparisons between studies [6]. In addition, the quality of reporting was largely insufficient for most studies, despite the fact that guidelines for conducting health economic evaluations have been widely available for many years.

Recently, a guideline for the conduct and reporting of economic evaluations in the field of osteoporosis has been designed by a working group convened by the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) and the US branch of the International Osteoporosis Foundation (IOF) [7]. Although several disease-specific recommendations for economic evaluations have been developed, this guideline is the first that provides a list of recommendations and minimum requirements

for the design, conduct, and reporting of an osteoporosis-specific economic evaluation. Osteoporosis-specific recommendations in this guideline, which supplement general and national guidelines, could guide researchers in designing appropriate and high-quality economic evaluations and help decision makers and reviewers to assess the quality of these studies, and further to improve the transparency and comparability of these studies and maintain methodologic standards [7]. Therefore, assessing how recent studies adhere to the osteoporosis-specific guideline is important in identifying the main limitations of these studies, and further to indicate some of the most important recommendations that should be taken into account in future studies.

An overview of currently available studies regarding cost-effectiveness analyses of drugs for osteoporosis would thus be useful to guide researchers in designing and conducting high-quality economic evaluations, in identifying gaps in current evidence, and to help administrators make decisions based on high-quality evidence. We therefore updated and undertook this review to (1) systematically identify and review economic evaluations published between 2013 and 2019 on drugs for osteoporosis and (2) to critically appraise their quality using the recent osteoporosis-specific guideline, and also to provide insight into key drivers of cost-effectiveness ratios.

METHODS

Literature Search

A systematic literature search was undertaken to identify recent cost-effectiveness analyses of drugs for osteoporosis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline [8]. The search was conducted using several databases including PubMed, EMBASE (Ovid), National Health Service Economic Evaluation Database (NHS EED) [the database ceased to be updated after March 2015] and the Cost-Effectiveness Analysis (CEA) Registry (the database can serve as an archive only until 2018). We restricted our analysis to articles published between 1 July, 2013 and 31 December, 2019, as prior articles were covered in the previous review [6]. An initial search was conducted in PubMed and EMBASE using a search strategy (see Appendix 1 in the Electronic Supplementary Material [ESM]) designed according to the Population, Intervention, Comparator, Outcome (PICO) criteria with the help of an expert library specialist. The key word ‘osteoporosis’ was used in the NHS EED and the CEA Registry database.

Study Selection

First, duplicates were identified and removed. Second, two reviewers (NL, DC) independently applied inclusion and exclusion criteria to screen titles and abstracts of the remaining articles. Third, full-text versions of eligible articles were screened in-depth by two independent reviewers (NL and DC, LS, DP, SS, or RB). A consensus meeting with a third reviewer (MH) was used to resolve discrepancies. Finally, reference lists and citations of eligible articles were checked manually for additional relevant studies.

Studies were included if they were published in English between July 2013 and December 2019 and contained a full economic evaluation (the comparative analysis of alternative interventions in terms of both costs and consequences) of anti-osteoporosis drugs. Non-original articles (e.g., editorials, reviews, conference proceedings), partial economic evaluations, and non-specific drug studies (e.g., only use vitamin D and/or calcium as interventions, studies regarding screening strategies, intervention thresholds, medication adherence, nutrition, model of care, fracture liaison services, and lifestyle) were excluded.

Data Extraction and Quality Assessment

A standardized data-extraction form was developed to collect data from eligible studies. Study characteristics regarding publication (author, year of publication, journal), study design (country, population, perspective, model type, outcome measure, time horizon, comparators, intervention duration, cost type, discount rates, year of valuation), study outcomes (results and sensitivity analysis), and funding source were extracted by one reviewer (NL) and checked by another reviewer (DC, LS, DP, SS, RB, or IK). Incremental cost-effectiveness ratios (ICERs) were reported as provided in the articles. Afterwards, for comparability reasons, all ICERs were converted into 2019 US dollars using the Organisation for Economic Cooperation and Development exchange rate and inflation rate [9]. We then synthetized and analyzed ICERs of active agents compared to traditional oral bisphosphonates (first-line treatments in most countries), and of sequential therapies (e.g., abaloparatide/teriparatide followed by alendronate) by using US$100,000 per quality-adjusted life-year (QALY) gained as the willingness-to-pay (WTP) threshold. Other information such as country, treatment duration, and annual drug cost was also extracted. In addition, we checked included studies, especially one-way sensitivity analyses, to identify key drivers of cost effectiveness; these were eventually chosen through team discussion.

The conduct and reporting quality of included articles were then appraised using the ESCEO-IOF guideline for economic evaluations in osteoporosis by two

independent reviewers (NL with DC, LS, DP, SS, RB, or IK). The whole assessment consisted of two parts. Part one included recommendations for the design and conduct of an economic evaluation in osteoporosis; 29 recommendations were addressed in nine categories (type of economic evaluation, method for the conduct of economic evaluation, modeling technique, base-case analysis and population, mortality, fracture costs and utility, treatment characteristics, sensitivity analyses, and outcomes). Part two was an osteoporosis-specific checklist with nine recommendations for reporting, including the reporting and justification of key modeling aspects (choice of model, transition probabilities, effect of fracture on costs, mortality, and utility) and key treatment characteristics (the effect of treatment per fracture site, the effect of treatment after discontinuation, the inclusion and approach used to model medication adherence, therapy costs, and side effects) [7].

Each recommendation of these two parts was scored using 'Yes' (fulfilled the requirement of reporting), 'No' (did not fulfill the requirement), 'Part' (partially fulfilled the requirement), or 'Not Applicable' according to the operationalization of the guideline (Appendix 2 in the ESM). To estimate a score for reporting, we assigned a score of 1 for 'Yes', 0.5 for 'Part', and 0 for 'No'. Discrepancies in rating were resolved by consensus and consultation with a third reviewer (MH). It is worth noting that in the scoring system we excluded recommendations that were not directly connected to the quality level of studies (i.e., 'use ICUROS data', 'use FRAX® or GARVAN® tools', 'consider sequential therapy as intervention', and 'in the absence of hip/wrist specific efficacy data, use non-vertebral or clinical fracture efficacy data as replacement').

RESULTS

Results of Study Selection

Figure 1 shows the PRISMA flowchart for the identification of studies. The database search retrieved 3860 records, of which 620 were found to be duplicates and removed. We reviewed all titles and abstracts of the remaining 3240 studies and subsequently excluded 3188 articles that did not meet our inclusion criteria. Upon review of the full text of the remaining 52 studies, 25 articles were excluded for reasons such as being non-original articles (n = 2), partial-economic evaluations (n = 4), reporting on non-specific drugs (n = 13), and studies included in previous review (n = 6). A total of 27 articles were included in our study for data extraction and quality assessment.

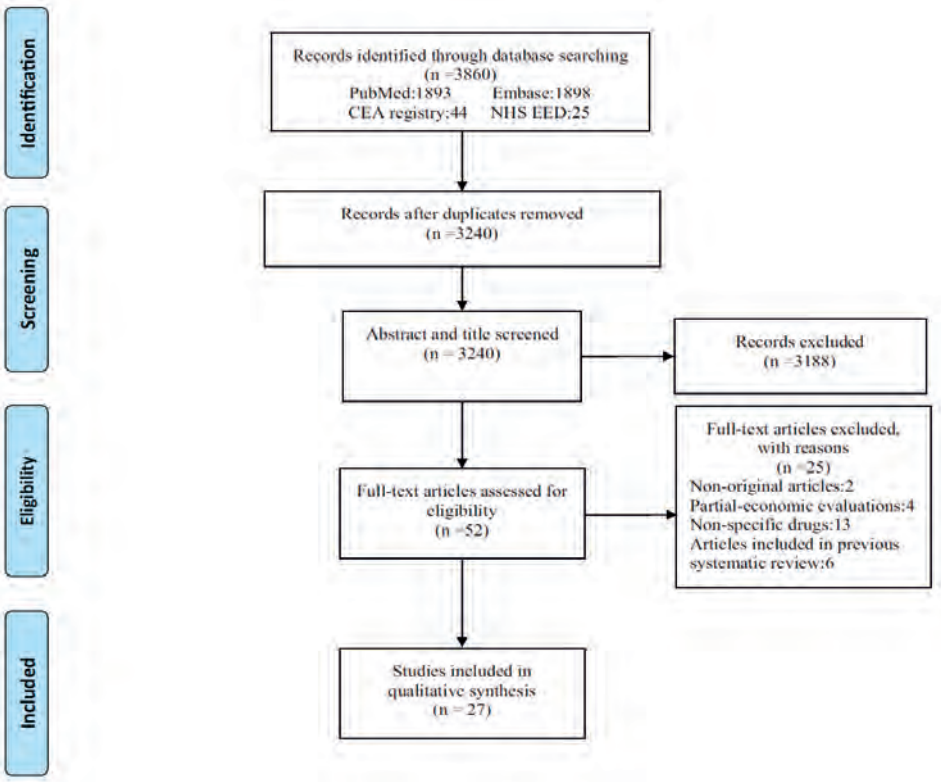

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart of study selection. CEA cost-effectiveness analysis, NHS EED National Health Service Economic Evaluation database

Overview of Included Studies

The characteristics of included studies are reported in Table 1. These studies were conducted in 15 different countries. The USA accounted for the largest number (n = 7); 12 studies were conducted in Asia, i.e., three each in Japan (n = 3), China (n = 3), and Iran (n = 3). Five studies were performed in five different European countries. Twelve of the 27 studies were published in osteoporosis journals, particularly in Osteoporosis International (n = 5).

Most studies used the healthcare perspective (n = 21), some with a societal perspective (n = 4), while one study used both societal and healthcare perspectives, and another study reported societal, healthcare, and governmental perspectives. All studies included direct costs and only three also considered indirect costs [15, 18, 20]. However, we found that some studies including both direct and indirect costs were not defined as having a societal perspective, although this was the original information stated by authors reported in Table 1; no adjustment and correction were made for this. Nineteen studies applied a lifetime horizon while others considered truncated time horizons [10–15]. A Markov model was used in 21 studies, consisting of a Markov cohort model (n = 12) or a Markov microsimulation model (n = 9). One study applied a discrete-event simulation model [16], another a decision-tree model [13]. Quality-adjusted life-years (QALYs) were used as the outcome in these 23 studies with a model. The remaining four studies used no model [10–12, 17]. One out of the four conducted a cost-minimization analysis [10], in which costs were compared. Another two studies [11, 12] used bone mineral density (BMD) as the final outcome and ICER was calculated based on the differences of costs and BMD of different interventions. Furthermore, the number of fracture events was regarded as the outcome in the fourth study [17], ICER was calculated based on the differences of average annual costs divided by the difference of numbers of hip fractures prevented between bisphosphonates and the combination of calcium and vitamin D. Fourteen studies were funded by pharmaceutical companies or national public funds, while 13 studies did not mention the source of funding or had no funding.

Table 1. Characteristics of published articles assessing the cost effectiveness of drugs for osteoporosis

References	Journal	Country	Study perspective[a]	Model type	Outcome measure	Time horizon	Cost type	Discount rates (costs, QALY)	Funding source
Active drug(s) vs no treatment/calcium + vitamin D									
Golmohamdi et al. [12]	Electronic Physician	Iran	Healthcare	No	BMD	12 and 36 months	Direct costs	NR	NR
Kwon et al. [32]	Journal of Bone Metabolism	Korea	Societal	Markov cohort model	QALY	Lifetime	Direct costs	5%, 5%	Takeda Pharmaceutical Company Limited, Korea
Ito et al. [36]	BMJ Open	USA	Healthcare	Markov cohort model	QALY	Lifetime	Direct costs	3%, 3%	NR
Mohd-Tahir et al. [17]	International Journal of Rheumatic Diseases	Malaysia	Healthcare	No	Fracture events	0–15 years	Direct costs	NR	NR
Cui et al. [34]	Osteoporosis International	China	Healthcare	Markov microsimulation model	QALY	Lifetime	Direct costs	3%, 3%	China Postdoctoral Science Foundation Grant, NSFC, Beijing Natural Science Foundation
Taheri et al. [33]	Iranian Journal of Pharmaceutical Research	Iran	Healthcare	Markov cohort model	QALY	Lifetime	Direct costs	7.2%, 5%	CinnaGen Corporation
Active drug(s) vs active drug(s)									
Parthan et al. [21]	Bone	Sweden	Healthcare	Markov cohort model	QALY	Lifetime	Direct costs	3%, 3%	NR
Venice et al. [10]	Journal of Clinical Densitometry	Mexico	Healthcare	No	All costs are compared	12 months	Direct costs	NR	NR
Waure et al. [26]	BioMed Research International	Italy	Healthcare	Markov cohort model	QALY	Lifetime	Direct costs	3%, 3%	Amgen Inc
Darbà et al. [25]	ClinicoEconomics and Outcomes Research	Spain	Healthcare	Markov cohort model	QALY	Lifetime	Direct costs	3%, 3%	Amgen SA Barcelona, Spain, and GSK
Miraci et al. [11]	International Journal of Pharmacy and Pharmaceutical Sciences	Albania	Healthcare	No	Average percentage of change in BMD	12 months	Direct costs	NR	NR

Table 1 (continued).

References	Journal	Country	Study perspective[a]	Model type	Outcome measure	Time horizon	Cost type	Discount rates (costs, QALY)	Funding source
Silverman et al. [22]	Journal of Osteoporosis	USA	Healthcare	Markov cohort model	QALY	Lifetime	Direct costs	3%, 3%	Amgen Inc
Chen et al. [31]	Patient Preference and Adherence	China	Healthcare	Markov microsimulation model	QALY	Lifetime	Direct costs	3%, 3%	NSFC and Jiangsu Research on Philosophy and Social Science in University of Education Department of Jiangsu Province
Karnon et al. [14]	Cost Effectiveness and Resource Allocation	Australia	Healthcare	Markov cohort model	QALY	10 years	Direct costs	5%, 5%	No funding
Azar et al. [13]	Medical journal of the Islamic Republic of Iran	Iran	Healthcare	Decision tree model	QALY	2 years	Direct costs	3%, 3%	NR
Mori et al. [18]	Osteoporosis International	Japan	Healthcare, societal and governmental	Markov microsimulation model	QALY	Lifetime	Direct and indirect costs	3%, 3%	NR
Mori et al. [19]	Osteoporosis International	USA	Societal	Markov microsimulation model	QALY	Lifetime	Direct costs	3%, 3%	Veterans Affairs Special Fellowship in Advanced Geriatrics
Moriwaki et al. [30]	Osteoporosis International	Japan	Healthcare	Markov microsimulation model	QALY	Lifetime	Direct costs	2%, 2%	Asahi Kasei Pharma Corporation
O'Hanlon et al. [35]	Clinical Therapeutics	USA	Healthcare	Markov cohort model	QALY	1.5 years; Lifetime	Direct costs	3%, 3%	NR
Yoshizawa et al. [29]	Archives of Osteoporosis	Japan	Societal	Markov cohort model	QALY	Lifetime	Direct costs	3%, 3%	NR
Chokchalermwong et al. [23]	Journal of the Medical Association of Thailand	Thailand	Societal	Markov microsimulation model	QALY	Lifetime	Direct costs	3%, 3%	NR
Coyle et al. [24]	Medical Decision Making Policy & Practice	Canada	Healthcare	Markov cohort model	QALY	Lifetime	Direct costs	1.5%, 1.5%	NR

Table 1 (continued).

References	Journal	Country	Study perspective[a]	Model type	Outcome measure	Time horizon	Cost type	Discount rates (costs, QALY)	Funding source
Hiligsmann et al. [27]	Osteoporosis International	France	Healthcare	Markov microsimulation model	QALY	Lifetime	Direct costs	3%, 3%	Teva and Theramex
Li et al. [15]	The Journal of the North American Menopause Society	China	Healthcare	Markov cohort model	QALY	40 years	Direct and indirect costs	3%, 3%	NSFC, Science and Technology Department of Fujian Province of China
Sequential therapies									
Hiligsmann et al. [28]	Seminars in Arthritis and Rheumatism	USA	Healthcare	Markov microsimulation model	QALY	Lifetime	Direct costs	3%, 3%	Radius Health, Inc., Waltham MA
Le et al. [16]	Annals of Pharmacotherapy	USA	Healthcare	Discrete-event simulation model	QALY	10 years	Direct costs	3%, 3%	Radius Health, Inc
Mori et al. [20]	JBMR PLUS	USA	Healthcare and societal	Markov microsimulation model	QALY	Lifetime	Direct and indirect costs	3%, 3%	JMDC Inc., SMS CO. and LTD

BMD bone mineral density, *NR* not reported, *NSFC* National Natural Science Foundation of China, *QALY* quality-adjusted life-year

[a]As stated by the authors

Table 2 presents characteristics of the studied population, the active intervention and comparator, year of costing valuation, sensitivity analysis, and the main results of the articles. Study populations differed between studies in BMD T-score, mean age, history of fracture, or even tolerance of oral bisphosphonates. Some studies included patients stratified for age and two studies included only a male population [21, 22].

Twelve active drugs were assessed in the studies, including various pharmacological treatments such as bisphosphonates (alendronate, etidronate, risedronate, ibandronate, and zoledronic acid), raloxifene, strontium ranelate, denosumab, and teriparatide, and including new agents such as abaloparatide, romosozumab, and gastro-resistant risedronate. Twelve studies included two or more active drugs in their analysis [13, 15–17, 21–28]. Oral bisphosphonates were included in 11 studies [13–15, 18, 21, 22, 24–26, 29, 30] and compared with other active interventions. There were three studies [16, 20, 28] considering sequential therapies as comparators, while six studies [15, 17, 30–32, 36] made the comparison between active osteoporotic drugs and calcium/vitamin D3 and ten studies [12, 18, 19, 23–25, 27–29, 33, 34] included no treatment as the comparator. Treatment duration in most studies was similar to randomized controlled trials, indications, or guidelines (e.g., 3 or 5 years for anti-resorptive agents, 12–24 months for anabolic agents). Both a deterministic sensitivity analysis (e.g., one-way, multivariate) and a probabilistic sensitivity analysis were conducted in 17 studies. Two studies [24, 26] applied only a probabilistic sensitivity analysis and three studies applied only a one-way sensitivity analysis [13, 32, 34]. Sensitivity analysis was not conducted in five studies [10–12, 17, 35]. We presented the WTP threshold in Table 2 as stated by the authors and no adjustment was made. The WTP threshold was shown to be different even through studies had been conducted in the context of the same country.

Table 2. Results of cost-effectiveness analyses of drugs for osteoporosis

References	Population (base case)	Comparators	Year of costing valuation	Sensitivity analysis	Results
Active drug(s) vs no treatment/calcium + vitamin D					
Golmohamdi et al. [12]	Postmenopausal women with osteoporosis	Zoledronic acid vs placebo	2013	No	One percent increase of BMD on femoral neck, hip trochanter, total hip, and lumbar spine requires further cost of US$386, US$264, US$388, and US$347, respectively. Zoledronic acid is a cheaper and better approach and can be considered as a dominant approach
Kwon et al. [32]	Postmenopausal women aged 55, 60, or 65 years with BMD T-scores from −2.0 to −2.4 at the femoral neck, and without previous osteoporotic fractures	Calcium/ vitamin D vs (raloxifene + calcium/ vitamin D) or (risedronate + calcium/vitamin D)	2014	One-way	In comparison with calcium/vitamin D supplements, drug therapy (raloxifene or risedronate + calcium/vitamin D) had an ICER of US$16,472 and US$6741 per QALY gained for treatment started at the age of 55 and 60 years, respectively. Given the WTP threshold (US$25,700), pharmaceutical treatment was cost effective. For older women starting medication at 65 years of age, pharmaceutical intervention was a dominant strategy
Ito et al. [36]	Women aged 85 years with BMD T-score ≤ −2.0 at the spine, hip, or radius who resided in nursing homes	(Zoledronic acid + calcium/vitamin D) vs usual care (calcium/ vitamin D)	2017	One-way probabilistic	In comparison with usual care, zoledronic acid had an ICER of US$207,400 per QALY gained. Given the WTP threshold (US$100,000), zoledronic acid was not cost effective

Table 2 (continued).

References	Population (base case)	Comparators	Year of costing valuation	Sensitivity analysis	Results
Mohd-Tahir et al. [17]	Adult patients diagnosed with osteoporosis related to glucocorticoid drugs use	Oral bisphosphonates (alendronate, risedronate or ibandronate) vs calcium/vitamin D	2014	No	Overall, in comparison with calcium/vitamin D, the use of bisphosphonates could not be considered cost effective for treatment of all patients with GIO. Bisphosphonates were considered cost effective if started in patients more than 60 years old. However, bisphosphonates were not cost effective in patients with GIOP secondary osteoporosis. The ICERs of bisphosphonates in patients with previous fracture or with rheumatoid arthritis were estimated at MYR 108,603 and MYR 25,699 per QALY gained, respectively. Given the WTP threshold (MYR 26,317), bisphosphonates were cost effective in patients with rheumatoid arthritis
Cui et al. [34]	Postmenopausal osteoporotic women	Zoledronic acid vs no treatment	2019	One-way	In comparison with no treatment, zoledronic acid had ICERs of US$26,637, US$22,129, US$20,338, US$19,285, US$18,181, US$16,680, US$15,047, and US$14,447 per QALY at FRAX threshold 0.02, 0.06, 0.07,0.08, 0.09, 0.1, 0.5, and 1, respectively. Zoledronic acid was cost effective when the 10-year probability of major osteoporotic fracture based on FRAX was above 7%

Table 2 (continued).

References	Population (base case)	Comparators	Year of costing valuation	Sensitivity analysis	Results
Taheri et al. [33]	Women aged 70 years, BMD T-score − 2.5 with previous fracture or BMD T-score -3.0 without prior fracture	Teriparatide vs no treatment	2018	One-way probabilistic	In comparison with no treatment, teriparatide was indicated to be more costly and associated with fewer fractures, more life-years, and more QALYs, with an ICER of IRR 254,750,619 per QALY gained. It could be considered as a cost-effective treatment in severe PMO at the WHO recommended threshold
Active drug(s) versus active drug(s)					
Parthan et al. [21]	Men aged 75 years and older with osteoporosis	Denosumab vs (generic alendronate, strontium ranelate, zoledronic acid, generic risedronate, ibandronate, and teriparatide)	2012	One-way probabilistic	Total lifetime costs for denosumab, generic alendronate, strontium ranelate, zoledronic acid, generic risedronate, ibandronate, and teriparatide were €31,004, €33,731, €34,788, €34,796, €34,826, €35,983, and €37,461, respectively. Total QALYs were 5.23, 5.15, 5.15, 5.17, 5.13, 5.12, and 5.22, respectively In comparison with other treatments, denosumab had the lowest costs and highest QALYs. Denosumab dominated all comparators
Venice et al. [10]	Postmenopausal women aged 45–79 years with low BMD in the lumbar spine and/or right hip, a Karnofsky index of 90–100	Alendronate vs zoledronic acid	2010	No	Compared with oral alendronate, zoledronic acid provided an annual savings of 15% of the direct costs for 1 year. Zoledronic acid infusion is also linked to a higher increase in BMD and compliance
Waure et al. [26]	Postmenopausal women aged 65 years with a BMD T-score < −4 SD	Denosumab vs (risedronate, generic and branded alendronate, ibandronate, and strontium ranelate)	2009	Probabilistic	The ICERs for denosumab, in comparison with risedronate, generic alendronate, branded alendronate, ibandronate, and strontium ranelate were estimated at €10,302, €18,047, €17,133, €2158, and €69 per QALY gained, respectively. Given the WTP threshold (€30,000), denosumab is cost effective

Table 2 (continued).

References	Population (base case)	Comparators	Year of costing valuation	Sensitivity analysis	Results
Darbà et al. [25]	Postmenopausal women age 65 years with BMD T-score ≤ 2.5 or less	Denosumab vs (alendronate, ibandronate, risedronate, strontium ranelate, and no treatment)	2013	Probabilistic, multivariate, univariate	The ICER for denosumab compared with no treatment, alendronate, risedronate, and ibandronate were estimated at €6823, €16,294, €4895, and €2205 per QALY gained, respectively. Given the WTP threshold (€20,000), denosumab is cost effective. Denosumab is a dominant treatment option in comparison with strontium ranelate
Miraci et al. [11]	Menopausal or postmenopausal women aged 50 years with T-score − 1 to -6, diagnosed for the first time	Ibandronate vs alendronate	NR	No	The cost/efficacy ratio (1% change of BMD) was 13.434 units for ibandronate and 31.677 units for alendronate type A1. Ibandronate is more effective and cost effective than alendronate in the treatment of osteoporosis
Silverman et al. [22]	Men with a mean age of 78 years with BMD T-score of − 2.12 and a vertebral fracture prevalence of 23%	Denosumab vs (generic alendronate, risedronate, ibandronate, teriparatide, and zoledronic acid)	2013	One-way probabilistic	Compared with generic alendronate, denosumab had an ICER of US $16,888 per QALY gained. Given the WTP threshold (US $100,000), denosumab is cost effective. Compared with risedronate, ibandronate, teriparatide, and zoledronic acid, denosumab is a dominant option
Chen et al. [31]	Postmenopausal women aged 65 years with BMD T-score ≤ -2.5 at the femoral neck and without previous fractures (initial population)	Raloxifene vs conventional treatment (calcitonin or alendronate or calcium/vitamin D)	2015	One-way probabilistic	Compared with conventional treatment, treatment with raloxifene had an ICER of US$36,891 per QALY gained. Given the WTP threshold of US$20,000), raloxifene was not cost effective
Kamon et al. [14]	Women with a mean age of 72 years (range 60–90 years) with a mean BMD T-score at the femoral neck of − 2.15, and with 24% of women having experienced a previous fracture	Patented denosumab vs generic alendronate	2012	Deterministic probabilistic	Compared with alendronate, denosumab had an ICER of AUD$246,749 per QALY gained. Given the WTP threshold (AUD$100,000), denosumab is not cost effective

Table 2 (continued).

References	Population (base case)	Comparators	Year of costing valuation	Sensitivity analysis	Results
Azar et al. [13]	Postmenopausal women aged over 60 years with BMD T-score ≤ 2.5 and with at least a previous spine, wrist, or hip fracture caused by osteoporosis	Risedronate vs (alendronate and teriparatide)	2014	One-way	Compared with risedronate, alendronate and teriparatide had ICERs of US$-2178 and US$483,783 per QALY gained. Given the WTP threshold (US$14,010), alendronate is the dominant and cost-effective treatment option. The treatment strategy of teriparatide is more expensive than risedronate and alendronate and is associated with very little increase in QALYs
Mori et al. [18]	Postmenopausal osteoporotic women without previous hip or vertebral fractures at various ages of therapy initiation (65, 70, 75, and 80 years)	Alendronate vs denosumab vs no treatment	2016	One-way probabilistic	For patients aged 75 and 80 years, denosumab was cost saving from any of the three perspectives, in comparison with alendronate For patients aged 65 and 70 years, denosumab had an ICER of US$25,700 and US$5000 per QALY gained, from a societal perspective, and did not exceed a WTP threshold (US$50,000). Therefore, denosumab was a cost-effective option
Mori et al. [19]	Community-dwelling non-Hispanic white women at different starting ages (65, 70, 75, and 80 years) and without previous hip, vertebral, or wrist fractures	Oral bisphosphonate vs no treatment, combined strategy (bisphosphonate + falls prevention exercise) and (falls prevention exercise only)	2014	One-way probabilistic	Compared with an oral bisphosphonate alone, the combined strategy had ICERs of US$202,020, US$118,460, US$46,870, and US$17,640 per QALY for patients aged 65, 70, 75, and 80 years, respectively. Given the WTP threshold (US $100,000), the combined strategy for patients ages 75 and 80 years was cost effective. The combined strategy provided better health at lower cost than the falls prevention exercise alone at ages 70, 75, and 80 years

Table 2 (continued).

References	Population (base case)	Comparators	Year of costing valuation	Sensitivity analysis	Results
Moriwaki et al. [30]	Women of 70 years with BMD T-score of − 2.5 and a previous vertebral fracture	Alendronate + basic treatment (placebo + calcium + vitamin D) vs basic treatment; (zoledronic acid + basic treatment) vs (alendronate + basic treatment)	2016	Deterministic probabilistic	For patients 70 years of age, zoledronic acid was dominated by alendronate. However, the incremental QALY is quite small in extent. Considering the advantage of annual zoledronic acid treatment in compliance and persistence, zoledronic acid may be a cost-effective treatment option compared to alendronate
O'Hanlon et al. [35]	Women of 70 years with BMD T-scores < − 2.5 and a previous vertebral fracture	Alternative bone-forming agent profiles vs the teriparatide reference case; alternative bone-forming agent profiles vs (sequential teriparatide + denosumab)	2016	No	In comparison with teriparatide, alternative bone-forming agent profiles produced a net monetary benefit of US$17,000,000 per 10,000 treated patients during the 1.5 years and US$80,000,000 over a lifetime horizon that included 3.5 years of maintenance treatment with denosumab
Yoshizawa et al. [29]	Women aged 75 years with BMD T-score − 2.87 and with a previous vertebral body fracture	Denosumab vs alendronate; alendronate vs no treatment	2016	Deterministic probabilistic	Compared with alendronate, denosumab had an ICER of US$40,241 per QALY gained. Assuming a WTP threshold (US$50,000), denosumab was cost effective
Chokchalermwong et al. [23]	Postmenopausal women aged ≥ 50 years with osteoporosis and without previous fractures	(Oral bisphosphonates, raloxifene, strontium ranelate, and denosumab) vs no treatment	2015	One-way probabilistic	In comparison with no treatment, none of the alternative drugs were cost effective at baseline case. For women from the age of 65 years, with a BMD T-score ≤ -2.5, oral bisphosphonates were the only drugs cost effective (the ICER was THB130,049), followed by denosumab and raloxifene, respectively. Strontium ranelate was dominated by no treatment

Table 2 (continued).

References	Population (base case)	Comparators	Year of costing valuation	Sensitivity analysis	Results
Coyle et al. [24]	Women aged 70–74 years with osteoporosis and without previous fractures who are able to tolerate oral bisphosphonates	Alendronate vs etidronate vs risedronate vs zoledronic acid vs denosumab vs no treatment	2017	Probabilistic	For patients who can tolerate oral bisphosphonates, in comparison with no treatment, alendronate, risedronate, zoledronic acid, and denosumab had ICERs of CAN$3751, CAN$85,557, CAN$83,503, and CAN$238,523 per QALY gained, respectively. Given the WTP threshold (CAN$50,000), alendronate was the only cost-effective drug. In comparison with alendronate, risedronate and etidronate were dominated, and zoledronic acid and denosumab were associated with a high ICER. For patients who are unable to tolerate oral bisphosphonates, dependent on age and fracture history, compared with no treatment, the ICER for zoledronic acid had a range from CAN$17,770 to CAN$94,365 per QALY. Denosumab was dominated by zoledronate or had an ICER greater than CAN$3.0 million
Hiligsmann et al. [27]	Postmenopausal women aged 60–80 years with BMD T-score ≤ -2.5 and/or prevalent vertebral fractures	Gastro-resistant risedronate vs (generic risedronate, alendronate and no treatment)	2017	One-way probabilistic	The ICER for GR risedronate, compared with alendronate, generic risedronate and no treatment, ranged from €2037 to €21,875 per QALY gained. Given the WTP threshold (€60,000), GR risedronate was cost effective In women aged 75 years and older, GR risedronate was even shown to be dominant

Table 2 (continued).

References	Population (base case)	Comparators	Year of costing valuation	Sensitivity analysis	Results
Li et al. [15]	Women aged over 60 years with BMD T-score ≤ 2.5 in the lumbar spine or femoral neck and without previous fractures	(Alendronate, zoledronic acid, raloxifene and teriparatide) vs calcium/vitamin D; (alendronate, raloxifene and teriparatide) vs zoledronic acid	2018	Univariate probabilistic	Compared with calcium/vitamin D, zoledronic acid had an ICER of US$7864 per QALY gained. Given the WTP threshold (US$28,624), zoledronic acid was cost-effective. The ICER of teriparatide versus zoledronic acid was US$470,797 per QALY gained, which exceeded the threshold. Alendronate and raloxifene were dominated by zoledronic acid
Sequential therapies					
Hiligsmann et al. [28]	Women aged 50–80 years with a BMD T-score ≤ -3.5 and without fracture history or with a BMD T-score − 2.5 to − 3.5 and a history of at least one osteoporotic fracture	(Sequential abaloparatide + alendronate) vs (sequential teriparatide + alendronate) and no treatment	2017	One-way probabilistic	In comparison with sequential TPTD/ALN therapy, sequential ABL/ALN therapy was dominant in all simulated populations. Compared with no treatment, in women with BMD T-score ≤ 3.5 (age over 70 years), the sequential ABL/ALN therapy was cost saving; and in women with a BMD T-score -2.5 to -3.5 and history of one osteoporotic fracture, the ICER was estimated at US$125,493, US$91,394, US$81,865, US$51,906, US$38,763, US$31,390, and US$28,086 for patients aged 50 years, 55 years, 60 years, 65 years, 70 years, 75 years, and 80 years, respectively. Given the WTP threshold (US$100,000), sequential ABL/ALN therapy was cost effective for patients aged over 55 years

Table 2 (continued).

References	Population (base case)	Comparators	Year of costing valuation	Sensitivity analysis	Results
Le et al. [16]	Postmenopausal women aged 68.8 years with osteoporosis	(Sequential abaloparatide + alendronate) vs (sequential teriparatide + alendronate) and (placebo + alendronate)	2017	One-way probabilistic	Compared with TPTD/ALN over a 10-year time horizon, ABL/ALN was dominant. In comparison with PBO/ALN, ABL/ALN had an ICER of US$333,266 per QALY gained. In high-risk women, ABL/ALN was also cost effective in comparison with TPTD/ALN, and had an ICER of US$188,891 per QALY gained relative to PBO/ALN
Mori et al. [20]	Community-dwelling white osteoporotic women aged 65, 70, 75, and 80 years with previous vertebral fracture	(Sequential teriparatide + alendronate) vs alendronate alone	2018	One-way probabilistic	Compared with alendronate alone from the societal perspective, sequential teriparatide/alendronate had an ICER of US$434,400, US$330,000, US$280,100, and US$290,800 per QALY for women aged 65, 70, 75, and 80 years, respectively. From a healthcare perspective, the ICERs were US$441,700, US$336,700, US$288,200, and US$299,100 per QALY, respectively. Given the WTP threshold (US$150,000), sequential teriparatide/alendronate was not cost effective unless the costs of generic/biosimilar teriparatide were heavily discounted with respect to the current brand cost

ABL abaloparatide, *ALN* alendronate, *AUD* Australian Dollar, *BMD* bone mineral density, *GIOP* glucocorticoid-induced osteoporosis, *GR* gastro-resistant, *ICER* incremental cost-effectiveness ratio, *IRR* Iranian Rial, *NR* not reported, *PBO* placebo, *PMO* postmenopausal osteoporosis, *PTH* parathyroid hormone, *QALY* quality-adjusted life-year, *MYR* Malaysian Ringgit, *THB* Thai Baht, *TPTD* teriparatide, *WTP* willingness to pay, *WHO* World Health Organization

Table 3 summarizes the results of the cost-effectiveness analysis between traditional oral bisphosphonates and other active drugs in 2019 US dollars. Annual drug costs for branded oral bisphosphonates had a range from US$123 to US$1874; the cost for generic oral bisphosphonates was much lower, from US$7 to US$458. The annual cost of denosumab differed steeply between countries, from US$608 to US$1811. Several studies made comparisons between denosumab and oral bisphosphonates.

Specifically, eight studies [14, 18, 21, 22, 24–26, 29] made comparisons between denosumab and oral alendronate, of which five studies [18, 22, 25, 26, 29] demonstrated that denosumab was cost effective, and one study [21] showed that denosumab was a dominant option if we applied US$100,000 per QALY gained as the WTP threshold. In addition, when compared with risedronate and ibandronate, denosumab was also shown to be cost effective [25, 26] or dominant [21, 22]. However, two studies [14, 24] showed that denosumab was not cost effective with large ICERs when compared with alendronate; this was caused by minimal incremental QALYs. In addition, comparisons between oral and non-oral bisphosphonates were performed in some studies. Three studies [15, 20, 24] were conducted between zoledronic acid and oral alendronate, with one study indicating that zoledronic acid was dominant [15]; in the other two studies, zoledronic acid was not cost effective or was dominated by alendronate [20, 24]. As a new formulation of bisphosphonates, gastro-resistant risedronate was cost effective in comparison with alendronate and risedronate in one study [27]. Furthermore, another study compared teriparatide with risedronate, showing that teriparatide was not cost effective. Overall, 67% studies (eight of a total 12 studies) or 82% of comparisons (23 of a total 28 studies) suggested that active interventions (denosumab, zoledronic acid, gastro-resistant risedronate, or teriparatide) were cost effective when compared with traditional oral bisphosphonates. Additionally, comparisons between active interventions were also made in some studies; two studies showed that denosumab was cost effective [26] or dominant [21] when compared with strontium ranelate. Zoledronate acid and teriparatide were dominated by denosumab in another two studies [21, 22].

Table 3. Cost-effective analyses between oral bisphophonates and other active drugs for osteporosis

References	Country	Intervention and comparator	Treatment duration (years)	Annual drug costs (intervention/comparator)	ICER
Coyle et al. [24]	Canada	Denosumab vs alendronate	2	US$663/US$123	US$2,376,812
Darbà et al. [25]	Spain	Denosumab vs alendronate	5	US$608/US$237	US$23,746
Waure et al. [26]	Italy	Denosumab vs generic alendronate	4	US$842/US$458	US$29,980
		Denosumab vs branded alendronate	4	US$842/US$502–528	US$28,462
Karnon et al. [14]	Australia	Patented denosumab vs generic alendronate	5	US$624/US$230	US$284,397
Mori et al. [18]	Japan	Denosumab vs alendronate (SP, 65 years)	5	US$799/US$246	US$27,375
		Denosumab vs alendronate (SP, 70 years)			US$5326
		Denosumab vs alendronate (HP, 65 years)			US$32,061
		Denosumab vs alendronate (HP, 70 years)			US$7137
		Denosumab vs alendronate (GP, 65 years)			US$28,546
		Denosumab vs alendronate (GP, 70 years)			US$6178
Parthan et al. [21]	Sweden	Denosumab vs generic alendronate	5	US$733/US$49	Dominant
Silverman et al. [22]	USA	Denosumab vs generic alendronate	5	US$1811/US$33	US$18,532
Yoshizawa et al. [29]	Japan	Denosumab vs alendronate	5	US$743/US$289	US$40,969
Darbà et al. [25]	Spain	Denosumab vs risedronate	5	US$608/US$414	US$7134
Waure et al. [26]	Italy	Denosumab vs risedronate	4	US$842/US$455	US$17,114
Parthan et al. [21]	Sweden	Denosumab vs generic risedronate	5	US$733/US$64	Dominant
Silverman et al. [22]	USA	Denosumab vs risedronate	5	US$1811/US$1874	Dominant
Darbà et al. [25]	Spain	Denosumab vs ibandronate	5	US$608/US$227	US$3213
Waure et al. [26]	Italy	Denosumab vs ibandronate	4	US$842/US$819	US$3585
Parthan et al. [21]	Sweden	Denosumab vs ibandronate	5	US$733/US$544	Dominant
Silverman et al. [22]	USA	Denosumab vs ibandronate	5	US$1811/US$1462	Dominant
Coyle et al. [24]	Canada	Zoledronic acid vs alendronate	2	US$298/US$123	US$535,359
Li et al. [15]	China	Zoledronic acid vs alendronate	3/5	US$536/US$555	Dominant
Moriwaki et al. [30]	Japan	Zoledronic acid vs alendronate	3	US$350/US$273	Dominant
Hiligsmann et al. [27]	France	GR risedronate vs alendronate	3	US$58/US$55	US$2401
Azar et al. [13]	Iran	Teriparatide vs generic risedronate	2	US$1757/US$7	US$522,424
Hiligsmann et al. [27]	France	GR risedronate vs generic risedronate	3	US$58/US$37	US$2759

GP governmental perspective, *GR* gastro-resistant, *HP* healthcare perspective, *ICER* incremental cost-effectiveness ratio, *SP* societal perspective

Table 4 presents three studies [16, 20, 28] that estimated the cost effectiveness of sequential therapies from the US perspective. Hiligsmann et al. [28] analyzed populations with different BMD T-scores at baseline, and the study of Mori et al. [20] assessed women at different ages and from both healthcare and societal perspectives. Hiligsmann et al. [28] and Le et al. [16] assessed sequential therapies starting with 1.5 years of abaloparatide or teriparatide, followed by 5 years of alendronate as the treatment duration. In the study of Mori et al. [20], 2 years of initial treatment with teriparatide was followed by 10 years of alendronate. The monthly drug costs for abaloparatide were similar between studies, at approximately US$1700; the cost of teriparatide was from US$1711 to US$3722 per month. Abaloparatide followed by alendronate was shown to be dominant when compared with teriparatide followed by alendronate in two studies [16, 28]. In addition, when compared with a placebo or no treatment, Hiligsmann et al. [28] showed that abaloparatide followed by alendronate was cost saving or cost effective in different populations. In the study of Le et al. abaloparatide or teriparatide followed by alendronate was not cost effective when compared with a placebo followed by alendronate [16]. Furthermore, Mori

et al. [20] compared sequential therapy (teriparatide followed by alendronate) with alendronate alone at different ages and economic perspectives, indicating that sequential therapy was not cost effective. The high drug costs of abaloparatide and teriparatide largely affected ICERs when compared with no treatment, a placebo, and with alendronate alone.

Table 4. Cost-effective analyses of sequential therapy

References	Country	Population	Comparator (treatment duration)	Monthly drug costs	ICER
Hiligsmann et al. [28]	USA	BMD T-score ≤ −3.5, age 70 or −3.5 ≤ BMD T-score ≤ −2.5 and history of one osteoporotic fracture, age 70 y	Sequential ABL(1.5y)/ALN(5y) vs sequential TPTD(1.5)/ALN(5y)	ABL US$1695 TPTD US$3387 ALN US$10	Dominant
Le et al. [16]	USA	Aged ≥ 65 y with a prior vertebral fracture	Sequential ABL(1.5y)/ALN(5y) vs sequential TPTD(1.5)/ALN(5y)	ABL US$1795 TPTD US$3722 ALN US$10	Dominant
Hiligsmann et al. [28]	USA	BMD T-score ≤ −3.5, age 70 y −3.5 ≤ BMD T-score ≤ −2.5 and history of one osteoporotic fracture, age 70 y	Sequential ABL(1.5y)/ALN(5y) vs no treatment	ABL US$1695 ALN US$10	Cost saving US$40,428
Le et al. [16]	USA	Aged ≥ 65 y with a prior vertebral fracture	Sequential ABL(1.5y)/ALN(5y) vs PBO/ALN(5y)	ABL US$1795 ALN US$10	US$347,577
			Sequential TPTD(1.5y)/ALN(5y) vs PBO/ALN(5y)	TPTD US$3722	US$991,854
Mori et al. [20]	USA	Age 65 y (SP)	Sequential TPTD(2y)/ALN(10y) vs ALN(10y)	TPTD US$1711 ALN US$17	US$442,263
		Age 70 y (SP)	Sequential TPTD(2y)/ALN(10y) vs ALN(10y)		US$335,973
		Age 75 y (SP)	Sequential TPTD(2y)/ALN(10y) vs ALN(10y)		US$285,170
		Age 80 y (SP)	Sequential TPTD(2y)/ALN(10y) vs ALN(10y)		US$296,063
		Age 65 y (HP)	Sequential TPTD(2y)/ALN(10y) vs ALN(10y)		US$449,695
		Age 70 y (HP)	Sequential TPTD(2y)/ALN(10y) vs ALN(10y)		US$342,794
		Age 75 y (HP)	Sequential TPTD(2y)/ALN(10y) vs ALN(10y)		US$293,416
		Age 80 y (HP)	Sequential TPTD(2y)/ALN(10y) vs ALN(10y)		US$304,514

ABL abaloparatide, *ALN* alendronate, *BMD* bone mineral density, *HP* healthcare perspective, *ICER* incremental cost-effectiveness ratio, *SP* societal perspective, *TPTD* teriparatide, *y* years

Critical Appraisal

Table 5 presents the results of the quality assessment of the design and conduct of economic evaluations in osteoporosis using the ESCEO-IOF guideline. Substantial differences were observed between studies with an average score of 17 out of 25 (range 2–25). Although some studies followed several recommendations of the guideline, room for improvement was observed for most studies.

Figure 2 shows the percentage of studies that fully, partially, or did not report the individual recommendations in the guideline. The most frequently unreported recommendations were ‘an additional effect after multiple fractures’ (i.e., an

additional effect on costs and/or utility should be modeled), 'adverse events' (i.e., important side effects that have an impact on costs and/or utility need to be included), and 'proportion attributed to the fracture' (i.e., a proportion of excess mortality attributed to the fracture should be included). In addition, some recommendations such as 'avoid hierarchy of fractures and restrictions after fracture events' (e.g., the absence of a non-hip fracture after a previous hip fracture or a limit to the number of fracture events) and 'multiple scenarios' (i.e., include age range and fracture risk levels) were frequently partially reported.

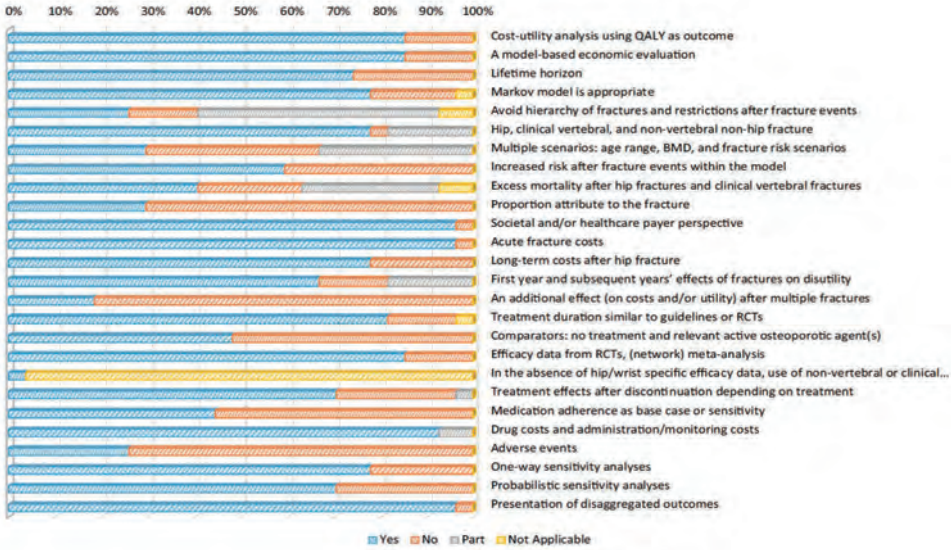

Figure 2. Proportion of studies meeting individual items recommended in ESCEO-IOF guideline (total studies: 27). BMD bone mineral density, QALY quality-adjusted life-year, RCTs randomized controlled trials

Table 5. Quality appraisal of cost-effectiveness analyses of drugs for osteoporosis using the ESCEO-IOF guideline

Item	Recommendation	Article references												
		[12]	[32]	[36]	[17]	[34]	[33]	[21]	[10]	[26]	[25]	[11]	[22]	[31]
Type of economic evaluation	Cost-utility analysis using QALY as the outcome	No	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes
Method for the conduct of an economic evaluation	A model-based economic evaluation	No	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes
Modeling technique	Lifetime horizon	No	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes
	Markov model is appropriate (6-month/1-year cycle length)	No	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes
	Avoid hierarchy of fractures and restrictions after fracture events	NA	Part	Part	No	Yes	Yes	Part	NA	Part	No	No	Part	Yes
	Hip, clinical vertebral, and non-vertebral non-hip fracture	Yes	Yes	Yes	Yes	Yes	Part	Yes	Part	Yes	Yes	No	Yes	Yes
Base-case analysis and population	Multiple scenarios: age range, BMD, and fracture risk scenarios	No	Yes	Part	Part	Part	No	No	No	No	Yes	No	No	Part
	The FRAX® or GARVAN® tools can be used to model fracture													
	Increased risk after fracture events within the model	No	Yes	Yes	No	Yes	No	No	No	No	Yes	No	No	Yes
Mortality	Excess mortality after hip fractures and clinical vertebral fractures	No	Yes	Yes	No	No	Part	Yes	No	No	Yes	No	Yes	Yes
	Proportion attributed to the fracture (e.g., 25–30%) mortality that is attributable to the fracture event	No	No	No	No	No	Yes	Yes	No	No	No	No	No	No
Fracture costs and utility	Societal and/or healthcare payer perspective	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
	Acute fracture costs	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
	Long-term costs after hip fracture (attributable to the fracture)	No	Yes	Yes	No	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes
	First year and subsequent years' effects of fractures on disutility	No	Part	Yes	No	Yes	Part	Yes	No	Yes	Yes	No	Yes	Yes
	National ICUROS data if available													
	An additional effect (on costs and/or utility) after multiple fractures	No	No	No	No	No	No	No	No	No	Yes	No	No	No
Treatment characteristics	Treatment duration similar to guidelines or RCTs	Yes	Yes	Yes	No	Yes	NA	Yes	No	Yes	Yes	No	Yes	Yes
	Comparators: no treatment and relevant active osteoporotic agent(s)	Yes	No	Yes	No	Yes	No	No	No	No	Yes	No	No	No
	Sequential therapy may be considered as intervention/comparators													
	Efficacy data from RCTs, (network) meta-analysis	No	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes
	In the absence of hip/wrist specific efficacy data, use of non-vertebral or clinical fracture efficacy data													
	Treatment effects after discontinuation depending on treatment	No	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes
	Medication adherence as base case or sensitivity	No	Yes	No	No	Yes	No	No	No	No	No	No	No	Yes
	Drug costs and administration/monitoring costs	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Adverse events	No	Yes	Yes	No	No	No	No	Yes	Yes	No	No	No	No
Sensitivity analyses	One-way sensitivity analyses	No	Yes	Yes	No	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes
	Probabilistic sensitivity analyses	No	No	Yes	No	No	Yes	Yes	No	Yes	Yes	No	Yes	Yes
Outcomes	Presentation of disaggregated outcomes, incremental costs, and outcomes for each intervention and incremental cost-effectiveness ratios	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Scoring		7	20	21	5.5	19.5	16.5	18.5	4.5	15.5	21	2	17.5	20.5

Item	Recommendation	Article references												
		[14]	[13]	[18]	[19]	[30]	[35]	[29]	[23]	[24]	[27]	[15]	[28]	[16]	[20]
Type of economic evaluation	Cost-utility analysis using QALY as outcome	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Method for the conduct of economic evaluation	A model-based economic evaluation	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Table 5 (continued).

Item	Recommendation	Article references													
		[14]	[13]	[18]	[19]	[30]	[35]	[29]	[23]	[24]	[27]	[15]	[28]	[16]	[20]
Modeling technique	Lifetime horizon	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
	Markov model is appropriate (6-month/1-year cycle length)	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes
	Avoid hierarchy of fractures and restrictions after fracture events	Yes	No	Part	Part	Yes	Part	Part	Part	Part	Yes	Part	Yes	Part	Part
	Hip, clinical vertebral, and non-vertebral non-hip fracture	Yes	Yes	Part	Yes	Yes	Yes	Part	Yes	Yes	Yes	Part	Yes	Yes	Yes
Base-case analysis and population	Multiple scenarios: age range, BMD, and fracture risk scenarios	Part	No	Part	Part	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Part	Part
	The FRAX® or GARVAN® tools can be used to model fracture														
	Increased risk after fracture events within the model	Yes	No	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Mortality	Excess mortality after hip fractures and clinical vertebral fractures	Part	No	Part	Part	Part	Yes	Part	No	Yes	Yes	Yes	Yes	Part	Part
	Proportion attributed to the fracture (e.g., 25–30%) mortality that is attributable to the fracture event	No	No	Yes	Yes	No	Yes	No	No	No	Yes	No	Yes	No	Yes
Fracture costs and utility	Societal and/or healthcare payer perspective	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Acute fracture costs	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Long-term costs after hip fracture (attributable to the fracture)	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	First year and subsequent years' effects of fractures on disutility	Yes	Yes	Yes	Yes	Yes	Part	Yes	Yes	Part	Yes	Yes	Yes	Yes	Part
	National ICUROS data if available														
	An additional effect (on costs and/or utility) after multiple fractures	Yes	No	No	No	No	No	No	Yes	No	Yes	No	Yes	No	No
Treatment characteristics	Treatment duration similar to guidelines or RCTs	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
	Comparators: no treatment and relevant active osteoporotic agent(s)	No	No	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
	Sequential therapy may be considered as intervention/comparators														
	Efficacy data from RCTs, (network) meta-analysis	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	In the absence of hip/wrist specific efficacy data, use of non-vertebral or clinical fracture efficacy data														
	Treatment effects after discontinuation depending on treatment	Yes	No	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Part	Yes	Yes	Yes
	Medication adherence as base case or sensitivity	Yes	No	Yes	Yes	Yes	No	Yes	No	No	Yes	No	Yes	Yes	Yes
	Drug costs and administration/monitoring costs	Yes	Yes	Yes	Yes	Yes	Part	Yes	Yes	Yes	Yes	Yes	Yes	Part	Yes
	Adverse events	No	No	No	No	No	No	No	Yes	No	No	No	Yes	Yes	No
Sensitivity analyses	One-way sensitivity analyses	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
	Probabilistic sensitivity analyses	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Outcomes	Presentation of disaggregated outcomes, incremental costs, and outcomes for each intervention and incremental cost-effectiveness ratios	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Scoring		20	11	21	21.5	20.5	15.5	20.5	19.5	18	24	16.5	25	20	20

Scoring: 'use ICUROS data', 'use FRAX® or GARVAN® tools', 'consider sequential therapy as intervention', and 'in the absence of hip/wrist specific efficacy data, use of non-vertebral or clinical fracture efficacy data as replacement' was not included in the scoring system

BMD bone mineral density, *NA* not applicable, *QALY* quality-adjusted life-year, *RCTs* randomized controlled trials

The results of reporting quality assessment are presented in Table 6; most recommendations were well reported with an average score of 6.8 out of 9 (range 0.5–9). The quality of reporting was suboptimal for 'treatment side effects' (i.e., describing the approaches and data sources used for costs and utilities effects of adverse events). Furthermore, 'medication adherence' (i.e., describing approaches and data sources used for modeling medication adherence) was poorly reported in some articles [10–13, 15, 17, 23, 26, 33], as well as 'treatment effect after discontinuation' in six articles (i.e., these studies did not assume a linear decrease of the effect after discontinuation for a period similar to the duration of treatment) [10–13, 23, 24].

Table 6. Quality of reporting of published articles assessing the cost effectiveness of drugs for osteoporosis using the ESCEO-IOF osteoporosis specific checklist

Item	Recommendation	Article references												
		[12]	[32]	[36]	[17]	[34]	[33]	[21]	[10]	[26]	[25]	[11]	[22]	[31]
Transition probabilities	Report the transition probabilities and how they were estimated (including increased fracture risk)	No	Yes	Yes	No	Yes	Yes	Yes	NA	Yes	Yes	No	Yes	Yes
Excess mortality after fractures	Describe approaches and data sources used for the excess mortality after fractures	No	Yes	Yes	No	No	Yes	Yes	NA	No	Yes	No	Yes	Yes
Fractures costs	Describe approaches and data sources used for fractures costs	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes
Fractures effects on utility	Describe approaches and data sources used for the effects of fractures on utility	No	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes
Treatment effect during treatment	Describe fully the methods used for the identification, selection, and synthesis of clinical effectiveness data (per fracture site)	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes
Treatment effect after discontinuation	Describe fully the methods used for the treatment effect after discontinuation	No	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes
Medication adherence	Describe approaches and data sources used for modeling medication adherence	No	Yes	Yes	No	Yes	No	Yes	No	No	Yes	No	Yes	Yes
Treatment costs	Describe approaches and data sources used for therapy costs	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Part	Yes	Yes	Yes	Yes	Yes
Treatment side effects	Describe approaches and data sources used for costs and utilities effects of adverse events	No	Yes	Yes	No	No	No	No	No	Yes	No	No	No	No
Scoring		2	9	9	3	7	7	8	0.5	7	8	1	8	8

Item	Recommendation	Article references												
		[14]	[13]	[18]	[19]	[30]	[35]	[29]	[23]	[24]	[27]	[15]	[28]	[16]	[20]
Transition probabilities	Report the transition probabilities and how they were estimated (including increased fracture risk)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Excess mortality after fractures	Describe approaches and data sources used for the excess mortality after fractures	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Fracture costs	Describe approaches and data sources used for fracture costs	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Fracture effects on utility	Describe approaches and data sources used for the effects of fractures on utility	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Treatment effect during treatment	Describe fully the methods used for the identification, selection, and synthesis of clinical effectiveness data (per fracture site)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Treatment effect after discontinuation	Describe fully the methods used for the treatment effect after discontinuation	Yes	No	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes
Medication adherence	Describe approaches and data sources used for modeling medication adherence	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes
Treatment costs	Describe approaches and data sources used for therapy costs	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Treatment side effects	Describe approaches and data sources used for costs and utilities effects of adverse events	No	No	No	No	No	No	No	Yes	No	No	No	Yes	Part	No
Scoring		8	5	8	8	8	8	8	6	7	8	6	9	8.5	8

NA not applicable

Key Drivers of Cost Effectiveness

Several drivers of cost effectiveness were identified, including baseline fracture risk, drug effect on the risk of fractures, drug cost, and medication adherence/persistence.

Baseline Fracture Risk

Most studies indicated that the increase of baseline fracture risk and the age of patients were associated with favorable results of cost-effectiveness analyses of osteoporotic drugs. For instance, Moriwaki et al. [30] indicated that the incremental costs and incremental QALYs of zoledronic acid compared with alendronate tended to be small, with an increase of T-scores. Moreover, Chokchalermwong et al. [23] reported that, compared to no treatment, the ICER of bisphosphonates was 130,049 THB per QALY when starting the drug from the age of 65 years, with a BMD T-score ≤ − 2.5. However, denosumab was cost effective from the age of 80 years and over.

Drug Effect on the Risk of Fractures

Twelve studies [15, 18, 20–23, 25, 29–32, 36] reported that the cost effectiveness result of osteoporotic drugs is most sensitive to changes in the effect of osteoporotic drugs on the risk of fractures. Silverman et al. [22] indicated that when the relative risk of hip fracture with denosumab is lowered from 0.38 (baseline) to 0.18, denosumab still dominates the generic alendronate. However, when this relative risk is increased to 0.78, denosumab is no longer a cost-effective option. This finding is similar to the study of Parthan et al. [21] and Yoshizawa et al. [29]. In addition, Moriwaki et al. [30] reported that the relative risk of hip fracture with zoledronic acid had a relatively strong effect on the estimated incremental net monetary benefit; compared to alendronate, zoledronic acid could be a cost-effective option if the relative risk was equal to 0.34 (lower limit).

Drug Cost

Variation in drug costs could lead to different cost-effectiveness results of anti-osteoporosis drugs. The strong effect of drug cost was reported in several studies [13, 14, 20, 23, 27–30, 33, 34]. Mori et al. [20] compared sequential therapy (teriparatide followed by alendronate) to alendronate alone and reported that results were most sensitive to the changes in the estimated cost of teriparatide. If the cost of a generic/biosimilar was estimated to be 15% of the brand (i.e., 85% less), the annual cost of teriparatide would be $6490 for a 65-year-old cohort; or if the cost of a generic/biosimilar was estimated to be 35% of the brand (i.e., 65% less), the annual cost of teriparatide would be $11,461 for a 75-year-old cohort; the ICERs of sequential teriparatide/alendronate were below the WTP threshold of $150,000/QALY. Moriwaki et al. [30] also reported that if the cost of zoledronic acid

was lowered by 30%, zoledronic acid could be a cost-effective option compared with alendronate. Additionally, Karnon et al. [14] indicated that there is a near-zero probability that denosumab is cost effective at a threshold of $100,000/QALY compared with alendronate at the current price; however, if the price of denosumab was reduced by 50%, the incremental cost per QALY gained falls to $50,068.

Medication Adherence/Persistence

Anti-osteoporosis medications have shown to be effective in reducing fracture risk; however, as a chronic disease, non-adherence to pharmacological treatment in osteoporosis is a well-recognized problem, which would result not only in deteriorating clinical outcomes, but also in decreased cost effectiveness of pharmacotherapy. Several studies [18, 20, 27, 29, 31, 34] reported that the persistence and adherence rates of osteoporosis medications have marked effects on the cost-effectiveness ratios. For instance, Mori et al. [18] indicated that denosumab was cost effective or even cost saving in comparison with weekly oral alendronate, mainly driven by the higher persistence rate of denosumab leading to higher efficacy. In addition, Hiligsmann et al. [27] also reported that the ICERs of gastro-resistant risedronate were markedly affected by the incremental difference in persistence between gastro-resistant risedronate and the active comparator treatment. Moreover, the study of Chen et al. [31] demonstrated that medication persistence and adherence had a great impact on clinical and cost effectiveness, high raloxifene persistence and adherence improved clinical effectiveness, but the costs were also higher. Raloxifene treatment became cost effective compared with a conventional treatment strategy if raloxifene persistence and adherence decreased by 30–50%.

DISCUSSION

This updated review identified 27 economic evaluations of drugs for osteoporosis published between July 2013 and 2019. Twelve active drugs were assessed in the studies, including bisphosphonates (alendronate, etidronate, risedronate, gastro-resistant risedronate, ibandronate, and zoledronic acid), romosozumab, raloxifene, strontium ranelate, denosumab, teriparatide, and abaloparatide. When compared with traditional oral bisphosphonates, 67% of the studies (eight of the total 12 studies) or 82% of the comparisons (23 of the total 28 comparisons) showed that the alternative drugs (denosumab, zoledronic acid, gastro-resistant risedronate, and teriparatide) were cost effective or dominant at the WTP threshold of US$100,000 per QALY gained. In particular, most studies suggested that denosumab was a cost-effective or dominant option compared with oral bisphosphonates. It should however be noted that recent studies have shown a rapid decrease of BMD and an

increased risk of vertebral fractures after discontinuation of denosumab [37, 38] and that these effects have not been included in economic evaluations; accordingly, the cost effectiveness of denosumab could be over-estimated.

Additionally, within the total 27 studies, the source of funding and the role of the funder were fully reported in only 14 studies. It is further interesting to note that three [22, 25, 26] out of eight studies conducted comparing denosumab with oral bisphosphonates, showing that denosumab was cost effective or dominant, were funded by industry. For the remaining five studies that did not mention funding or had no funding, only three (60%) indicated that denosumab was cost effective or dominant. The potential bias in industry-sponsored studies may therefore exist; however, given the limited studies, it is difficult to draw a clear conclusion. Previously, another study [39] comparing economic evaluations of bisphosphonates for the treatment of osteoporosis suggested that the funding source (industry vs non-industry) did not seem to significantly affect the reporting of ICERs below the US$20,000 and US$50,000 thresholds.

Furthermore, some new formulations of bisphosphonates also led to a higher health benefit than traditional oral tablet bisphosphonates. One of the included studies showed that gastro-resistant risedronate was cost effective when compared with traditional oral alendronate [27]. In addition, some recent studies also indicated that new effervescent formulation of alendronate could be an intriguing option in reducing the occurrence of adverse gastrointestinal events in anti-osteoporosis treatment, thus increasing adherence to therapy and anti-fracture efficacy [40]. More research is needed to investigate both the clinical and economic benefits of these new formulations of oral bisphosphonates.

With emerging evidence about the value of sequential therapy [41, 42], sequential therapy was included in three studies [16, 20, 28]. When mutually comparing anabolic agents, sequential treatment starting with abaloparatide followed by alendronate was shown to be dominant compared with sequential therapy starting with teriparatide followed by alendronate. These three studies also compared the cost effectiveness of sequential therapy with no treatment, placebo, or alendronate alone, indicating mixed results. Incremental cost-effectiveness ratios were strongly affected by the extremely high drug costs of anabolic agents. One study [20] demonstrated that their results were sensitive to the cost of teriparatide, reporting that the cost of a generic/biosimilar product needed to be 65–85% lower than the brand for sequential teriparatide/alendronate to be cost effective.

After our search period, another study suggested that sequential treatment starting with abaloparatide followed by alendronate was cost effective in comparison to generic alendronate monotherapy for US postmenopausal women aged ≥ 60 years at an increased risk of fractures. This also dominated sequential treatment starting with alendronate followed by abaloparatide and then again by alendronate [43].

This review updates a previous systematic review of cost-effectiveness analyses of drugs for postmenopausal osteoporosis [6]. The previous review identified 39 economic evaluations of drugs in postmenopausal osteoporosis published in the period 2008–13, an average of 6.5 studies per year. In our review, 4.5 studies per year were identified. Given that new osteoporosis medications continue to emerge on the market, the previous review does not include some medications that were not available that time, but are currently frequently used. The cost effectiveness of some medications was not conclusive because of the limited number of studies in the previous review, but the evidence became clearer in our updated review. In addition, with newer evidence being available after the publication of the previous review, the comparator in the economic evaluation might also changed. For example, vitamin D and calcium (or no treatment) were common comparators in previous studies. However, most studies (74%) in our review made comparisons between active osteoporotic interventions and traditional oral bisphosphonates, as well as mutual comparisons between different alternatives.

Moreover, in comparison with the previous review, where evaluations were mainly conducted in Europe, many evaluations in the updated review were conducted outside of Europe and especially in Asia, where osteoporosis is an increasing burden [44]. Thirty-three percent of the studies in our review applied the Markov microsimulation model in comparison with 21% in the previous review, indicating the increasing use of Markov microsimulation model in recent years, which supports the suggestion that the Markov microsimulation model is an evolution of a health economic model used in osteoporosis. The Markov individual state-transition model overcomes the memory-less nature of the Markov cohort model and is preferred to capture all the interactions between events and the changing risks of future fractures and mortality [45].

There are several extra findings identified in our review in comparison with the previous review. However, a comparison between the two studies remains difficult owing to the large heterogeneity in country setting, model structure, fracture risk, drug costs, and incorporation of medication adherence. In addition, the use of FRAX® or GARVAN® tools [46] indicates a slight increase (5%) in comparison with studies included in the previous review, but it is still inadequate (22%).

To assess the quality of included studies, unlike the general checklist applied in the previous review, we used an osteoporosis-specific guideline [7] to critically appraise the studies included in this review. In comparison with the general quality assessment tools relied on in the previous review, the osteoporosis-specific guideline serves as a minimum standard for all economic analyses in osteoporosis; the guideline's specificity enables better identification of unmet quality issues within recent studies and indicates some highly important criteria that should be met and improved in future studies, and further helps to reduce inter-study heterogeneity, thereby facilitating inter-study comparisons. Although a few studies followed several of the guideline's recommendations, given that most of the studies were published prior to the osteoporosis-specific guideline, the guide was not available to assist researchers in designing appropriate and high-quality economic evaluations, which may be why most studies did not adhere to several recommendations/criteria of the guideline and scored poorly for some criteria. Room for improvement was observed.

With regard to osteoporosis-specific recommendations, the frequently unmet/unreported recommendations such as 'an additional effect after multiple fractures on cost and/or utility', 'important adverse events', and 'a proportion of excess mortality attributed to the fracture' should be modeled/included in future studies. As for osteoporosis-specific checklist for reporting, considering several partially or not reported recommendations including 'treatment side effects', 'medication adherence', and 'treatment effect after discontinuation' would limit transparency, comparability, and use by decision maker; these missing or partially reported recommendations should receive more attention and be modeled/included in future studies. Therefore, the osteoporosis-specific guideline, which supplements the generally accepted methodologic standards, can be useful in improving the transparency, quality, and comparability of economic evaluations in osteoporosis, thus increasing its potential for use by decision makers and leading to a more effective allocation of resources [7].

Moreover, it is important that researchers should be aware of and use the guideline. Interestingly, since the publication of the ESCEO-IOF guideline (between October 2018 and August 2020), nine economic evaluations have used and referenced the guideline. Specifically, these nine studies all reported that the conduct of the economic evaluation adheres to this recent published osteoporosis-specific guideline. However, only four studies [20, 28, 34, 47] clearly showed how their studies followed the recommendations of the guideline. Therefore, to successfully implement this guideline, we recommend that future studies include a table in the main text or appendix stating clearly how the criteria were met, and/or the reasons for non-adherence (if appropriate), which would lead to improved study transparency.

Additionally, some key drivers of cost effectiveness were identified in this review, including baseline fracture risk, drug effect on the risk of fractures, drug cost, and medication adherence/persistence. These key drivers were frequently reported to be the most influential factors in the cost-effectiveness ratio, and should therefore be incorporated in future economic evaluations.

Although the present study followed recommendations for conducting reviews of economic evaluations [48], there may have been some potential limitations to our study. First, because of limited space in Table 2 and for clarity, only base-case results were included in our results analysis. Second, reviewers involved in the quality assessment proposed different opinions in scoring for some recommendations; discrepancies in rating were resolved by a third reviewer (MH) and reached a consensus with the first author (NL). In addition, differentiating between partially or fully reported was difficult for some recommendations; the final interpretation/assessment was performed by the first author in agreement with a third reviewer (MH), who assessed all papers. Third, although the osteoporosis-specific guideline aimed to complement and align with most general guidelines for economic evaluations, some differences can be observed. For instance, the ESCEO-IOF guideline treats one-way and probabilistic sensitivity analyses equally in scoring, while other guidelines may treat them separately. Fourth, some key drivers of cost effectiveness were identified during the review of the articles. We did not perform a systematic quantitative assessment to identify key drivers of cost effectiveness.

CONCLUSIONS

In comparison with evaluations listed in a previous review, recent economic evaluations were conducted in more countries, and included more active drugs and sequential therapy as comparators. A comparison between studies remains difficult. In total, this updated review included 27 studies on the cost effectiveness of drugs for osteoporosis, suggesting that some active interventions (denosumab, zoledronic acid, gastro-resistant risedronate, or teriparatide) were cost effective or dominant when compared with oral bisphosphates. However, given the limited number of studies on the cost-effectiveness of sequential therapy that have been conducted so far, further research would be needed to investigate adequate evidence of the beneficial effect of this new form of intervention over single anti-osteoporosis interventions alone. In addition, the results of a quality appraisal indicate that greater adherence to the osteoporosis-specific guideline is expected to improve the transparency, quality, and comparability of future studies.

ELECTRONIC SUPPLEMENTARY MATERIAL

Appendix 1 Search strategy of the systematic review (based on PICO criteria)

Database	Population	Outcome
Pubmed	"Bone Diseases, Metabolic"[Mesh:NoExp] OR "Osteoporosis" [Mesh] OR "Bone Demineralization, Pathologic"[Mesh] OR "Bone Density"[MeSH] OR "Osteoporotic Fractures"[Mesh] OR metabolic bone disease*[tiab] OR osteopenia*[tiab] OR osteoporo*[tiab] OR bone demineralization[tiab] OR bone demineralisation[tiab] OR pathologic decalcification*[tiab] OR bone densit*[tiab] OR bone mineral densit*[tiab] OR bone mineral content*[tiab] OR bone loss*[tiab] OR bone decreas* [tiab] OR bone deterioration*[tiab] OR osteoporotic fracture* [tiab]	"Costs and cost analysis"[MeSH:NoExp] OR "Cost-Benefit Analysis"[Mesh] OR "Health Care Costs"[Mesh] OR "Health Expenditures "[Mesh] OR "Economics, Pharmaceutical"[Mesh] OR "Economics,Medical"[Mesh] OR cost[tiab] OR costs[tiab] OR costing[tiab] OR costly[tiab] OR health expenditure*[tiab] OR pharmacoeconomic*[tiab] OR expenditure*[tiab] OR economic*[tiab] OR economy[tiab]
Embase	exp metabolic bone disease/ OR metabolic bone disease.ti,ab,kw. OR exp osteoporosis/ OR Osteoporosis.ti,ab,kw. OR exp bone demineralization/ OR bone demineralization.ti,ab,kw. OR exp bone density/ OR bone density.ti,ab,kw. OR exp fragility fracture/ OR fragility fracture.ti,ab,kw.	exp "cost utility analysis"/ OR exp "cost benefit analysis"/ OR exp "health care cost"/ OR exp "cost"/ OR exp "cost effectiveness analysis"/ OR exp "drug cost"/ OR exp pharmacoeconomics/ OR pharmacoeconomics.ti,ab,kw. OR "cost utility analysis".ti,ab,kw. OR "cost benefit analysis". ti,ab,kw. OR "health care cost".ti,ab,kw. OR "cost effectiveness analysis".ti,ab,kw. OR "drug cost".ti,ab,kw.

Appendix 2 Operationalization of ESCEO-IOF guideline

Table 1. Operationalization of recommendations for the conduct of an economic evaluation in osteoporosis

Items	Recommendations	Operationalization
Type of economic evaluation	Cost-utility analysis using QALY as outcome	*Yes: if uses method of cost-utility analysis and uses QALY as outcome
		*No: if does not use method of cost-utility analysis and does not use QALY as outcome
Method for the conduct of economic evaluation	A model-based economic evaluation	*Yes: if uses economic model to simulate fracture events
		*No: if does not use economic model to simulate fracture events
Modeling technique	Lifetime horizon	*Yes: if uses a lifetime horizon to capture long-term costs and outcomes
		*No: if does not use a lifetime horizon to capture long-term costs and outcomes
	Markov model is appropriate (6 months/1 year cycle length)	*Yes: if uses a Markov modeling technique to reflect health states
		*No: if does not use a Markov modeling technique to reflect health states
		*Not applicable: if the use of a Markov modeling technique is not applicable
	Avoid hierarchy of fractures and restrictions after fracture events	*Yes: if there is no hierarchy of fractures and no limit to the number of facture events
		*No: if there is a hierarchy of fractures and the number of facture events is limited
		*Part: if there is a hierarchy of fractures or a limit to the number of facture events
		*Not applicable: If there is no Markov model used, this item is not applicable
	Hip, clinical vertebral, and non-vertebral non-hip fracture	*Yes: if includes hip, clinical vertebral, and non-vertebral non-hip fractures
		*No: if does not include hip, clinical vertebral, and non-vertebral non-hip fractures
		*Part: if includes hip or clinical vertebral or non-vertebral non-hip fractures
Base-case analysis and population	Multiple scenarios: age range, BMD, and fracture risk scenarios	*Yes: if includes age range and fracture risk levels
		*No: if does not include age range and fracture risk levels
		*Part: if includes age range or fracture risk levels
	The FRAX® or GARVAN® tools can be used to model fracture risk	
	Increased risk after fracture events within the model	*Yes: if incorporates an increased risk after new fracture events
		*No: if does not incorporate an increased risk after new fracture events

Table 1 (continued)

Items	Recommendations	Operationalization
Mortality	Excess mortality after hip fractures and clinical vertebral fractures	*Yes: if models an excess mortality after hip fractures and clinical vertebral fractures
		*No: if does not model an excess mortality after hip fractures and clinical vertebral fractures
		*Part: if models an excess mortality after hip fractures or clinical vertebral fractures
	Proportion attribute to the fracture (e.g., 25–30%)	*Yes: if includes a proportion of excess mortality that is attributable to the fracture event
		*No: if does not include a proportion of excess mortality that is attributable to the fracture event
Fracture costs and utility	Societal and/or healthcare payer perspective	*Yes: if conducts evaluation from societal and/or healthcare payer perspective
		*No: if does not conduct evaluation from societal and/or healthcare payer perspective
	Acute fracture costs	*Yes: if includes the hospitalization cost related to fractures
		*No: if does not include the hospitalization cost related to fractures
	Long-term costs after hip fracture (attributable to the fracture)	*Yes: if includes long-term costs of nursing homes after hip fracture
		*No: if does not include long-term costs of nursing homes after hip fracture
	First year and subsequent years' effects of fractures on disutility	*Yes: if applies the disutility multipliers following fractures by fracture site in the first year and subsequent years
		*No: if does not apply the disutility multipliers following fractures by fracture site in the first year and subsequent years
		*Part: if applies the disutility multipliers following fractures by fracture site in the first year or subsequent years
	National ICUROS data if available	
	An additional effect (on costs and/or utility) after multiple fractures	*Yes: if models an additional effect on costs and/or utility after multiple fractures
		*No: if does not model an additional effect on costs and/or utility after multiple fractures

Table 1 (continued)

Items	Recommendations	Operationalization
Treatment characteristics	Treatment duration similar to guidelines or RCTs (e.g., 3 or 5 years for antiresoptive, 12-24 months for anabolics)	*Yes: if models treatment duration which is similar to RCTs, indications, or guidelines *No: if models treatment duration which is not similar to RCTs, indications, or guidelines
	Comparators: no treatment and relevant active osteoporotic agent(s)	*Yes: if includes comparator as no treatment and relevant active osteoporotic agent(s) *No: if does not include comparator as no treatment and relevant active osteoporotic agent(s)
	Sequential therapy may be considered as intervention/ comparators	
	Efficacy data from RCTs, (network) meta-analysis	*Yes: if extracts efficacy data from RCT or meta-analysis *No: if does not extract efficacy data from RCT or meta-analysis
	In the absence of hip/ wrist specific efficacy data, use of non-vertebral or clinical fracture efficacy data	
	Treatment effects after discontinuation depending on treatment	*Yes: if models effects of treatment discontinuation, which can be different between drug options *No: if does not model effects of treatment discontinuation
	Medication adherence as sensitivity	*Yes: if includes real-world medication adherence in sensitivity analyses of varying adherence levels *No: if does not include real-world medication adherence in sensitivity analyses
	Drug costs and administration/ monitoring costs(e.g., regular visit to GP,BMD mearsurement and injection/infusion cost)	*Yes: if includes drug costs and administration costs *No: if does not include drug costs and administration costs *Part: if includes drug costs or administration costs
	Adverse events	*Yes: if includes important side effects or extra-skeletal benefits of treatment *No: if does not include important side effects or extra-skeletal benefits of treatment
Sensitivity analyses	One-way sensitivity analyses	*Yes: if includes one-way sensitivity analyses *No: if does not include one-way sensitivity analyses
	Probabilistic sensitivity analyses	*Yes: if includes probabilistic sensitivity analyses *No: if does not include probabilistic sensitivity analyses
Outcomes	Presentation of disaggregated outcomes, incremental costs,and outcomes for each intervention and incremental cost-effectiveness ratios	*Yes: if presents disaggregated outcomes *No: if does not present disaggregated outcomes

Some recommendations (i.e., 'use ICUROS data', 'use FRAX® or GARVAN® tools', 'consider sequential therapy as intervention' and 'in the absence of hip/wrist specific efficacy data, use of non-vertebral or clinical fracture efficacy data as replacement') were not included in the scoring system; therefore no operationalization were provided.

Table 2. Operationalization of the osteoporosis-specific checklist

Items	Recommendations	Operationalization
Transition probabilities	Report the transition probabilities and how they were estimated (including increased fracture risk)	*Yes: if reports the transition probabilities and how they were estimated *No: if does not report the transition probabilities and how they were estimated *Not applicable: if there is no model used, this item is not applicable
Excess mortality after fractures	Describe approaches and data sources used for the excess mortality after fractures	*Yes: if describes approaches and data sources used for the excess mortality after fractures *No: if does not describe approaches and data sources used for the excess mortality after fractures
Fractures costs	Describe approaches and data sources used for fractures costs	*Yes: if describes approaches and data sources used for costs of fractures *No: if does not describe approaches and data sources used for costs of fractures
Fractures effects on utility	Describe approaches and data sources used for the effects of fractures on utility	*Yes: if describes approaches and data sources used for the effects of fractures on utility *No: if does not describe approaches and data sources used for the effects of fractures on utility
Treatment effect during treatment	Describe fully the methods used for the identification, selection, and synthesis of clinical effectiveness data (per fracture site)	*Yes: if fully describes the methods used for the identification, selection, and synthesis of clinical effectiveness data *No: if does not fully describe the methods used for the identification, selection, and synthesis of clinical effectiveness data
Treatment effect after discontinuation	Describe fully the methods used for the treatment effect after discontinuation	*Yes: if fully describes the methods used for the treatment effect after discontinuation *No: if does not fully describe the methods used for the treatment effect after discontinuation
Medication adherence	Describe approaches and data sources used for modeling medication adherence	*Yes: if describes approaches and data sources used for modeling medication adherence *No: if does not describe approaches and data sources used for modeling medication adherence
Treatment costs	Describe approaches and data sources used for therapy costs	*Yes: if describes approaches and data sources used for therapy costs *No: if does not describe approaches and data sources used for therapy costs
Treatment side effects	Describe approaches and data sources used for costs and utilities effects of adverse events	*Yes: if describes approaches and data sources used for costs and utilities effects of adverse events *No: if does not describe approaches and data sources used for costs and utilities effects of adverse events *Part: if describes approaches and data sources used for costs or utilities effects of adverse events

REFERENCES

1. Morizio P, Burkhart JI, Ozawa S. Denosumab: a unique perspective on adherence and cost effectiveness compared with Oral bisphosphonates in osteoporosis patients. *Annals of Pharmacotherapy*. 2018 Oct;52(10):1031-41.
2. Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. *Osteoporosis international*. 2006 Dec 1;17(12):1726-33.
3. Hernlund E, Svedbom A, Ivergård M, Compston J, Cooper C, Stenmark J, McCloskey EV, Jönsson B, Kanis JA. Osteoporosis in the European Union: medical management, epidemiology and economic burden. *Archives of osteoporosis*. 2013 Dec 1;8(1-2):136.
4. Kanis JA, Cooper C, Rizzoli R, Reginster JY. Executive summary of the European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Calcified tissue international*. 2019 Mar 15;104(3):235-8.
5. Parthan A, Kruse M, Yurgin N, Huang J, Viswanathan HN, Taylor D. Cost effectiveness of denosumab versus oral bisphosphonates for postmenopausal osteoporosis in the US. *Applied health economics and health policy*. 2013 Oct 1;11(5):485-97.
6. Hiligsmann M, Evers SM, Sedrine WB, Kanis JA, Ramaekers B, Reginster JY, Silverman S, Wyers CE, Boonen A. A systematic review of cost-effectiveness analyses of drugs for postmenopausal osteoporosis. *Pharmacoeconomics*. 2015 Mar 1;33(3):205-24.
7. Hiligsmann M, Reginster JY, Tosteson AN, Bukata SV, Saag KG, Gold DT, Halbout P, Jiwa F, Lewiecki EM, Pinto D, Adachi JD. Recommendations for the conduct of economic evaluations in osteoporosis: outcomes of an experts' consensus meeting organized by the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) and the US branch of the International Osteoporosis Foundation. *Osteoporosis International*. 2019 Jan 18;30(1):45-57.
8. Moher D, Liberati A, Tetzlaff J, Altman DG, Prisma Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS med*. 2009 Jul 21;6(7):e1000097.
9. http://www.oecd.org/std/purchasingpowerparitiespppsdata.htm#eurodenominatedseries
10. Chávez-Valencia V, Arce-Salinas CA, Espinosa-Ortega F. Cost-minimization study comparing annual infusion of zoledronic acid or weekly oral alendronate in women with low bone mineral density. *Journal of Clinical Densitometry*. 2014 Oct 1;17(4):484-9.
11. MiraÇi M, Demeti A, Ylli Z, KelliÇi S, Tarifa D. The cost-effectiveness of ibandronate and alendronate for the treatment of osteoporosis in a specialized clinic in Tirana. *Int J Pharm Pharm Sci.* 2015;7(10):207-11.
12. Golmohamdi FR, Abbasi M, Karyani AK, Sari AA. Cost-Effectiveness of Zoledronic Acid to Prevent and Treat Postmenopausal Osteoporosis in Comparison with Routine Medical Treatment. *Electronic physician.* 2016 Dec;8(12):3434.
13. Azar AA, Rezapour A, Alipour V, Sarabi-Asiabar A, Gray S, Mobinizadeh M, Yousefvand M, Arabloo J. Cost-effectiveness of teriparatide compared with alendronate and risedronate for the treatment of postmenopausal osteoporosis patients in Iran. *Medical journal of the Islamic Republic of Iran.* 2017;31:39.
14. Karnon J, Shafie AS, Orji N, Usman SK. What are we paying for? A cost-effectiveness analysis of patented denosumab and generic alendronate for postmenopausal osteoporotic women in Australia. *Cost*

Effectiveness and Resource Allocation. 2016 Dec;14(1):11.

15. Li N, Zheng B, Liu M, Zhou H, Zhao L, Cai H, Huang J. Cost-effectiveness of antiosteoporosis strategies for postmenopausal women with osteoporosis in China. *Menopause*. 2019 Aug 1;26(8):906-14.
16. Le QA, Hay JW, Becker R, Wang Y. Cost-effectiveness analysis of sequential treatment of abaloparatide followed by alendronate versus teriparatide followed by alendronate in postmenopausal women with osteoporosis in the United States. A*nnals of Pharmacotherapy.* 2019 Feb;53(2):134-43.
17. Mohd-Tahir NA, Thomas P, Mohamed-Said MS, Makmor-Bakry M, Li SC. Cost-effectiveness of bisphosphonates for prevention of fracture related to glucocorticoid-induced osteoporosis in Malaysia. *International journal of rheumatic diseases*. 2018 Mar;21(3):647-55.
18. Mori T, Crandall CJ, Ganz DA. Cost-effectiveness of denosumab versus oral alendronate for elderly osteoporotic women in Japan. *Osteoporosis International.* 2017 May 1; 28(5):1733-44.
19. Mori T, Crandall CJ, Ganz DA. Cost-effectiveness of combined oral bisphosphonate therapy and falls prevention exercise for fracture prevention in the USA. *Osteoporosis international*. 2017 Feb 1;28(2):585-95.
20. Mori T, Crandall CJ, Ganz DA. Cost-Effectiveness of Sequential Teriparatide/Alendronate Versus Alendronate-Alone Strategies in High-Risk Osteoporotic Women in the US: Analyzing the Impact of Generic/Biosimilar Teriparatide. *JBMR plus.* 2019 Nov;3(11):e10233.
21. Parthan A, Kruse M, Agodoa I, Silverman S, Orwoll E. Denosumab: a cost-effective alternative for older men with osteoporosis from a Swedish payer perspective. *Bone*. 2014 Feb 1;59:105-13.
22. Silverman S, Agodoa I, Kruse M, Parthan A, Orwoll E. Denosumab for elderly men with osteoporosis: a cost-effectiveness analysis from the US payer perspective. *Journal of osteoporosis.* 2015 Jan 1;2015.
23. Chokchalermwong S, Lochid-amnuay S, Kapol N, Wiroonpochid E, Ongphiphadhanakul B. Economic Evaluation of Drug Treatment for Fracture Prevention in Thai Postmenopausal Women with Osteoporosis without Fracture History. *Journal of the medical association of Thailand*. 2019 Jan 1;102(1):62-70.
24. Coyle D. Cost-Effectiveness of Pharmacological Treatments for Osteoporosis Consistent with the Revised Economic Evaluation Guidelines for Canada. *MDM policy & practice.* 2019 Jan;4(1):2381468318818843.
25. Darbà J, Kaskens L, Vilela FS, Lothgren M. Cost-utility of denosumab for the treatment of postmenopausal osteoporosis in Spain. *ClinicoEconomics and outcomes research: CEOR*. 2015;7:105.
26. De Waure C, Specchia ML, Cadeddu C, Capizzi S, Capri S, Di Pietro ML, Veneziano MA, Gualano MR, Kheiraoui F, La Torre G, Nicolotti N. The prevention of postmenopausal osteoporotic fractures: results of the health technology assessment of a new antiosteoporotic drug. *BioMed research international.* 2014;2014.
27. Hiligsmann M, Reginster JY. Cost-effectiveness of gastro-resistant risedronate tablets for the treatment of postmenopausal women with osteoporosis in France. *Osteoporosis International*. 2019 Mar 5;30(3):649-58.
28. Hiligsmann M, Williams SA, Fitzpatrick LA, Silverman SS, Weiss R, Reginster JY. Cost-effectiveness of sequential treatment with abaloparatide vs. teriparatide for United States women at increased risk of fracture. *InSeminars in arthritis and rheumatism* 2019 Oct 1;49(2) :184-196.
29. Yoshizawa T, Nishino T, Okubo I, Yamazaki M. Cost-effectiveness analysis of drugs for osteoporosis treatment in elderly Japanese women at high risk of fragility fractures: Comparison of denosumab and

weekly alendronate. A*rchives of osteoporosis.* 2018 Dec 1;13(1):94.

30. Moriwaki K, Mouri M, Hagino H. Cost-effectiveness analysis of once-yearly injection of zoledronic acid for the treatment of osteoporosis in Japan. *Osteoporosis International.* 2017 Jun 1;28(6):1939-50.
31. Chen M, Si L, Winzenberg TM, Gu J, Jiang Q, Palmer AJ. Cost-effectiveness of raloxifene in the treatment of osteoporosis in Chinese postmenopausal women: impact of medication persistence and adherence. *Patient preference and adherence.* 2016;10:415.
32. Kwon JW, Park HY, Kim YJ, Moon SH, Kang HY. Cost-effectiveness of pharmaceutical interventions to prevent osteoporotic fractures in postmenopausal women with osteopenia. *Journal of bone metabolism.* 2016 May 1;23(2):63-77.
33. Taheri S, Fashami FM, Peiravian F, Yousefi P. Teriparatide in the Treatment of Severe Postmenopausal Osteoporosis: A Cost-Utility Analysis. I*ranian journal of pharmaceutical research: IJPR.* 2019;18(2):1073.
34. Cui L, He T, Jiang Y, Li M, Wang O, Jiajue R, Chi Y, Xu Q, Xing X, Xia W. Predicting the intervention threshold for initiating osteoporosis treatment among postmenopausal women in China: a cost-effectiveness analysis based on real-world data. *Osteoporosis International.* 2020 Feb;31(2):307-16.
35. O'Hanlon CE, Parthan A, Kruse M, Cartier S, Stollenwerk B, Jiang Y, Caloyeras JP, Crittenden DB, Barron R. A model for assessing the clinical and economic benefits of bone-forming agents for reducing fractures in postmenopausal women at high, near-term risk of osteoporotic fracture. *Clinical therapeutics.* 2017 Jul 1;39(7):1276-90.
36. Ito K. Cost-effectiveness of single-dose zoledronic acid for nursing home residents with osteoporosis in the USA. *BMJ open.* 2018 Sep 1;8(9):e022585.
37. Anastasilakis AD, Polyzos SA, Makras P, Aubry-Rozier B, Kaouri S, Lamy O. Clinical features of 24 patients with rebound-associated vertebral fractures after denosumab discontinuation: systematic review and additional cases. *Journal of Bone and Mineral Research.* 2017 Jun;32(6):1291-6.
38. Cummings SR, Ferrari S, Eastell R, Gilchrist N, Jensen JE, McClung M, Roux C, Törring O, Valter I, Wang AT, Brown JP. Vertebral fractures after discontinuation of denosumab: a post hoc analysis of the randomized placebo-controlled FREEDOM trial and its extension. *Journal of Bone and Mineral Research.* 2018 Feb;33(2):190-8.
39. Fleurence RL, Spackman DE, Hollenbeak CS. Does the funding source influence the results in economic evaluations?: A case study in bisphosphonates for the treatment of osteoporosis. *PharmacoEconomics.* 2010 Jan 1;28(4):295-306.
40. Invernizzi M, Cisari C, Carda S. The potential impact of new effervescent alendronate formulation on compliance and persistence in osteoporosis treatment. *Aging clinical and experimental research.* 2015 Apr 1;27(2):107-13.
41. Cosman F, Nieves JW, Dempster DW. Treatment sequence matters: anabolic and antiresorptive therapy for osteoporosis. *Journal of bone and mineral research.* 2017 Feb;32(2):198-202.
42. Kanis JA, Cooper C, Rizzoli R, Reginster JY. Review of the guideline of the American College of Physicians on the treatment of osteoporosis. *Osteoporosis International.* 2018 Jul 1;29(7):1505-10.
43. Hiligsmann M, Williams SA, Fitzpatrick LA, Silverman SS, Weiss R, Reginster JY. Cost-Effectiveness of Sequential Treatment with Abaloparatide followed by Alendronate vs. Alendronate Monotherapy in Women at Increased Risk of Fracture: a US Payer Perspective. *InSeminars in Arthritis and Rheumatism*

2020 Feb 13;50 (3):394-400.

44. Xia W, Cooper C, Li M, Xu L, Rizzoli R, Zhu M, Lin H, Beard J, Ding Y, Yu W, Cavalier E. East meets West: current practices and policies in the management of musculoskeletal aging. *Aging clinical and experimental research.* 2019 Oct 1:1-23.
45. Si L, Winzenberg TM, Palmer AJ. A systematic review of models used in cost-effectiveness analyses of preventing osteoporotic fractures. *Osteoporosis International.* 2014 Jan 1;25(1):51-60.
46. Kanis JA, Harvey NC, Johansson H, Liu E, Vandenput L, Lorentzon M, Leslie WD, McCloskey EV. A decade of FRAX: how has it changed the management of osteoporosis?. *Aging Clinical and Experimental Research.* 2020 Feb 11:1-0.
47. Peng K, Yang M, Tian M, Chen M, Zhang J, Wu X, Ivers R, Si L. Cost-effectiveness of a multidisciplinary co-management program for the older hip fracture patients in Beijing. *Osteoporosis International.* 2020 Mar 26:1-9.
48. Jefferson T, Demicheli V, Vale L. Quality of systematic reviews of economic evaluations in health care. *Jama*. 2002;287(21):2809–12.

CHAPTER 3

Cost Effectiveness Analyses of Interventions for Osteoporosis in Men: A Systematic Literature Review

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ABSTRACT

Background Osteoporosis is often considered to be a disease of women. Over the last few years, owing to the increasing clinical and economic burden, the awareness and imperative for identifying and managing osteoporosis in men have increased substantially. With the approval of agents to treat men with osteoporosis, more economic evaluations have been conducted to assess the potential economic benefits of these interventions. Despite this concern, there is no specific overview of costeffectiveness analyses for the treatment of osteoporosis in men.

Objectives This study aims (1) to systematically review economic evaluations of interventions for osteoporosis in men; (2) to critically appraise the quality of included studies and the source of model input data; and (3) to investigate the comparability of results for studies including both men and women.

Methods A literature search mainly using MEDLINE (via Ovid) and Embase databases was undertaken to identify original articles published between 1 January, 2000 and 30 June, 2022. Studies that assessed the cost effectiveness of interventions for osteoporosis in men were included. The Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases and the International Osteoporosis Foundation osteoporosis-specific guideline was used to assess the quality of design, conduct, and reporting of included studies.

Results Of 2973 articles identified, 25 studies fulfilled the inclusion criteria, classified into economic evaluations of active drugs (n=8) or nutritional supplements (n=4), intervention thresholds (n=5), screening strategies (n=6), and postfracture care programs (n=2). Most studies were conducted in European countries (n=15), followed by North America (n=9). Bisphosphonates (namely alendronate) and nutritional supplements were shown to be generally cost effective compared with no treatment in men over 60 years of age with osteoporosis or prior fractures. Two other studies suggested that denosumab was cost effective in men aged 75 years and older with osteoporosis compared with bisphosphates and teriparatide. Intervention thresholds at which bisphosphonates were found to be cost effective varied among studies with a 10-year probability of a major osteoporotic fracture that ranged from 8.9 to 34.2% for different age categories. A few studies suggested cost effectiveness of screening strategies and post-fracture care programs in men. Similar findings regarding the cost effectiveness of drugs and intervention thresholds in women and men were captured, with slightly greater incremental cost-effectiveness ratios in men. The quality of the studies included had an average score of 18.8 out of 25 (range 13-23.5). Hip fracture incidence and mortality risk

were mainly derived from studies in men, while fracture cost, treatment efficacy, and disutility were commonly derived from studies in women or studies combining both sexes.

Conclusions Anti-osteoporosis drugs and nutritional supplements are generally cost effective in men with osteoporosis. Screening strategies and post-fracture care programs also showed economic benefits for men. Cost-effectiveness and intervention thresholds were generally similar in studies conducted in both men and women, with slightly greater incremental cost-effectiveness ratios in men.

Key Points for Decision Makers

- Medicines for osteoporosis and nutritional supplements are cost effective in men aged 60 years and older with prior fractures or with a diagnosis of osteoporosis. Based on expert societies' practice guidelines, reimbursement for these active drugs should be considered as part of the standard of care.
- Similar findings regarding the cost effectiveness of drugs and intervention thresholds in women and men with osteoporosis were captured, with a moderate increase in incremental cost-effectiveness ratios in men. Fracture risk reduction is the primary consideration in the treatment for osteoporosis irrespective of sex.

INTRODUCTION

Osteoporosis is commonly recognized as a disease in women following menopause, which is often overlooked in men mainly because there is no aging process in men analogous to menopause with a resultant rapid loss of bone mass. In men, secondary osteoporosis is more frequent; common causes include glucocorticoid excess, hypogonadism, and alcohol abuse [1]. In particular, androgen deficiency (hypogonadism) that can result from androgen deprivation therapy for prostate cancer is accompanied by a decline in bone mineral density (BMD) within the first 6–9 months of initiation and an increase in fracture risk of nearly 20% after 5 years of therapy [2].

Osteoporotic fractures are not limited to postmenopausal women; one in five men (compared to one in two women) over 50 years of age will sustain an osteoporotic fracture in their remaining lifetime [3, 4]. A US study reported that men account for 29% of osteoporotic fractures and 25% of the cost of fractures (with the total annual expense for all osteoporosis-related fractures in the USA at approximately $57 billion in 2018, which is comparable to the annual cost of €56 billion estimated in 2019 for Europe) [5–7]. In addition, the consequences of fractures, in particular hip fractures, were shown to be greater in men than in women [8], as suggested by the increased relative risk of a subsequent fracture and mortality following the initial fractures. This rising clinical and economic burden of osteoporosis in men has led to increased attention recently.

With the availability of pharmacological therapies as well as the implementation of post-fracture care programs for the prevention of secondary fractures, cost-effectiveness assessments of these interventions have been conducted to inform decision making or to determine cost-effective osteoporosis intervention thresholds (i.e., 10-year fracture probabilities at which treatment can be cost effective). Most of the studies were conducted in women and are summarized in previous systematic reviews [9, 10]. To our knowledge, there is currently no overview of published cost-effectiveness analyses for the treatment of osteoporosis in men. Such information may inform payers about the economic value of treating osteoporosis in men, identify relevant gaps and opportunities, and provide pertinent information for further economic studies. Therefore, the objective of this study is to systematically review cost-effectiveness analyses in men with osteoporosis, to critically appraise these studies, to investigate the source of model input data, and to assess the comparability of costeffectiveness results among studies including both men and women.

METHODS

The 2020 Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement [9] was used for the entire procedure (identify, select, appraise, and synthesize studies) of this systematic review. A protocol was registered in PROSPERO with the registration number CRD42022331820 [11]. Covidence software as a systematic review management tool was used to manage search results, including the removal of duplicates, abstract and title screening, and full-text screening.

Literature Search

The literature search was restricted to articles published between January 2000 and June 2022 (given the first osteoporosis-related study including men was published in 2004). MEDLINE (via Ovid) and Embase databases were searched initially in January 2022 and were updated in June 2022 using adapted search strategies (based on the previous search strategies of Li et al. [9]). As suggested by a guideline for systematic reviews of economic evaluations [12], two other economic evaluation databases were also searched: the National Health Service Economic Evaluation Database and the Cost-Effectiveness Analysis Registry, using two keywords ("osteoporosis" and "men"). However, it should be noted that updates to National Health Service Economic Evaluation database were discontinued in 2015. In addition, reference lists and citations of included articles and previously published systematic reviews (of economic evaluations of interventions for osteoporosis) were reviewed as additional studies of interest. Details of search strategies are in the Electronic Supplementary Material (ESM).

Study Selection

Peer-reviewed studies from any country or type of healthcare system were considered eligible if they contained a full economic evaluation comparing at least an intervention and a comparator in both costs and outcomes, either placebo or an alternative intervention as comparator(s). Eligible studies are cost-effectiveness analyses, cost-utility analyses, cost-benefit analyses, and cost-minimization analyses for any type of interventions or management (drugs, screening, intervention thresholds, adherence intervention, nutrition, fracture liaison services [FLS]). Particularly, studies were included if they reported outcomes for men (studies in men only, or studies including both men and women but separately reporting cost-effectiveness results for men). Nonoriginal articles (e.g., case reports, reviews, letters to the editors, conference abstracts, opinion pieces, protocols) and studies published in non-English language were excluded [13].

Using these criteria, two reviewers (NL, CB) independently identified studies through title and abstract screening. Then, these reviewers conducted a full-text screening to determine eligibility, discrepancies were resolved by a consensus meeting with a third reviewer (MH).

Data Extraction and Synthesis

Included studies were classified into four categories: active drugs or nutritional supplements, intervention threshold, screening strategies, and post-fracture care programs. A standardized data extraction form was developed and pre-tested on a sample of five of the eligible studies to extract data from these studies by one independent reviewer (NL) and a second reviewer (CB) checked these results to assure the quality of the form. Study characteristics extracted included publication information (author, year of publication, journal), study design (country setting, target population, economic perspective, model type, time horizon, intervention and comparators, intervention duration, outcome measure, cost type, year of valuation, discount rates), study outcomes (base-case and sensitivity analyses), and funding source. It should be noted that for studies combining both women and men, only male data were extracted. The outcomes varied according to study categories. For studies investigating the cost effectiveness of active drugs or nutritional supplements, screening strategies, and post-fracture care programs, incremental cost-effectiveness ratios (ICERs) were extracted as originally reported along with the conclusions on the cost effectiveness of the intervention determined by the authors. Furthermore, information on the duration of drug/nutrition treatment, screening time and drug/nutrition treatment, and the duration of post-fracture care programs as the intervention duration was also collected. Intervention thresholds (i.e., the threshold of fracture probability at which an intervention becomes cost effective) [14] were extracted as the main study outcome of the intervention threshold studies, and the duration of drug/nutritional treatment was reported as the intervention duration.

Studies that reported outcomes separately for both men and women were further categorized into two groups according to the type of outcome (ICER or intervention threshold). In studies using ICER as the outcome, the difference in ICERs was displayed using +/− with the data from the women as the reference (+ means men had higher ICERs than women, − means men had lower ICERs than women), and the conclusion on cost effectiveness was also shown for both sexes using Yes/No. For studies using an intervention threshold as the outcome, thresholds were separately reported for men and women, and absolute change was calculated with the data from the women as the reference.

Quality Assessment

The conduct and reporting quality of included studies were appraised by two independent researchers (NL, CB) using the osteoporosis-specific guideline formulated by the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases and the International Osteoporosis Foundation (ESCEO-IOF) [15]. Discrepancies were discussed and resolved with a third researcher (MH). The ESCEO-IOF guideline includes 29 items; four items (a. the FRAX® or GARVAN® tools can be used to model fracture; b. national ICUROS data if available; c. sequential therapy may be considered as intervention/comparators; d. in the absence of hip/wrist-specific efficacy data, use of non-vertebral or clinical fracture efficacy data) were not included in the scoring system as these recommendations are not compulsory or not applicable to all eligible studies. Each of the remaining 25 items was scored with a Yes, No, Partial, Not reported, or Not applicable to indicate if the requirement was fulfilled. A quality score was obtained for each study by assigning a score of 1 for any Yes, a score of 0.5 for Partially, and a score of 0 for No, not reported, and not applicable, for a total possible score of 25 points.

Additionally, another form was used to extract the source of the most important model parameters (i.e., fracture incidence, fracture cost, baseline utility and fracture disutility, baseline mortality, and excess mortality, treatment efficacy, side effects, and medication adherence/persistence) and to determine whether these data were derived from studies in men exclusively, from women, or from studies including both sexes.

RESULTS

Study Selection

Figure 1 shows the PRISMA flow chart for the identification of studies. The database search identified 2973 records, of which 782 were removed as duplicates. Fifty-two full economic evaluations were identified after title and abstract screening. Of those, 14 articles were conference abstracts and therefore rejected; 38 studies were thus assessed for eligibility by full-text screening. Thirteen studies were subsequently excluded for reasons such as duplicates (n = 5), not the original article (n = 2), and not the target population or not specific outcomes for men (n = 6), leaving a total of 25 articles included in the analysis. No new studies were identified through screening of reference lists and citations of included articles.

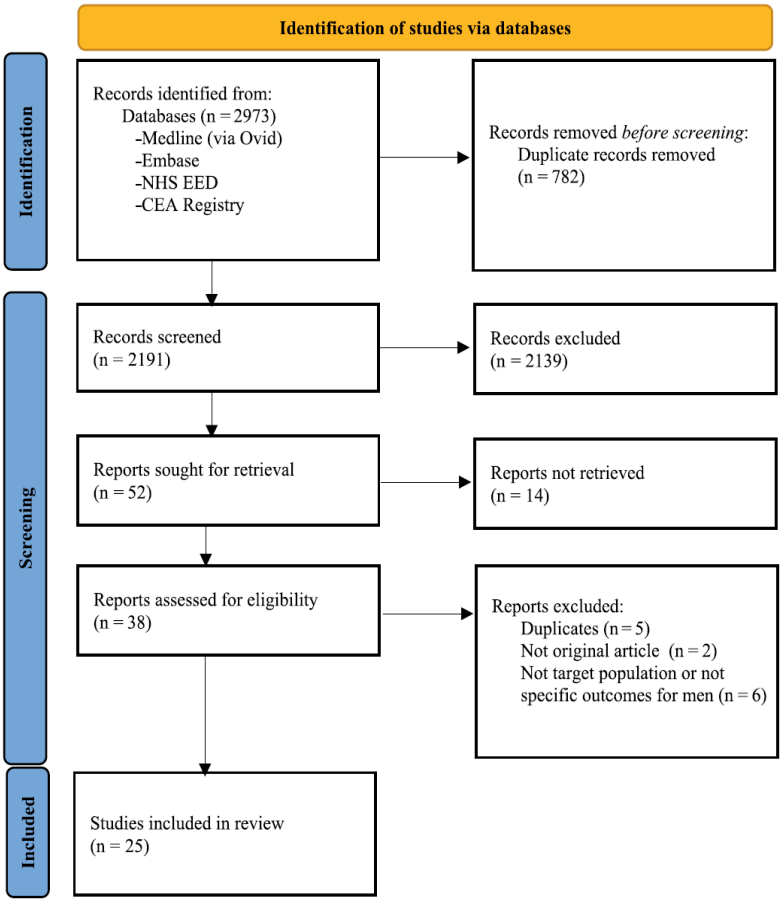

Figure 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA 2020) flowchart of study selection. CEA Registry Cost-Effectiveness Analysis Registry, NHS EED National Health Service Economic Evaluation Database

Overview of Included Studies

Table 1 presents the characteristics of included studies. Most assessed active drugs or nutritional (primarily vitamin D alone or with calcium) supplements (n=12) followed by screening strategies (n=6), intervention thresholds (n=5), and post-fracture care programs (n=2). Sixteen out of 25 studies were conducted before 2015, only two studies [16, 17] were published in the past 5 years. Most studies were conducted in European countries (n=15), especially in Sweden (n=4), Belgium (n=3), and the UK (n=3), followed by the USA (n=9), with one study performed in Asia.

Regarding the study population, nine studies included only men and 16 included both men and women. A wide variability in patient characteristics was observed, including patients with osteoporosis, low bone mass, or at high risk of fracture; patients or the general population with or without prior/recent fracture, men with prostate cancer beginning androgen deprivation therapy, and patients prescribed oral glucocorticoids. A healthcare perspective (typically including direct medical and non-medical costs) was used in 15 studies incorporating only direct costs, seven with a societal perspective (also including productivity losses arising from patients' inability to work) and the remaining three studies with both societal and healthcare perspectives. All included studies used a Markov model consisting of a Markov microsimulation model (n=10) and a Markov cohort model (n=15). Most studies (n=21) considered a lifetime horizon; only four studies [16, 18–20] applied a fixed time horizon such as 5, 6, or 10 years. One study [21] used the life-year as the outcome while the remaining studies used quality-adjusted life-years (QALYs). Most studies (n= 15) applied 3% as the discount rate for both costs and QALYs. Nine studies were funded by industry and another nine by national public funds while seven studies did not mention the source of funding (n=3) or had no funding (n=4).

Table 1. Characteristics of studies assessing the cost-effectiveness of interventions for men with osteoporosis

Reference	Year of publication	Country	Population	Perspective	Model type	Outcome measure	Time horizon	Cost type	Discount rate (costs, QALY)	Funding source
Active drugs or nutritional supplements										
Hiligsmann et al. [27]	2017	France	General population (women and men) aged 60 years and older	Healthcare	Markov microsimulation	QALY	Lifetime	Direct costs	3%, 3%	CNIEL
Ethgen et al. [21]	2015	Belgium	General population, patients (women and men) with osteoporosis and a PVF or hip fracture aged 50 years and older	Healthcare	Markov microsimulation	LY	Lifetime	Direct costs	3%, 1.5%	None
Silverman et al. [25]	2015	USA	Men aged 75 years and older with osteoporosis	Healthcare	Markov cohort	QALY	Lifetime	Direct costs	3%, 3%	Amgen Inc.
Hiligsmann et al. [28]	2014	Belgium	Patients (women and men) aged 60 years and older with osteoporosis	Healthcare	Markov microsimulation	QALY	Lifetime	Direct costs	3%, 1.5%	SMB Belgium
Parthan et al. [26]	2014	Sweden	Men aged 75 years and older with osteoporosis	Healthcare	Markov cohort	QALY	Lifetime	Direct costs	3%, 3%	NR
Hiligsmann et al. [40]	2013	Belgium	Men aged 65–90 years with BMD T-score ≤ -2.5 or PVF	Healthcare	Markov microsimulation	QALY	Lifetime	Direct costs	3%, 1.5%	Servier

Table 1. (continued)

Reference	Year of publication	Country	Population	Perspective	Model type	Outcome measure	Time horizon	Cost type	Discount rate (costs, QALY)	Funding source
Kouta et al. [23]	2010	USA	Men aged 70 years with locally advanced or high-risk localized prostate cancer starting a 2-year course of ADT after radiation therapy	Societal	Markov cohort	QALY	Lifetime	Direct costs	3%, 3%	None
Kreck et al. [18]	2008	Germany	Patients (women and men) with osteopenia or osteoporosis due to inflammatory bowel disease	Societal	Markov cohort	QALY	10 years	Direct and indirect costs	5%, 5%	German Federal Ministry of Education and Research
Schousboe et al. [22]	2007	USA	White men aged 65 years and older with osteoporosis	Societal	Markov microsimulation	QALY	Lifetime	Direct and indirect costs	3%, 3%	National Institutes of Health funding
Van Staa et al. [20]	2007	UK	Patients (women and men) aged 40 years and older who were prescribed an oral GC and who were registered in the GPRD	Healthcare	Markov microsimulation	QALY	6 years	Direct costs	6%, 1.5%	None
Borgstrom et al. [24]	2004	Sweden	Men aged 55–80 years with low bone mass and radiographically identified CV	Societal and healthcare	Markov cohort	QALY	Lifetime	Direct and indirect costs	3%, 3%	Merck and Co., Inc.

Table 1. (continued)

Reference	Year of publication	Country	Population	Perspective	Model type	Outcome measure	Time horizon	Cost type	Discount rate (costs, QALY)	Funding source
Fleurence et al. [39]	2004	UK	Patients (women and men) aged 70 years and older who were at high risk and general risk of fracture	Healthcare	Markov cohort	QALY	Lifetime	Direct costs	6%, 6%	Eli Lilly and UK Medical Research Council
Intervention threshold										
Chan et al. [29]	2017	Taiwan, China	Patients (women and men) aged 50 years and older at different probabilities of MOF and hip fracture	Healthcare	Markov cohort	QALY	NR	Direct costs	1.36%, 1.36%	Grant DOH102-TD-M-113-102006
Makras et al. [30]	2015	Greece	Patients (women and men) aged 50 years and older at different probabilities of MOF and hip fracture	Healthcare	Markov cohort	QALY	Lifetime	Direct costs	NR	NR
Lippuner et al. [32]	2012	Switzerland	Patients (women and men) aged 50 years and older at different probabilities for a MOF	Healthcare	Markov cohort	QALY	Lifetime	Direct costs	3%, 3%	MSD Switzerland AG
Tosteson et al. [31]	2008	USA	Patients (women and men) aged 50 years and older at different probabilities for a hip fracture	Healthcare	Markov cohort	QALY	Lifetime	Direct costs	3%, 3%	National Osteoporosis Foundation and National Institutes of Health

Table 1. (continued)

Reference	Year of publication	Country	Population	Perspective	Model type	Outcome measure	Time horizon	Cost type	Discount rate (costs, QALY)	Funding source
Kanis et al. [33]	2005	Sweden	Patients (women and men) aged 50 years and older at different probabilities for a hip fracture	Healthcare and societal	Markov cohort	QALY	Lifetime	Direct costs	3%, 3%	IOF, Pfizer, Alliance for Better Bone Health, IGEA, Lilly Research Centre, Hologic, Novartis, Wyet, and Roche
Screening strategies										
Ito et al. [17]	2020	USA	Community-dwelling men aged 65 years who had fallen at least once in the past year	Societal	Markov cohort	QALY	Lifetime	Direct cost	3%, 3%	NR
Pisu et al. [16]	2019	USA	Patients (women and men) aged 65 years and older with an abdominal CT scan but without a recent DXA, and without osteoporosis treatment, or had no disqualifying conditions for an osteoporosis diagnostic screen	Healthcare	Markov cohort	QALY	5 years	Direct costs	3%, NR	National Institutes of Health
Nayak et al. [34]	2016	USA	Community-dwelling men aged 50 years and older	Societal	Markov microsimulation	QALY	Lifetime	Direct costs	3%, 3%	National Institutes of Health

Table 1. (continued)

Reference	Year of publication	Country	Population	Perspective	Model type	Outcome measure	Time horizon	Cost type	Discount rate (costs, QALY)	Funding source
Schousboe et al. [35]	2013	USA	Caucasian patients (women and men) aged 55 years and older without a prior clinical fracture but with femoral neck osteoporosis and a 10-year hip fracture risk of ≥3%	Healthcare	Markov microsimulation	QALY	Lifetime	Direct costs	3%, 3%	National Institutes of Health
Ito et al. [37]	2009	USA	Community-dwelling white men aged 70 years without a history of clinical osteoporotic fractures	Societal	Markov cohort	QALY	Lifetime	Direct costs	3%, 3%	None
Schwenkglenks et al. [36]	2007	Switzerland	Patients (women and men) aged 50 years with osteoporosis	Healthcare	Markov microsimulation	QALY	Lifetime	Direct costs	3%, 3%	Merck Sharp and Dohme-Chibret AG
Post-fracture care programs										
DPhil et al. [38]	2017	UK	Patients (women and men) aged 60 years and older with a hip fracture	Healthcare and societal	Markov microsimulation	QALY	Lifetime	Direct costs	3.5%, 3.5%	NIHR HS and DR
Johansson et al. [19]	2008	Sweden	Community-dwelling persons (women and men) aged 65 years and older	Societal	Markov cohort	QALY	6 years	Direct and indirect costs	3%, 3%	Stockholm County Council

ADT androgen deprivation therapy, *BMD* bone mineral density, *CT* computerized tomography, *CV* clinical vertebral fracture, *DXA* dual-energy X-ray absorptiometry, *GC* glucocorticoid, *GPRD* general practice research database, *LY* life-year, *MOF* major osteoporosis fracture, *NR* not reported, *PVF* prevalent vertebral fracture, *QALY* quality-adjusted life-year

Cost Effectiveness of Interventions

Table 2 reports information on the intervention and comparator, intervention duration, year of costing valuation, sensitivity analysis, and the main results of included articles. In eight studies that included active drugs (n = 8), bisphosphonates were included as the intervention in five studies [18, 20, 22–24] along with BMD testing or calcium/cholecalciferol and were compared to no treatment or nutrition supplements (sodium fluoride and/or calcium/cholecalciferol) alone. Two of these studies [20, 24] indicated that the bisphosphonate strategy alone was considered cost effective in patients aged 55 years and older with a fracture history, low bone mass, rheumatoid arthritis, or use of high-dose glucocorticoid doses (15 mg/day). Another two studies [22, 23] reported bone densitometry followed by bisphosphonates was cost effective for men aged 70 years or older with osteoporosis caused by androgen deprivation therapy, or for men aged over 65 years with a self-reported prior clinical fracture and for men aged 80–85 years with no prior fracture. Denosumab was included in two studies [25, 26] in comparison with bisphosphonates (generic alendronate, zoledronate, risedronate, and ibandronate) and teriparatide, with findings suggesting denosumab was cost effective in men aged 75 years and older with osteoporosis. Three studies [21, 27, 28] included vitamin D-fortified dairy products or calcium/vitamin D supplementation and indicated nutritional supplements were cost effective in men aged over 80 years, and in men over 60 years of age with osteoporosis when compared with usual care or no treatment.

In five studies [29–33] that investigated cost-effective intervention thresholds, three used FRAX® as the measure of fracture risk. Bisphosphonates were used as the intervention in four studies (branded alendronate was used in two studies; however, the name of the bisphosphonate used in the other two studies was not mentioned) [29–32] compared with no treatment or calcium and vitamin D alone; the drug intervention was found to be cost effective with a 10-year probability of a major osteoporotic fracture (MOF) or hip fracture that ranged from 8.9 to 34.2% and from 0.8 to 7.5% for different age categories, respectively. The intervention thresholds at which an intervention is cost effective generally increases with the age of the population.

In six studies [16, 17, 34–37] that compared the screening strategy (followed by drug treatment) with no screening strategy or non-intervention strategy (both screening type and medications were not included), four studies [16, 17, 34, 35] reported that screening via bone density was cost effective in men aged 65 years and older. The screen-and-treat strategy was not cost effective compared with no intervention for all age groups as reported by Schwenkglenks and Lippuner [36].

One study [35] reported that bone densitometry followed by drug therapy was cost effective for men aged 55, 75, and 80 years without a prior fracture when the body weight thresholds were below 67, 101, and 108 kg, respectively.

Two studies [19, 38] indicated that post-fracture care programs were cost effective compared with the usual care or do-nothing alternative in men aged over 60 years with a recent fracture. For studies including active drugs, treatment costs encompassing drug costs, physician visit costs (and frequency) as well as BMD testing costs (and frequency) were removed from the analysis but are included in the ESM. These costs differ greatly among studies (with teriparatide having the highest annual cost and generic alendronate having the lowest annual cost in general). Most studies assumed a physician visit once per year and BMD testing once every 2 years.

Table 2. Main results of studies assessing the cost-effectiveness of interventions for men with osteoporosis

Reference	Intervention	Comparators	Intervention duration	Year of valuation	Results	
					Base-case analysis	Sensitivity analysis
Active drugs or nutritional supplements						
Hiligsmann et al. [27]	Vit D-fortified dairy products	Usual care	1 year (two dairy products per day)	2015 EUR	In men aged over 60 years, the intake of two Vit D-fortified dairy products per day had an ICER of €106,113/QALY compared to usual care. The ICER was below a threshold of €30,000 / QALY in men aged over 80 years	One-way SA
Ethgen et al. [21]	CA/Vit D dietary supplementation	The absence of appropriate intake	1 year: a daily dairy supplementation containing 1000 mg of CA and 800 IU of Vit D	2014 EUR	The daily intake of Vit-D-rich dairy products was cost effective in general men aged over 70 years and in male patients at increased risk of osteoporotic fractures	None
Silverman et al. [25]	Denosumab	Bisphosphonates (generic alendronate, branded zoledronate, branded risedronate, branded ibandronate), and teriparatide	5 years: denosumab, bisphosphonates 2 years: teriparatide	2013 USD	Denosumab had an ICER of $16,888/QALY compared to generic alendronate and dominated all other treatments	One-way and probabilistic SA
Hiligsmann et al. [28]	CA/Vit D supplementation	No treatment (no CA/Vit D supplementation)	3 years	2012 EUR	Compared to no treatment, CA/Vit D supplementation had an ICER of €23,477/QALY and €10,250/QALY in men aged 60 years and 70 years, respectively, which was cost saving in men aged 80 years, suggesting CA/Vit D supplementation was cost effective for men with osteoporosis aged over 60 years	One-way and probabilistic SA
Parthan et al. [26]	Denosumab	Bisphosphonates (generic alendronate, branded zoledronate, generic risedronate, branded ibandronate), strontium ranelate, and teriparatide	5 years: bisphosphonates, strontium ranelate, denosumab 2 years: teriparatide	2012 EUR	Compared to other treatments, denosumab had the lowest costs and highest QALYs, indicating denosumab dominated all other treatments	One-way and probabilistic SA

Table 2. (continued)

Reference	Intervention	Comparators	Intervention duration	Year of valuation	Results	
					Base-case analysis	Sensitivity analysis
Hiligsmann et al. [40]	Strontium ranelate	No treatment (no active drug treatment)	3 years	2010 EUR	Compared to no treatment, strontium ranelate had an ICER of €49,798/QALY and €25,584/QALY using ITT and PPS efficacy data, respectively in entire patients. The ICER falls below thresholds in partial patients with a BMD T-score ≤ − 2.5 or with PVF. Strontium ranelate could be considered cost effective compared with no treatment for male osteoporosis	One-way and probabilistic SA
Kouta et al. [23]	Selective branded alendronate therapy + BMD test	(Universal branded alendronate therapy without BMD test) or (no BMD test and no therapy)	5 years: branded alendronate	2008 USD	The ICERs for the strategy of a BMD test and selective alendronate therapy for patients with osteoporosis and universal alendronate therapy without a BMD test were US$66,800/QALY and $178,700/QALY, respectively, which was cost effective for those with osteoporosis	One-way SA
Kreck et al. [18]	Branded ibandronate+ calcium/colecalciferol	Fluoride strategy (sodium fluoride + calcium/colecalciferol), and calcium strategy (calcium/colecalciferol alone)	42 months	2004 EUR	The calcium strategy dominated the fluoride strategy. Compared to the calcium strategy, the ibandronate strategy had an ICER of €1,042,295/QALY in male patients aged over 65 years with a BMD T-score at baseline of −3.0. The ibandronate strategy is not cost effective	One-way, two-way, and probabilistic SA

Table 2. (continued)

Reference	Intervention	Comparators	Intervention duration	Year of valuation	Results	
					Base-case analysis	Sensitivity analysis
Schousboe et al. [22]	Branded bisphosphonate + bone densitometry	No intervention (no drug treatment, no screening)	5 years: oral bisphosphonate	2004 USD	Compared with no intervention, the densitometry and follow-up treatment strategy had an ICER less than USD 50,000/QALY for men aged 65 years or older with a prior clinical fracture and for men aged 80 years or older without a prior fracture. The strategy may be cost effective in these patients	One-way and probabilistic SA
Van Staa et al. [20]	Branded bisphosphonate + GC	GC	5 years: GC, bisphosphonate	2003/2004 IB	With the use of 5mg GCs daily, compared to no bisphosphonate, the bisphosphonate strategy had an ICER of £40,000, £43,000, £35,000 in men aged < 60 years, 60–79 years, and 80+ years, respectively. With the use of GC 15 mg daily, which was £22,000, £34,000, and £33,000, respectively. Bisphosphonates can be considered cost effective in patients with higher fracture risks and younger patients with a fracture history, low body mass index, rheumatoid arthritis, or using high GC doses	One-way SA
Borgstrom et al. [24]	Branded alendronate	No treatment (no active drug treatment)	5 years	2001 EUR	Compared to no treatment, alendronate had an ICER of €14,843/QALY and €5314/QALY from the societal and healthcare perspective, respectively. Alendronate was projected to be cost effective	One-way and probabilistic SA

Table 2. (continued)

Reference	Intervention	Comparators	Intervention duration	Year of valuation	Results	
					Base-case analysis	Sensitivity analysis
Fleurence et al. [39]	Scenario 1: VitD/CA Scenario 2: VitD/CA + hip protectors	Scenario 1: hip protectors and no treatment (no VitD/CA) Scenario 2: no treatment (no VitD/CA, no hip protector)	All preventive treatments would be used during the remaining lifetime of the patients. Patients would need two hip protectors every 2 years	2000 USD	Vit D and CA alone was dominated by hip protectors in all patients. In the general-risk male population, compared to no treatment, hip protectors had an ICER of USD 47,426/QALY. In the male high-risk population, hip protectors had an ICER of USD 17,017/QALY, which was cost effective	Probabilistic SA
Intervention threshold						
Chan et al. [29]	Branded alendronate	No treatment (no active drug treatment)	5 years	2010 USD	The hip fracture and MOF intervention threshold were 6% and 12.5% for men, respectively. For both MOF and hip fracture, interventions were cost effective only for men aged 55–85 years in the NHIA model, and for men aged over 75 years in the fracture model	One-way SA

Table 2. (continued)

Reference	Intervention	Comparators	Intervention duration	Year of valuation	Results	
					Base-case analysis	Sensitivity analysis
Makras et al. [30]	(18% generic +82% branded) bisphosphonate-like intervention (combination of drugs)	Standard treatment (CA/Vit D)	5 years	2013 EUR	Drug intervention was found to be cost effective with a 10-year probability for a MOF at or above 20%, 9.5%, 9.5%, and 11% for men aged 50–54, 55–64, 65–74, and over 75 years, respectively. In addition, the drug intervention aiming at reducing the fracture risk was found to be cost effective with a 10-year probability for a hip fracture at/or above 1.4%, 1.2%, 2.3%, and 5.7% for men aged 50–54, 55–64, 65–74, and over 75 years, respectively	One-way SA
Lippuner et al. [32]	Branded alendronate	No treatment (no active drug treatment)	5 years	2008 CHF	Drug intervention was cost effective with a 10-year probability for a MOF at or above 15.1% (range 9.9–19.9%). Using the translational approach, the treatment was cost-effective or cost saving after the age of 55 years in men who had a previous fragility fracture	One-way SA
Tosteson et al. [31]	Generic bisphosphonate-like therapy	No treatment (no active drug treatment)	5 years	2005 USD	The treatment was cost effective when the 10-year hip fracture probability reached approximately 3% (range 2.4–4.9%) in men. The results were similar across race/ethnicity groups	One-way SA

Table 2. (continued)

Reference	Intervention	Comparators	Intervention duration	Year of valuation	Results	
					Base-case analysis	Sensitivity analysis
Kanis et al. [33]	A hypothetical intervention	No treatment (no active drug treatment)	5 years	2001 USD	The treatment in men was cost effective with a 10-year hip fracture probability that ranged from 2.0% at 50 years to 6.46% at 80 years	One-way SA
Screening strategies						
Ito et al. [17]	Screening strategy followed by bisphosphonate	Usual care (no screening)	Drug therapy: 5 years of alendronate therapy for those diagnosed with osteoporosis	2019 USD	Compared to usual care, the screening strategy was cost effective having an ICER of USD 33,169/QALY. The screening strategy would become more effective and less costly for men 77 years and older	One-way and probabilistic SA
Pisu et al. [16]	Biomechanical computed tomography	Usual care; no screening	BCT screening: in year 1 Drug therapy: 2 years of generic alendronate therapy for 50% of patients	2016 USD	Compared to both usual care and no screening strategy, the BCT program was a dominant strategy, it provided greater clinical benefit at a lower cost. BCT was cost saving compared to usual care and no screening ($7000)	One-way SA
Nayak et al. [34]	Different bone density screening strategies	No screening	Screening: repeat screening intervals of 5 years or 10 years Drug therapy: 5 years of bisphosphonate therapy for those screened positive with a particular strategy, or those who sustained a clinical fracture	2014 USD	No screening was a less effective and more expensive option than all other strategies, indicating no screening was "dominated" by screening with DXA or the Osteoporosis Self-Assessment Tool at all evaluated screening initiation ages and repeat screening intervals	One-way and probabilistic SA

Table 2. (continued)

Reference	Intervention	Comparators	Intervention duration	Year of valuation	Results	
					Base-case analysis	Sensitivity analysis
Schousboe et al. [35]	Bone density screening + (generic + branded) bisphosphonate therapy	No intervention (no screening, no drug treatment)	Drug therapy: 5 years	2010 USD	The bone densitometry followed by drug therapy was cost effective for men aged 55, 75, and 80 years without a prior fracture when the body weight thresholds were below 67, 101, and 108 kg, respectively	One-way and probabilistic SA
Ito et al. [37]	Selective bone densitometry using the Osteoporosis Self-Assessment Tool	No bone densitometry or universal bone densitometry	Drug therapy: 5 years of generic alendronate therapy for those diagnosed with osteoporosis	2006 USD	Selective bone densitometry would cost US$100,700/LY compared to the no bone densitometry strategy. Universal bone densitometry would cost US$483,500/LY compared to selective bone densitometry. When quality adjustments were introduced into the analysis, selective and universal bone densitometry became approximately 15% more cost effective	One-way SA
Schwenkglenks et al. [36]	Screen-and-treat strategy (DXA followed by branded alendronate)	No intervention (no screening, no drug treatment)	5 years: branded alendronate The main screening ages were 65, 75, and 85 years	2000 CHF	In men who entered the model at 50 years, the screen-and-treat strategy is not cost effective compared with no intervention for all age groups	One-way and probabilistic SA

Table 2. (continued)

Reference	Intervention	Comparators	Intervention duration	Year of valuation	Results	
					Base-case analysis	Sensitivity analysis
Post-fracture care programs						
DPhil et al. [38]	OG and nurse-led fracture liaison service	Usual care	NR	2012/2013 IB	The OG-led service was the most effective and cost-effective model of care at a threshold of £30,000/QALY. An OG-led or a nurse-led fracture liason service was cost effective when compared with usual care. If only healthcare costs are considered, an OG-led service was cost-effective at £14,525 for men aged 83 years	One-way and probabilistic SA
Johansson et al. [19]	A safety promotion program	Do nothing (no care was provided)	The program is 6 years	2004 SEK	The do-nothing alternative was dominated by the post-intervention	One-way SA

ADT androgen deprivation therapy, *BCT* biomechanical computed tomography, *BMD* bone mineral density, *CA* calcium, *CHF* Swiss Franc, *DXA* dual-energy X-ray absorptiometry, *EUR* Euro, *GC* glucocorticoid, *GDP* gross domestic product, *HRQoL* health-related quality of life, *IB* Pound, *ICER* incremental cost-effectiveness ratio, *ITT* intention-to-treat, *LY* life-year, *MOF* major osteoporosis fracture, *NHIA* National Health Insurance Administration, *NR* not reported, *OG* orthogeriatric, *OST* osteoporosis self-assessment tool, *PPS* per protocol studies, *PVF* prevalent vertebral fracture, *QALY* quality-adjusted life-year, *SA* sensitivity analysis, *SEK* Swedish Krona, *USD* US dollar, *Vit D* vitamin D, *WTP* willingness to pay

Comparison in Cost Effectiveness Between Men and Women

Tables 3 and 4 present synthesized studies (n = 14) that reported results of different (age, fracture risk, or intervention) characteristics for men and women. These studies were further categorized by use of ICERs (Table 3, n=9) or intervention thresholds (Table 4, n=5) as the outcome. Specifically, nine studies [16, 18, 20, 21, 27, 28, 36, 38, 39] used ICERs as the main outcome, leading to a total of 33 comparisons from these studies. Among these, 73% (24) of comparisons reported higher ICERs in men than in women; the relative difference in ICERs was larger with increasing age and a higher fracture risk at baseline in general. Despite differences in ICERs between men and women, five studies [16, 18, 21, 28, 38] and 24 of 33 comparisons (73%) reported similar conclusions about the cost effectiveness of the intervention. The remaining 27% revealed the intervention was cost effective only for women (men yielded higher ICERs). In five studies with intervention thresholds [29–33] (containing a total of 43 comparisons), 21 out of 43 comparisons (49%) reported lower intervention thresholds for men compared with women (particularly those that assessed the 10-year probability of hip fracture in men over the age of 70 years), the other half of the comparisons indicated higher intervention thresholds in women, suggesting no major differences were identified between men and women.

Table 3. Results of comparison between men and women for studies using ICER as the outcome (base case)

Reference	ICER				Cost-effective (yes/no)	
	Scenarios	Women	Men	Difference (women as reference)	Women	Men
Hiligsmann et al. [27]	All ages	€38,526	€106,113	+	No	No
	60–69 years	€155,006	€218,176	+	No	No
	70–79 years	€24,997	€92,676	+	Yes	No
	80+ years	€1907	€27,683	+	Yes	Yes
Ethgen et al. [21]	*Osteoporosis*					
	50 years	€300,277	€203,563	–	No	No
	60 years	€174,359	€121,582	–	No	No
	70 years	€74,707	€61,349	–	Yes	Yes
	80 years	€19,910	€24,231	+	Yes	Yes
	Prevalent fracture					
	50 years	€168,701	€118,823	–	No	No
	60 years	€96,744	€70,057	–	Yes	Yes
	70 years	€35,687	€31,423	–	Yes	Yes
	80 years	€3369	€8916	+	Yes	Yes
Hiligsmann et al. [28]	60 years	€40,578	€23,477	+	Yes	Yes
	70 years	€7912	€10,250	+	Yes	Yes
	80 years	−€12,815 (cost saving)	−€6723 (cost saving)	+	Yes	Yes
Kreck et al. [18]	*BMD T-score − 3.0*					
	65 years	€407,375	€1,042,295	+	No	No
Van Staa et al. [20]	GC 5 mg					
	< 60 years	£41,000	£40,000	–	No	No
	60–79 years	£17,000	£43,000	+	Yes	No
	80 + years	£5000	£35,000	+	Yes	No
	GC 15 mg					
	< 60 years	£17,000	£22,000	+	Yes	Yes
	60–79 years	£13,000	£34,000	+	Yes	No
	80 + years	£15,000	£33,000	+	Yes	No
Fleurence et al. [39]	*General population*					
	Hip pad	$11,722	$47,426	+	Yes	No
	Hip pad + VitD/CA	$25,123	$80,998	+	No	No
	High-risk population					
	Hip pad	−$450 (cost saving)	$17,017	+	Yes	Yes
	Hip pad + VitD/CA	$6572	$33,565	+	Yes	No
Pisu et al. [16]	Vs no screening	−$49,261 (cost saving)	−$4487 (cost saving)	+	Yes	Yes
	Vs usual care	−$38,305 (cost saving)	−$4729 (cost saving)	+	Yes	Yes
Schwenkglenks et al. [36]	65 years	CHF70,995	CHF197,460	+	No	No
	75 years	CHF35,412	CHF123,094	+	Yes	No
	85 years	CHF28,170	CHF118,945	+	Yes	No
DPhil et al. [38]	FLS vs usual care	£20,421	£19,955	–	Yes	Yes
	OG vs FLS	£22,709	£23,407	+	Yes	Yes

BMD bone mineral density, CA calcium, CHF Swiss Franc, FLS fracture liaison service, GC glucocorticoid, ICER incremental cost-effectiveness ratio, OG orthogeriatric, Vit D vitamin D, + indicates men had higher ICERs than women, – indicates men had lower ICERs than women

Table 4. Results of comparison between men and women for studies using intervention threshold as the outcome (base case)

References	Threshold in women	Women	Men	Absolute change (women as the reference)
Chan et al. [29]	*10-year probability of hip fracture*			
	All ages	7.0%	6.0%	− 1.0%
	10-year probability of MOF			
	All ages	15.0%	12.5%	− 2.5%
Makras et al. [30]	*10-year probability of MOF*			
	50 years	20.4%	34.2%	+ 13.8%
	55 years	7.8%	9.6%	+ 1.8%
	60 years	9.1%	9.3%	+ 0.2%
	65 years	8.7%	10.0%	+ 1.3%
	70 years	9.2%	8.9%	− 0.3%
	75 years	13.0%	10.5%	− 2.4%
	80 years	16.0%	11.2%	− 4.8%
	85 years	16.0%	11.2%	− 4.8%
	10-year probability of hip fracture			
	50 years	1.7%	1.8%	+ 0.1%
	55 years	0.9%	0.8%	− 0.1%
	60 years	1.5%	1.5%	0%
	65 years	1.8%	2.2%	+ 0.4%
	70 years	2.6%	2.4%	− 0.2%
	75 years	4.7%	4.5%	− 0.2%
	80 years	7.1%	5.9%	− 1.2%
	85 years	7.8%	6.6%	− 1.2%
Lippuner et al. [32]	*10-year probability of MOF*			
	All ages	13.8%	15.1%	+ 1.3%
	55 years	14.1%	9.9%	− 4.2%
	60 years	14.4%	12.0%	− 4.4%
	65 years	12.8%	13.9%	+ 1.1%
	70 years	14.4%	17.5%	+ 3.1%
	75 years	14.8%	19.9%	+ 5.1%
	80 years	15.0%	19.0%	+ 4.0%
	85 years	10.8%	13.5%	+ 2.7%
Tosteson et al. [31]	*10-year probability of hip fracture (white)*			
	50 years	2.5%	2.4%	− 0.1%
	55 years	2.8%	4.2%	+ 1.4%
	60 years	3.0%	4.1%	+ 1.1%
	65 years	2.8%	3.5%	+ 0.7%
	70 years	4.0%	4.8%	+ 0.8%
	75 years	4.4%	3.9%	− 0.5%
	80 years	4.0%	4.0%	0%
	85 years	3.3%	3.1%	− 0.2%

Table 4 (continued)

References	Threshold in women	Women	Men	Absolute change (women as the reference)
Kanis et al. [33]	*10-year probability of hip fracture*			
	50 years	0.9%	1.6%	+ 0.6%
	55 years	1.5%	1.9%	+ 0.4%
	60 years	2.3%	2.6%	+ 0.2%
	65 years	3.5%	3.4%	− 0.1%
	70 years	4.8%	4.6%	− 0.2%
	75 years	6.1%	5.6%	− 0.5%
	80 years	7.9%	7.1%	− 0.8%
	85 years	6.9%	7.5%	+ 0.6%
	90 years	7.7%	7.4%	− 0.2%

MOF major osteoporosis fracture

Quality Assessment

Results of the quality appraisal of the design and conduct of the economic evaluation in men with osteoporosis are presented in the ESM. The quality of included studies was relatively good with an average score of 18.8 out of 25 (range 13–23.5). The average score for studies that included active drugs or nutritional supplements, intervention thresholds, screening strategies, and post-fracture care programs as the intervention was 19.2, 17.1, 21.0, and 14.0, respectively; 44% of included studies scored more than 20 points.

Figure 2 displays the proportion of studies that included the individual items recommended in the ESCEO-IOF guidelines and whether an item was fully reported, partially reported, or not reported in the cited studies. The most frequently unreported items were 'an additional effect on costs and/or utility after multiple fractures,' 'the effect of adverse events on costs and/or utility,' 'avoid hierarchy of fractures and restrictions after fracture events,' and 'proportion of excess mortality attributed to the fracture'. In addition, two items ('comparators: no treatment and relevant active osteoporotic agents' and 'excess mortality after hip and clinical vertebral fractures') were frequently partially reported.

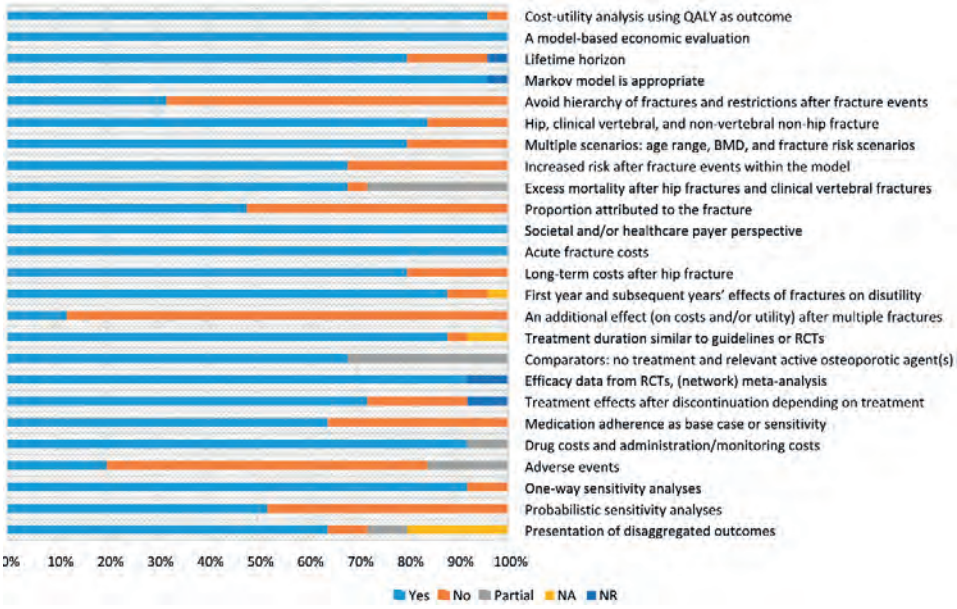

Figure 2. Proportion of studies meeting individual items recommended in the Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases and the International Osteoporosis Foundation guideline (total studies: 25). BMD bone mineral density, NA not applicable, NO not reported, NR not reported, Partial partially reported, QALY quality-adjusted life-year, RCTs randomized controlled trials, Yes fully reported

Source of Model Input Data

Table 5 displays the source of model parameters for each study. For fracture incidence, specific male data were used for hip fracture in all included studies. One study [39] indicated their vertebral fracture incidence data were adjusted from female data, and the incidence of other fractures was obtained from a study combining both sexes. However, given the absence of country-specific fracture incidence data, four studies [18, 29, 32, 40] derived relevant data from other countries. The source of fracture cost data varies significantly among studies. Most studies (n=13) obtained hip fracture cost data from studies including both men and women; only eight studies fully obtained and used male hip fracture cost data. For non-hip fracture costs, only three studies [25, 28, 32] reported the use of male-specific data. With regard to utility data, nine studies [16, 17, 19, 22, 25, 26, 31, 34, 37] used male-specific baseline utilities; however, over 90% of the studies derived disutility data from studies encompassing both sexes. In addition, nearly all studies obtained male-specific baseline mortality data, and male excess mortality data were used in half of the studies (n=13). With regard to treatment efficacy data, only three studies [22, 34, 37] extracted male efficacy data from meta-analyses based

on randomized controlled trials of alendronate in men, most studies (n=14) used female efficacy data or obtained relevant data from studies combining both sexes. Most studies did not include treatment adverse events (n=16) and medication adherence (n=9) in their models. In five studies [23, 32, 34, 37, 40] that modeled the adverse events, only one study [34] included the rare but serious side effects of osteonecrosis of the jaw, and subtrochanteric femoral fracture. For studies that indicated the source of these two parameters, female data or assumptions were frequently used.

Table 5. Source of model input data (men, women, or combined studies including both sexes)

References	Fracture incidence		Fracture cost		Baseline utilities	Fracture disutility		Baseline mortality	Fracture effects on mortality	Treatment efficacy	Side effects	Medication adherence/persistence
	Hip	Non-hip	Hip	Non-hip		Hip	Non-hip					
Active drugs or nutritional supplements												
Hiligsmann et al. [27]	M	M	C	C	C	C	C	M	M	C	NA	A (only SA)
Ethgen et al. [21]	M	M	Hos: M Extra: W[b]	A	NR	NR	NR	M	C	C	NA	None
Silverman et al. [25]	M	M	M	M	M	C	CV: C Others: W	M	M	W	None	W
Hiligsmann et al. [28]	M	M	M	M	C	C	C	M	M	C	NA	None
Parthan et al. [26]	M	M	M	C	M	C	CV: C Others: W	M	M	W	None	W
Hiligsmann et al. [40]	M	M[a]	Hos: M Extra: W[b]	A	C	C	C	M	M	W	A and EO	W
Kouta et al. [23]	M	NA	C	NA	A	M	NA	M	M	A	C	A
Kreck et al. [18]	M	M[a]	C	C	C	C	C	M	HF: C CV: M	W[b]	None	None
Schousboe et al. [22]	M	M	C	C	M	C	C	M	NR	M	None	W
Van Staa et al. [20]	M	M	W	W	C	W	W	M	M	A	None	None
Borgstrom et al. [24]	M	M	M	C	NR	C and A	C and A	M	M	W	None	None
Fleurence et al. [39]	M	CV: W[b] Colles' fx: M Others: C	W	W	C	C	C	M	A	C and A	NA	C
Intervention threshold												
Chan et al. [29]	M[a]	M[a]	C	C	C	C	C	C	M[a]	C	None	None
Makras et al. [30]	M	M	C[a]	C[a]	NR	NR	NR	M	HF and CV: M Others: A	A	None	A
Lippuner et al. [32]	M	CV and WF: M Others: M[a]	M	M	C[a]	C[a]	C[a]	M	HF and CV: M WF: A Others: W	C	A	C
Tosteson et al. [31]	M	M	C	CV and WF: C Others: M	M	C	CV and WF: C Others: M	M	HF: C Others: none	A	None	A
Kanis et al. [33]	M	M	M	M (A)	NR	C	C	M	C	A	None	None
Screening strategies												
Ito et al. [17]	M	M	C	C	M	C	C	M	M	W	None	C
Pisu et al. [16]	M	NA	M	NA	M	C	NA	M	C	W	None	W
Nayak et al. [34]	M	M	C	C (A for HF)	M	C	C	M	M	M	C	A

Table 5. (continued)

References	Fracture incidence		Fracture cost		Baseline utilities	Fracture disutility		Baseline mortality	Fracture effects on mortality	Treatment efficacy	Side effects	Medication adherence/persistence
	Hip	Non-hip	Hip	Non-hip		Hip	Non-hip					
Schousboe et al. [35]	M	M	C	C	C (A)	C	C	M	C	C	None	W
Ito et al. [37]	M	M	C	C	M	C	C	M	C	M	W	C
Schwenkglenks et al. [36]	M	M	C	C	C	M	M	M	M	W	None	W
Post-fracture care programs												
DPhil et al. [38]	M	M	M	NA	C	C	NA	M	NR	NR	None	None
Johansson et al. [19]	M	NA	C	NA	M	C	NA	M	M	A	None	None

A assumption, *C* combination, *CV* clinical vertebral fracture, *EO* expert opinion, *Fx* fracture, *HF* hip fracture, *HF* humerus fracture, *Hos* hospitalization, *M* men, *NA* not applicable, *None* parameters were not incorporated in the model, *NR* not reported, *W* women, *WF* wrist fracture

DISCUSSION

This systematic review identified 25 cost-effectiveness analyses of interventions for osteoporosis in men published between 2000 and June 2022. Most of the studies assessed active drugs (n=8) or nutritional supplements (n=4) followed by screening strategies (n=6), intervention thresholds (n=5), and post-fracture care programs (n=2). A comparison to two previous reviews [9, 10] of cost-effectiveness analyses of drugs for postmenopausal osteoporosis by Hiligsmann et al. [10] (n=39, between 1 January, 2008 and 31 December, 2013) and Li et al. [9] (n = 27, between 1 July, 2013 and 31 December, 2019), shows that the number of economic evaluations of interventions in men (n=25) with osteoporosis is limited. Nearly all studies included in this review were conducted in Europe and North America, and only two studies [16, 17] were published in the past 5 years. In contrast, cost-effectiveness studies in women were performed in a large number of countries (a total of 23 countries in Europe, three in North America, three in the Asia-Pacific region, one in the Middle East, and one in Australia), and the number of publications identified were published in recent years [9]. Compared with postmenopausal women, economic evaluations in men are largely insufficient and relatively outdated, even though some of the medicines for osteoporosis are approved for use in men. This could be owing to the lack of attention given to the treatment of osteoporosis in men, and some active drugs that have yet to be approved or reimbursed for men in some countries.

With regard to active drugs (referring to anti-osteoporosis medication rather than nutritional supplements), four out of five studies [18, 20, 22–24] revealed that bisphosphonates (with/without BMD testing) were generally cost effective compared with no treatment or nutritional supplements in men aged 55 years and older with a fracture history, low bone mass, or rheumatoid arthritis. However, there was no study comparing the cost effectiveness between bisphosphonate types. More future studies are needed. Although glucocorticoid excess and hypogonadism (e.g., androgen deprivation therapy for prostate cancer) are two main factors to increase the risk of secondary osteoporosis [1] and fracture in men, only two cost-effectiveness analyses [20, 23] were published and reported that alendronate therapy in conjunction with BMD testing was cost effective in patients starting adjuvant androgen deprivation therapy for locally advanced or high-risk localized prostate cancer, and bisphosphates were cost effective in patients using high doses of glucocorticoids. However, it should be noted that heterogeneity in interventions being compared in the target population of the included studies in terms of BMD status, fracture risk, and prior fracture (yes/no) was identified, which made it difficult to conduct comparisons between the studies and synthesize data.

Only two studies (in the USA and Sweden) were identified to assess the cost effectiveness of denosumab in men with osteoporosis [25, 26], compared with 17 studies in women as reported by a recent systematic review [41]. Although both studies indicated denosumab was cost effective compared to bisphosphonates (alendronate, zoledronate, risedronate, and ibandronate), the results should be further confirmed. Moreover, considering denosumab is also approved for the treatment of bone loss in men with prostate cancer undergoing hormone ablation therapy, and for men with glucocorticoid-induced osteoporosis, future studies are highly needed to reveal the potential economic benefits of denosumab for men with glucocorticoid use or hypogonadism.

Most studies assessed the cost effectiveness in primary prevention (i.e., patients with osteoporosis) and only one study [40] compared the cost effectiveness of strontium ranelate to no treatment in various populations (BMD T-score$\leqslant -2.5$ and/or prevalent vertebral fracture), suggesting improved cost effectiveness (lower ICERs) in patients with previous fractures. No economic evaluations have been performed in men with osteoporosis treated with teriparatide despite its approval in 2002 by the US Food and Drug Administration and in 2003 by the European Medicines Agency to increase bone mass in men. Only two studies [25, 26] used it as a comparator and reported teriparatide was not cost effective compared to denosumab. The recent availability of biosimilar teriparatide could potentially affect this finding.

Recently, one study [42] reported that abaloparatide, a human parathyroid hormone-related peptide(1–34) analog, in men with osteoporosis leads to rapid and significant improvements in BMD with a safety profile similar to women, suggesting abaloparatide can be considered as an effective anabolic treatment option for men with osteoporosis. However, relevant economic data of abaloparatide in men are still lacking, and future economic studies are needed.

There is emerging economic evidence about the value of sequential therapy (anabolic agents followed by antiresorptive agents) in postmenopausal women [43–45], no relevant studies were identified in men. Economic research on sequential therapy in men may be of interest for future research. Our review found that most cost-effectiveness analyses in men were based on bridging studies, the small-scaled studies with a shorter duration that use BMD as a surrogate endpoint to support an indication in men. When an agent in a bridging study for men increases BMD to a magnitude comparable to that observed in the larger, longer, and more extensive studies (e.g., including assessment of the effect on fracture risk) required for approval in postmenopausal women, the validation of this treatment in men

is considered sufficient. This strategy is the accepted approach by regulators and payers, and acceptable from a health economics perspective [46].

Several economic evaluations included in our study were performed to assess the cost effectiveness of screening strategies for osteoporosis. Though four out of six studies (in our review) indicated BMD screening was cost effective in men, there is ongoing debate regarding the benefits of a widespread systematic screening approach for osteoporosis in men [47]. In the USA, dual-energy X-ray absorptiometry-based osteoporosis screening is recommended by some societies and guidelines (but not widely covered by insurance) for men aged over 70 years or over 50 years who have sustained a fracture [48]. Within the included studies, we found that most studies assumed/reported BMD testing once every 2 years for patients with osteoporosis. The frequency of BMD testing could, however, depend on BMD T-scores, and less frequent testing has been recommended for patients with osteopenia [49].

For patients requiring a fracture risk assessment, the threshold at which treatment should be initiated will vary according to factors such as healthcare provision, willingness to pay, and cost of medications [47]. The most recent guidelines [50, 51] suggest treating patients whose FRAX 10-year major osteoporotic fracture risk scores are $\geqslant$ 20%. However, a recently published study [52] indicated that assessment by the FRAX algorithm appears to underestimate the risk in older people, thus the therapeutic choice for these patients needs to be adjusted. Diagnostic-therapeutic decision making in real-world practice must consider a wider assessment focused on the specific needs of the individual patient [52]. Another concern is that intervention thresholds varied significantly across studies and settings because consensus on whether the threshold level should be fixed or age and sex dependent is lacking. All five studies included in our systematic review reported age- and sex-dependent thresholds, and the intervention thresholds increased with age, which was in line with National Osteoporosis Guideline Group in the UK [53].

With the wide implementation of post-fracture care programs, such as FLS, there has been an increase in the number of cost-effectiveness analyses conducted [54] and most of these studies only focused on women. Studies in our review indicated that post-fracture care programs were cost effective in men, the economic benefits of FLS in men might be further supported in future studies.

The cost-effectiveness estimations (ICERs or intervention thresholds) for men and women were quite similar. Specifically, over 70% of comparisons reported similar

conclusions about the cost effectiveness of the intervention in men and women, despite men yielding higher ICERs that led to noncost-effective estimations in the remaining few comparisons resulting mainly from differences in fracture incidence. This could be because fracture incidence at baseline was comparably lower for men than for women. It might be interesting to confirm in future studies. In addition, no major differences were identified between men and women concerning costeffective intervention thresholds, suggesting that intervention thresholds are probably similar in men and women from an economic point of view. Given the similar ICERs and intervention thresholds between men and women, fracture risk reduction is the primary consideration in the treatment of osteoporosis irrespective of sex, which is also indicated by romosozumab for the treatment of severe osteoporosis in Australia by the Pharmaceutical Benefits Advisory Committee [55].

An osteoporosis-specific guideline [15] was used in our study for quality appraisal of the studies included. This guideline can serve as a guide for the design, conduct, and reporting of economic evaluations in osteoporosis to improve their transparency, comparability, and methodologic standards, and to further facilitate inter-study comparisons. Although the quality of the studies included in our review was relatively high, some items were frequently missing or only partially reported , which is in alignment with a previous systematic review [9], and these items deserve attention in future studies.

Regarding the source of model input data, male-specific data were commonly used for fracture incidence, baseline mortality, and baseline utility data. However, some data, for example, fracture cost and disutility, were commonly retrieved from studies including both men and women, and treatment efficacy was mostly obtained from women based on a meta-analysis or randomized controlled trial. This is not an incorrect use of data per se as the effect of fracture on utility has been shown to be similar between men and women as reported by a recent study [56] revealing that men and women had a similar trajectory of health-related quality-of-life recovery following fragility fracture at any skeletal site. Similarly, one systematic review and meta-analysis [57] reported the efficacy of treatment options to reduce osteoporotic fracture risk in men was comparable to women, therefore it might not weaken the analysis to use female data in the absence of male-specific treatment efficacy data. It is however important that male-specific data be used for several parameters owing to the differences between men and women, in particular for fracture incidence, increased risk after subsequent fractures, mortality excess, and fracture costs.

There are several implications of our review. First, this study summarizes the current economic evidence of costeffectiveness analyses of interventions in men

with osteoporosis and reveals the knowledge gap (insufficient economic data and publications) when compared with studies in women. Second, our study indicates the overall comparability of conclusions on the cost effectiveness of interventions in men and women, with greater ICERs in men. Third, we highlight that some male-specific data are needed in the design of an economic evaluation in men. Adhering to the ESCEO-IOF guideline [15] as well as CHEERS 2022 [58] is also important for future economic evaluations in osteoporosis to improve the quality of studies. These guidelines provide recommendations for the conduct and reporting of economic evaluations (in osteoporosis) and are important to improve the quality and standardization of these studies.

Our study has two main limitations. First, the osteoporosis-specific guideline is more appropriate to appraise costeffectiveness analyses of active drugs for osteoporosis, thus some items for studies that investigated other interventions such as screening strategies and intervention thresholds might not be applicable and underscored. Second, the source of model input data in some studies cannot be identified, therefore it is difficult to make a fully precise summary on the proportion of study using male-specific data for these model parameters.

CONCLUSIONS

Our systematic review included 25 studies on the cost effectiveness of interventions for osteoporosis in men, covering active drugs or nutritional supplements, intervention thresholds, screening strategies, and post-fracture care programs between 1 January, 2000 and 30 June, 2022. Overall, antiosteoporosis drugs and nutritional supplements are generally cost effective in men with osteoporosis. Screening strategies and post-fracture care programs also showed economic benefits for men. Cost-effectiveness and intervention thresholds were generally rather similar in studies conducted in both men and women, with slightly greater ICERs in men. More high-quality and national studies in men with osteoporosis are needed to close the current research gap and further inform decision making.

ELECTRONIC SUPPLEMENTARY MATERIAL I:
Search strategies

Table Search strategies

Database	Search strategy
Medline	1 exp Osteoporosis/ 2 Bone Diseases, Metabolic/ 3 Bone Density/ 4 Bone Demineralization, Pathologic/ 5 Osteoporotic Fractures/ 6 osteoporo*.ti,ab,kf. 7 osteopenia*.ti,ab,kf. 8 (bone* adj1 (densit* or content)).ti,ab,kf. 9 (bone* adj1 (demineralization or demineralisation of loss* or decreas* or deterioration*)).ti,ab,kf. 10 metabolic bone disease*.ti,ab,kf. 11 (osteoporo* adj1 fracture*).ti,ab,kf. 12 or/1-11 13 "Costs and Cost Analysis"/ 14 Cost-Benefit Analysis/ 15 Health Care Costs/ 16 Health Expenditures/ 17 Economics, Pharmaceutical/ 18 Economics, Medical/ 19 (cost or costs or costing or costly).ti,ab,kf. 20 expenditure*.ti,ab,kf. 21 (economic* or economy or pharmacoeconomic*).ti,ab,kf. 22 or/13-21 23 12 and 22 24 (men or man or male* or boy* or masculin).ti,ab,kf. 25 23 and 24 26 limit 25 to yr="2000 -Current"
Embase	1 exp metabolic bone disease/ 2 exp osteoporosis/ 3 exp bone demineralization/ 4 exp bone density/ 5 exp fragility fracture/ 6 Osteoporos*.ti,ab,kw. 7 osteopenia.ti,ab,kf. 8 (bone* adj1 (densit* or content)).ti,ab,kf. 9 (bone* adj1 (demineralization or demineralisation of loss* or decreas* or deterioration*)).ti,ab,kw. 10 metabolic bone disease*.ti,ab,kf. 11 (osteoporo* adj1 fracture*).ti,ab,kf. 12 or/1-11 13 exp "cost utility analysis"/ 14 exp "cost benefit analysis"/ 15 exp "health care cost"/ 16 exp "cost"/ 17 exp "cost effectiveness analysis"/ 18 exp pharmacoeconomics/ 19 (cost or costs or costing or costly).ti,ab,kf. 20 expenditure*.ti,ab,kf. 21 (economic* or economy or pharmacoeconomic*).ti,ab,kf. 22 or/13-21 23 12 and 22 24 (men or man or male* or boy* or masculin).ti,ab,kf. 25 23 and 24 26 limit 25 to yr="2000 -Current"

ELECTRONIC SUPPLEMENTARY MATERIAL II:
Treatment (active drug) costs

Table Treatment costs of interventions and/or comparators in included studies

Reference	Country	Year of valuation	Active drugs	Treatment costs		
				Drug cost/year	Physician visit cost	BMD testing cost
Silverman et al. [25]	USA	2013 USD	Denosumab Generic alendronate Branded zoledronate Branded risedronate Branded ibandronate Teriparatide	$1,650 $30 $1,084 $1,708 $1,332 $14,514	$100 once per year	$243 once every 2 years
Parthan et al. [26]	Sweden	2012 EUR	Denosumab Generic alendronate Branded zoledronate Generic risedronate Branded ibandronate Strontium ranelate Teriparatide	€512 €34 €474 €45 €380 €503 €5,086	€151 once per year	€193 once every 2 years
Hiligsmann et al. [40]	Belgium	2010 EUR	Strontium ranelate	€477	€22.67 once per year	€58.05 once every 2 years
Kouta et al. [23]	USA	2008 USD	Branded alendronate	$600	NR	$131 once
Kreck et al. [18]	Germany	2004 EUR	Branded ibandronate	€819*	€169*once	€103 once
Schousboe et al. [22]	USA	2004 USD	Branded bisphosphonate	$1000	$52 once per year	$82 after 2 years of drug therapy
Van Staa et al. [20]	UK	2003/2004 IB	Branded bisphosphonate	£284	£18 once per year	£34 once
Borgstrom et al. [24]	Sweden	2001 EUR	Branded alendronate	€447	€128 once per year	€87 once every 2 years
Chan et al. [29]	Taiwan, China	2010 USD	Branded alendronate	$450	$173 (clinic visits and outpatient rehabilitation) per year	$40 per year
Makras et al. [30]	Greece	2013 EUR	Alendronate Risedronate Ibandronate Zolendronate Raloxifene Strontium ranelate Parathyroid hormone Teriparatide Alendronate/ Cholecalciferol Bazedoxifene Denosumab	€193 €135 €660 €150 €132 €279 €3191 €3271 €132 €229 €325	€10 once	€60 per year
Lippuner et al. [32]	Switzerland	2008 CHF	Branded alendronate	CHF 504	CHF 40 for 15 min	CHF326 once
Tosteson et al. [31]	USA	2005 USD	Generic bisphosphonate	$600	$49 once per year	$82 in the second year after treatment initiation

Table (continued).

Reference	Country	Year of valuation	Active drugs	Treatment costs		
				Drug cost/year	Physician visit cost	BMD testing cost
Ito et al. [17]	USA	2019 USD	Branded alendronate Branded zolendronic acid	$250 $515	$76.06 once per year	$39.99 in the second and fourth year after treatment initiation
Pisu et al. [16]	USA	2016 USD	Generic alendronate	$100	NR	$100 once
Nayak et al. [34]	USA	2014 USD	Bisphosphonate	$200	$73 once	$159 once
Schousboe et al. [35]	USA	2010 USD	(Generic + branded) bisphosphonate	$500 and $250#	NR	$97.41 per person
Ito et al. [37]	USA	2006 USD	Generic alendronate	$350	$52 once	$82 once
Schwenkglenks et al. [36]	Switzerland	2000 CHF	Branded alendronate	CHF736*	NR	CHF300 once

BMD bone mineral density, NR not reported
*Calculated based on available data
#Based on assumption

ELECTRONIC SUPPLEMENTARY MATERIAL III:

Quality assessment

Table Quality appraisal of cost-effectiveness analyses of interventions for osteoporosis in men using a guideline developed by ESCEO-IOF

Items	Recommendations	Active drugs or nutrition supplements											
		[27]	[21]	[25]	[28]	[26]	[40]	[23]	[18]	[22]	[20]	[24]	[39]
Type of economic evaluation	Cost-utility analysis using QALY as outcome	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Method for the conduct of economic evaluation	A model-based economic evaluation	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Modeling technique	• Lifetime horizon	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes
	• ·Markov model is appropriate (6 months/1 year cycle length)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes
	• Avoid hierarchy of fractures and restrictions after fracture events	Yes	Yes	No	Yes	No	No	No	No	Yes	No	No	No
	• Hip, clinical vertebral, and non-vertebral non-hip fracture	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Base-case analysis and population	• Multiple scenarios: age range, BMD, and fracture risk scenarios	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes
	• The FRAX® or CARVAN® tools can be used to model fracture	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	• Increased risk after fracture events within the model	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Mortality	• Excess mortality after hip fractures and clinical vertebral fractures	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Part	Yes	Yes	Part
	• Proportion attributed to the fracture (e.g. 25–30%) mortality that is attributable to the fracture event	Yes	No	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	No

Table (continued).

Items	Recommendations	Active drugs or nutrition supplements											
		[27]	[21]	[25]	[28]	[26]	[40]	[23]	[18]	[22]	[20]	[24]	[39]
Fracture costs and utility	• Societal and/or healthcare payer perspective	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	• Acute fracture costs	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	• Long-term costs after hip fracture (attributable to the fracture)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No
	• First year and subsequent years' effects of fractures on disutility	Yes	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
	• National ICUROS data if available	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	• An additional effect (on costs and/or utility) after multiple fractures	No	No	No	Yes	No	No	No	No	No	No	Yes	No
Treatment characteristics	• Treatment duration similar to guidelines or RCTs	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	• Comparators: no treatment and relevant active osteoporotic agent(s)	Yes	Yes	Part	Yes	Part	Part	Part	Part	Part	Part	Part	Yes
	• Sequential therapy may be considered as intervention/comparators	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	• Efficacy data from RCTs, (network) meta-analysis	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	• In the absence of hip/wrist specific efficacy data, use of non-vertebral or clinical fracture efficacy data	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	• Treatment effects after discontinuation depending on treatment	No	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No
	• Medication adherence as base case or sensitivity	Yes	No	Yes	No	Yes	Yes	Yes	No	Yes	No	No	Yes
	• Drug costs and administration/monitoring costs	Part	Part	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	• Adverse events	NA	NA	No	NA	No	Yes	Yes	No	No	No	No	NA
Sensitivity analyses	• One-way sensitivity analyses	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
	• Probabilistic sensitivity analyses	No	No	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes

Table (continued).

Items	Recommendations	Active drugs or nutrition supplements											
		[27]	[21]	[25]	[28]	[26]	[40]	[23]	[18]	[22]	[20]	[24]	[39]
Outcomes	Presentation of disaggregated outcomes, incremental costs, and outcomes for each intervention and incremental cost-effectiveness ratios	Part	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Part	Yes	Yes
Scoring		**20**	**14.5**	**19.5**	**23**	**19.5**	**22.5**	**17.5**	**19.5**	**21**	**15**	**20.5**	**17.5**

ESCEO-IOF European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases and the US branch of the International Osteoporosis Foundation, QALY quality-adjusted life-year, BMD bone mineral density, ICUROS The International Costs and Utilities Related to Osteoporotic fractures Study, RCT randomized controlled trial, NA not applicable, NR not reported, Part partial.

Scoring: 'use ICUROS data', 'use FRAX® or GARVAN® tools', 'consider sequential therapy as intervention' and 'in the absence of hip/wrist specific efficacy data, use of non-vertebral or clinical fracture efficacy data as replacement' were not included in the scoring system. A total of 25 items were scored.

Note: (1) item 'Multiple scenarios: age range, BMD, and fracture risk scenarios', if the study met one of these scenarios, it was scored 'Yes';

(2) item 'Comparators: no treatment and relevant active osteoporotic agent', for studies that included active osteoporotic drug as the intervention, the comparator should be no treatment and at least another active drug. For studies included nutrition supplements, screening strategies, threshold, or post-fracture care programs as the intervention, this restriction of item was relaxed, i.e. if any comparator was included, it was scored 'Yes';

(3) item 'Medication adherence as base case or sensitivity' and 'Adverse events', if no information was identified, they were scored 'No'

(4) item 'Presentation of disaggregated outcomes, incremental costs, and outcomes for each intervention and incremental cost-effectiveness ratios', this item is not applicable to studies investigated intervention threshold, therefore they were scored 'NA', and the total score for these studies is 24 points.

Table (Continued).

Items	Recommendations	Intervention threshold					Screening strategies						Post-fx care programs	
		[29]	[30]	[32]	[31]	[33]	[17]	[16]	[34]	[35]	[37]	[36]	[38]	[19]
Type of economic evaluation	Cost-utility analysis using QALY as outcome	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Method for the conduct of economic evaluation	A model-based economic evaluation	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Modeling technique	• Lifetime horizon	NR	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No
	• Markov model is appropriate (6 months/1 year cycle length)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	• Avoid hierarchy of fractures and restrictions after fracture events	No	No	No	No	No	Yes	No	Yes	Yes	No	Yes	No	No
	• Hip, clinical vertebral, and non-vertebral non-hip fracture	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No
Base-case analysis and population	• Multiple scenarios: age range, BMD, and fracture risk scenarios	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes
	• The FRAX® or GARVAN® tools can be used to model fracture	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	• Increased risk after fracture events within the model	No	No	No	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	No
Mortality	• Excess mortality after hip fractures and clinical vertebral fractures	No	Yes	Yes	Part	Yes	Yes	Yes	Part	Part	Part	Part	Yes	Yes
	• Proportion attributed to the fracture (e.g. 25–30%) mortality that is attributable to the fracture event	No	Yes	Yes	No	No	No	No	No	Yes	Yes	Yes	No	No
Fracture costs and utility	• Societal and/or healthcare payer perspective	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	• Acute fracture costs	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	• Long-term costs after hip fracture (attributable to the fracture)	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
	• First year and subsequent years' effects of fractures on disutility	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	• National ICUROS data if available	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	• An additional effect (on costs and/or utility) after multiple fractures	No	No	No	No	No	No	No	No	Yes	No	Yes	No	No

Table (continued).

Items	Recommendations	Intervention threshold					Screening strategies						Post-fx care programs	
		[29]	[30]	[32]	[31]	[33]	[17]	[16]	[34]	[35]	[37]	[36]	[38]	[19]
Treatment characteristics	• Treatment duration similar to guidelines or RCTs	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	NA	NA
	• Comparators: no treatment and relevant active osteoporotic agent(s)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	• Sequential therapy may be considered as intervention/comparators	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	• Efficacy data from RCTs, (network) meta-analysis	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	NR
	• In the absence of hip/wrist specific efficacy data, use of non-vertebral or clinical fracture efficacy data	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	• Treatment effects after discontinuation depending on treatment	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	NR
	• Medication adherence as base case or sensitivity	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No
	• Drug costs and administration/monitoring costs	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	• Adverse events	No	No	Yes	No	No	No	No	Yes	No	Yes	No	No	No
Sensitivity analyses	• One-way sensitivity analyses	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	• Probabilistic sensitivity analyses	No	No	No	No	No	Yes	No	Yes	Yes	No	Yes	Yes	No
Outcomes	Presentation of disaggregated outcomes, incremental costs, and outcomes for each intervention and incremental cost-effectiveness ratios	NA	NA	NA	NA	NA	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Scoring		**14**	**18**	**20**	**17.5**	**16**	**22**	**15**	**21.5**	**22.5**	**21.5**	**23.5**	**15**	**13**

ESCEO-IOF European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases and the US branch of the International Osteoporosis Foundation, QALY quality-adjusted life-year, BMD bone mineral density, ICUROS The International Costs and Utilities Related to Osteoporotic fractures Study, RCT randomized controlled trial; NA not applicable, Part partial, NR not reported, Fx fracture

Scoring: 'use ICUROS data', 'use FRAX® or GARVAN® tools', 'consider sequential therapy as intervention' and 'in the absence of hip/wrist specific efficacy data, use of non-vertebral or clinical fracture efficacy data as replacement' were not included in the scoring system. A total of 25 items were scored.

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(2) item 'Comparators: no treatment and relevant active osteoporotic agent', for studies that included active osteoporotic drug as the intervention, the comparator should be no treatment and at least another active drug. For studies included nutrition supplements, screening strategies, threshold, or post-fracture care programs as the intervention, this restriction of item was relaxed, i.e. if any comparator was included, it was scored 'Yes';

(3) item 'Medication adherence as base case or sensitivity' and 'Adverse events', if no information was identified, they were scored 'No'

(4) item 'Presentation of disaggregated outcomes, incremental costs, and outcomes for each intervention and incremental cost-effectiveness ratios', this item is not applicable to studies investigated intervention threshold, therefore they were scored 'NA'. and the total score for these studies is 24 points.

REFERENCES

1. Vilaca T, Eastell R, Schini M. Osteoporosis in men. *Lancet Diabetes Endocrinol*. 2022;10(4):273-283. doi:10.1016/S2213-8587(22)00012-2
2. Walsh PC. Risk of fracture after androgen deprivation for prostate cancer. *J Urol*. 2005;174(3):929-930. doi:10.1097/S0022-5347(01)68451-9
3. Adler RA. Osteoporosis in men: A review. *Bone Res*. 2014;2(April):1-8. doi:10.1038/boneres.2014.1
4. International Osteoporosis Foundation. Fragility fractures-Epidemiology. https://www.osteoporosis.foundation/health-professionals/fragility-fractures/epidemiology
5. Burge R, Dawson-Hughes B, Solomon DH, Wong JB, King A, Tosteson A. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. *J Bone Miner Res*. 2007;22(3):465-475. doi:10.1359/jbmr.061113
6. Kanis JA, Norton N, Harvey NC, et al. SCOPE 2021: a new scorecard for osteoporosis in Europe. *Arch Osteoporos*. 2021;16(1). doi:10.1007/s11657-020-00871-9
7. Lewiecki EM, Ortendahl JD, Vanderpuye-Orgle J, et al. Healthcare Policy Changes in Osteoporosis Can Improve Outcomes and Reduce Costs in the United States. *JBMR Plus*. 2019;3(9):1-7. doi:10.1002/jbm4.10192
8. Kaufman JM. Management of osteoporosis in older men. *Aging Clin Exp Res*. 2021;33(6):1439-1452. doi:10.1007/s40520-021-01845-8
9. Li N, Cornelissen D, Silverman S, et al. An Updated Systematic Review of Cost-Effectiveness Analyses of Drugs for Osteoporosis. *Pharmacoeconomics*. 2021;39(2):181-209. doi:10.1007/s40273-020-00965-9
10. Hiligsmann M, Evers SM, Ben Sedrine W, et al. A Systematic Review of Cost-Effectiveness Analyses of Drugs for Postmenopausal Osteoporosis. *Pharmacoeconomics*. 2015;33(3):205-224. doi:10.1007/s40273-014-0231-1
11. https://www.crd.york.ac.uk/prospero/.
12. Thielen FW, Van Mastrigt GAPG, Burgers LT, et al. How to prepare a systematic review of economic evaluations for clinical practice guidelines: database selection and search strategy development (part 2/3). *Expert Rev Pharmacoeconomics Outcomes Res*. 2016;16(6):705-721. doi:10.1080/14737167.2016.1246962
13. Morrison A, Polisena J, Husereau D, et al. The effect of english-language restriction on systematic review-based meta-analyses: A systematic review of empirical studies. *Int J Technol Assess Health Care*. 2012;28(2):138-144. doi:10.1017/S0266462312000086
14. Kanis JA, McCloskey E V., Harvey NC, et al. Intervention thresholds and diagnostic thresholds in the management of osteoporosis. *Aging Clin Exp Res*. 2022;34(12):3155-3157. doi:10.1007/s40520-022-02216-7
15. Hiligsmann M, Reginster J, Tosteson ANA, et al. Recommendations for the conduct of economic evaluations in osteoporosis : outcomes of an experts ' consensus meeting organized by the European Society for Clinical and Economic Aspects of Osteoporosis , Osteoarthritis and Musculoskeletal Diseases (ESCEO . Published online 2019:45-57.
16. Pisu M, Kopperdahl DL, Lewis CE, Saag KG, Keaveny TM. Cost-Effectiveness of Osteoporosis Screening

Using Biomechanical Computed Tomography for Patients With a Previous Abdominal CT. *J Bone Miner Res*. 2019;34(7):1229-1239. doi:10.1002/jbmr.3700

17. Ito K. Cost-effectiveness of Screening for Osteoporosis in Older Men With a History of Falls. *JAMA Netw open*. 2020;3(12):e2027584. doi:10.1001/jamanetworkopen.2020.27584
18. Kreck S, Klaus J, Leidl R, et al. Cost effectiveness of ibandronate for the prevention of fractures in inflammatory bowel disease-related osteoporosis: Cost-utility analysis using a Markov model. *Pharmacoeconomics*. 2008;26(4):311-328. doi:10.2165/00019053-200826040-00004
19. Johansson P, Sadigh S, Tillgren P, Rehnberg C. Non-pharmaceutical prevention of hip fractures - A cost-effectiveness analysis of a community-based elderly safety promotion program in Sweden. *Cost Eff Resour Alloc*. 2008;6:1-12. doi:10.1186/1478-7547-6-11
20. van Staa TP, Geusens P, Zhang B, Leufkens HGM, Boonen A, Cooper C. Individual fracture risk and the cost-effectiveness of bisphosphonates in patients using oral glucocorticoids. *Rheumatology*. 2007;46(3):460-466. doi:10.1093/rheumatology/kel249
21. Ethgen O, Hiligsmann M, Burlet N, Reginster JY. Public health impact and cost-effectiveness of dairy products supplemented with vitamin D in prevention of osteoporotic fractures. *Arch Public Heal*. 2015;73(1):1-7. doi:10.1186/s13690-015-0099-3
22. Schousboe JT, Taylor BC, Fink HA, et al. Cost-effectiveness of bone densitometry followed by treatment of osteoporosis in older men. *J Am Med Assoc*. 2007;298(6):629-637. doi:10.1001/jama.298.6.629
23. Kouta Ito, Elena B. Elkin, Monica Girotra and MJM. Cost-Effectiveness of Fracture Prevention in Men Who Receive Androgen Deprivation Therapy for Localized Prostate Cancer. *Ann Intern Med*. 2010;152(10):621-629. doi:10.7326/0003-4819-152-10-201005180-00002.Cost-Effectiveness
24. Borgström F, Johnell O, Jönsson B, Zethraeus N, Sen SS. Cost effectiveness of alendronate for the treatment of male osteoporosis in Sweden. *Bone*. 2004;34(6):1064-1071. doi:10.1016/j.bone.2003.12.028
25. Silverman S, Agodoa I, Kruse M, Parthan A, Orwoll E. Denosumab for Elderly Men with Osteoporosis: A Cost-Effectiveness Analysis from the US Payer Perspective. *J Osteoporos*. 2015;2015. doi:10.1155/2015/627631
26. Parthan A, Kruse M, Agodoa I, Silverman S, Orwoll E. Denosumab: A cost-effective alternative for older men with osteoporosis from a Swedish payer perspective. *Bone*. 2014;59:105-113. doi:10.1016/j.bone.2013.11.002
27. Hiligsmann M, Burlet N, Fardellone P, Al-Daghri N, Reginster JY. Public health impact and economic evaluation of vitamin D-fortified dairy products for fracture prevention in France. *Osteoporos Int*. 2017;28(3):833-840. doi:10.1007/s00198-016-3786-1
28. Hiligsmann M, Sedrine W Ben, Bruyère O, Evers SM, Rabenda V, Reginster JY. Cost-effectiveness of vitamin D and calcium supplementation in the treatment of elderly women and men with osteoporosis. *Eur J Public Health*. 2015;25(1):20-25. doi:10.1093/eurpub/cku119
29. Chan DC, McCloskey E V., Chang C Bin, et al. Establishing and evaluating FRAX® probability thresholds in Taiwan. *J Formos Med Assoc*. 2017;116(3):161-168. doi:10.1016/j.jfma.2016.03.006
30. Makras P, Athanasakis K, Boubouchairopoulou N, et al. Cost-effective osteoporosis treatment thresholds in Greece. *Osteoporos Int*. 2015;26(7):1949-1957. doi:10.1007/s00198-015-3055-8
31. Tosteson ANA, Melton LJ, Dawson-Hughes B, et al. Cost-effective osteoporosis treatment thresholds: The United States perspective. *Osteoporos Int*. 2008;19(4):437-447. doi:10.1007/s00198-007-0550-6

32. Lippuner K, Johansson H, Borgström F, Kanis JA, Rizzoli R. Cost-effective intervention thresholds against osteoporotic fractures based on FRAX® in Switzerland. *Osteoporos Int*. 2012;23(11):2579-2589. doi:10.1007/s00198-011-1869-6
33. Kanis JA, Johnell O, Oden A, et al. Intervention thresholds for osteoporosis in men and women: A study based on data from Sweden. *Osteoporos Int*. 2005;16(1):6-14. doi:10.1007/s00198-004-1623-4
34. Nayak S, Greenspan SL. Cost-Effectiveness of Osteoporosis Screening Strategies for Mens. *J Bone Min Res*. 2016;31(6):1189-1199. doi:10.1002/jbmr.2784.Cost-Effectiveness
35. Schousboe JT, Gourlay M, Fink HA, et al. Cost-effectiveness of bone densitometry among Caucasian women and men without a prior fracture according to age and body weight. *Osteoporos Int*. 2013;24(1):163-177. doi:10.1007/s00198-012-1936-7
36. Schwenkglenks M, Lippuner K. Simulation-based cost-utility analysis of population screening-based alendronate use in Switzerland. *Osteoporos Int*. 2007;18(11):1481-1491. doi:10.1007/s00198-007-0390-4
37. Ito K, Hollenberg JP, Charlson ME. Using the osteoporosis self-assessment tool for referring older men for bone densitometry: A decision analysis. *J Am Geriatr Soc*. 2009;57(2):218-224. doi:10.1111/j.1532-5415.2008.02110.x
38. Leal J, Gray AM, Hawley S, et al. Cost-Effectiveness of Orthogeriatric and Fracture Liaison Service Models of Care for Hip Fracture Patients: A Population-Based Study. *J Bone Miner Res*. 2017;32(2):203-211. doi:10.1002/jbmr.2995
39. Fleurence RL. Cost-effectiveness of fracture prevention treatments in the elderly. *Int J Technol Assess Health Care*. 2004;20(2):184-191. doi:10.1017/S0266462304000960
40. Hiligsmann M, Ben Sedrine W, Bruyère O, Reginster JY. Cost-effectiveness of strontium ranelate in the treatment of male osteoporosis. *Osteoporos Int*. 2013;24(8):2291-2300. doi:10.1007/s00198-013-2272-2
41. Wan Y, Zeng F, Tan H, et al. *Cost-Effectiveness Analyses of Denosumab for Osteoporosis: A Systematic Review*. Vol 33.; 2022. doi:10.1007/s00198-021-06268-9
42. Lewiecki EM, Adachi J, Knychas D. The Efficacy and Safety of Abaloparatide-SC in Men with Osteoporosis : A Randomized Clinical Trial. :0-3. doi:10.1002/jbmr.4719
43. Hiligsmann M, Williams SA, Fitzpatrick LA, Silverman SS, Weiss R, Reginster JY. Cost-effectiveness of sequential treatment with abaloparatide vs. teriparatide for United States women at increased risk of fracture. *Semin Arthritis Rheum*. 2019;49(2):184-196. doi:10.1016/j.semarthrit.2019.01.006
44. Le QA, Hay JW, Becker R, Wang Y. Cost-effectiveness Analysis of Sequential Treatment of Abaloparatide Followed by Alendronate Versus Teriparatide Followed by Alendronate in Postmenopausal Women With Osteoporosis in the United States. *Ann Pharmacother*. 2019;53(2):134-143. doi:10.1177/1060028018798034
45. Mori T, Crandall CJ, Ganz DA. Cost-Effectiveness of Sequential Teriparatide/Alendronate Versus Alendronate-Alone Strategies in High-Risk Osteoporotic Women in the US: Analyzing the Impact of Generic/Biosimilar Teriparatide. *JBMR Plus*. 2019;3(11):1-11. doi:10.1002/jbm4.10233
46. Kaufman J, Cooper C. Europe PMC Funders Group Treatment of osteoporosis in men. 2013;53(1):134-144. doi:10.1016/j.bone.2012.11.018.Treatment

47. Elaine Dennison. *Osteoporosis Treatment: A Clinical Overview*.; 2021.
48. Cosman F, de Beur SJ, LeBoff MS, et al. Clinician's Guide to Prevention and Treatment of Osteoporosis. *Osteoporos Int*. 2014;25(10):2359-2381. doi:10.1007/s00198-014-2794-2
49. https://www.uptodate.com/contents/bone-density-testing-beyond-the-basics.
50. Kanis JA, McCloskey E V., Harvey NC, Johansson H, Leslie WD. Intervention thresholds and the diagnosis of osteoporosis. *J Bone Miner Res*. 2015;30(10):1747-1753. doi:10.1002/jbmr.2531
51. Kanis JA, Harvey N, Cooper C, et al. A systematic review of intervention thresholds based on FRAX: A report prepared for the National Osteoporosis Guideline Group and the International Osteoporosis Foundation. *Arch Osteoporos*. 2016;11(1). doi:10.1007/s11657-016-0278-z
52. Zoccarato F, Ceolin C, Trevisan C, et al. Comparison between real-world practice and application of the FRAX algorithm in the treatment of osteoporosis. *Aging Clin Exp Res*. 2022;(0123456789). doi:10.1007/s40520-022-02212-x
53. Compston J, Cooper A, Cooper C, et al. UK clinical guideline for the prevention and treatment of osteoporosis. *Arch Osteoporos*. 2017;12(1). doi:10.1007/s11657-017-0324-5
54. Wu CH, Kao IJ, Hung WC, et al. Economic impact and cost-effectiveness of fracture liaison services: a systematic review of the literature. *Osteoporos Int*. 2018;29(6):1227-1242. doi:10.1007/s00198-018-4411-2
55. https://www.pbs.gov.au/medicine/item/12301K.
56. Talevski J, Sanders KM, Watts JJ, et al. Sex differences in recovery of quality of life 12 months post-fracture in community-dwelling older adults: analyses of the Australian arm of the International Costs and Utilities Related to Osteoporotic Fractures Study (AusICUROS). *Osteoporos Int*. 2022;33(1):67-75. doi:10.1007/s00198-021-06058-3
57. Nayak S, Greenspan SL. Osteoporosis Treatment Efficacy for Men: A Systematic Review and Meta-Analysis. *J Am Geriatr Soc*. 2017;65(3):490-495. doi:10.1111/jgs.14668
58. Hiligsmann M, Li N, Cooper C, et al. Improving the reporting of economic evaluation in osteoporosis: the value of CHEERS 2022 statement. *Osteoporos Int*. 2022;(0123456789):1-2. doi:10.1007/s00198-022-06400-3

CHAPTER 4

Effective Risk Communication and Improving Adherence

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INTRODUCTION

Despite the substantial human, economic and societal burden of osteoporotic fractures and the availability of effective and safe osteoporosis medications, osteoporosis remains largely underdiagnosed and undertreated. The treatment gap, discussed in detail in the previous chapter and defined as the percentage of eligible individuals not receiving treatment with osteoporosis medication in the largest five countries of the European Union plus Sweden, was estimated to be 73% for women and 63% for men in 2017 [1]. In addition, adherence to osteoporosis medications remains poor and suboptimal, with numerous patients not appropriately taking their medicines or discontinuing therapies earlier [2].

The decision by an individual patient to take an osteoporosis medication or engage in healthy lifestyle behaviours (e.g. taking calcium, vitamin D and taking regular exercise), depends on the patient's understanding of their individual fracture risk, their understanding of the risks and benefits of taking action and the risks of not taking action, and the barriers to implementing an action plan. Patients at risk for fractures who do not take actions to reduce risk may not be recognizing their own vulnerability to fracture. Once individuals do understand that they are at risk of future fracture and that they wish to consider taking medication or change behaviour, they need to overcome whatever barriers exist and then initiate that behaviour or medication (i.e. primary adherence). They will need to take the medication as prescribed by the health care professional (i.e. implementation or compliance). They will need to continue taking the medication or maintain lifestyle change for the long term (i.e. secondary adherence or persistence). If they are taking medication, they may stop or change medications due to perceived or experienced risks and/or perceived lack of efficacy or simply decide they do not wish to take medication. They may simply choose not to persist with lifestyle changes.

In this chapter we will start by understanding factors involved in adherence or persistence to medication and behaviours and then try to understand the complexities of the communication of risk to an individual.

ADHERENCE TO OSTEOPOROTIC MEDICATION

Definition of Medication Adherence

Adherence to medication is a crucial part of patient care and necessary for reaching clinical goals [3] while non-adherence leads to poor clinical outcomes, higher morbidity and death rates, and unnecessary healthcare expenditure. A World Health

Organisation (WHO) report underlines the fact that adherence to chronic treatments is often as low as 50% [4]. Poor or non-adherence to medication therefore remains a major problem in most chronic diseases, including osteoporosis [2].

Medication adherence has been defined in several ways. The WHO defined adherence in 2001 as "the degree to which the person's behaviour corresponds with the agreed recommendations from a health care provider [5]." In 2012, a collaboration of European research groups in the field of medication adherence funded by the European Commission suggested the ABC taxonomy for describing and defining adherence to medications, which consisted of three components: (a) initiation, (b) implementation and (c) discontinuation [6]. Initiation occurs when the patient takes the first dose of a prescribed medication, discontinuation marks the end of therapy, when the next dose to be taken is omitted and no more doses are taken thereafter, and implementation is the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen, from initiation until the last dose. Medication persistence is further defined as the length of time between initiation and the last dose, which immediately precedes discontinuation [6].This definition is in agreement with the definition of the Group for the Respect of Ethics Excellence in Science in osteoporosis [7], with the exception that implementation has replaced compliance, and initiation is preferred over primary adherence [2].

Measures of Adherence

Quantification of adherence is crucial to provide researchers, clinicians, and patients with meaningful metrics and further to estimate the effectiveness of prescribed therapies. Different methods are available to quantify medication adherence, consisting of direct and indirect methods. A description of the methods of adherence measurements including advantages and disadvantages can be found in Table 1.

Direct methods include measurements of the drug (or a metabolite) concentration in body fluids [8]. Although it may be considered as being an adequate and precise method, some variables should be taken into account, including drug metabolism, individual variation in the pharmacokinetics of the drug, drug-drug interactions and drug-food interactions, which may interfere with the accuracy of the method. In addition, direct methods are difficult to use in practice by reason of being costly and time-consuming, and could be viewed as invasive by some patients. Therefore, various indirect methods are more commonly currently used to measure medication adherence, including self-report, pill count, electronic monitoring and the use of prescription and refill databases.

Self-reporting such as by diaries or retrospective questionnaires, is the simplest method for measuring adherence. It may be useful for assessing very recent drug use [9], however, it tends to overestimate adherence over a long time period, in comparison to direct methods, since the patients may be influenced by recall or reporting bias due to selective disclosure of non-adherence information by the patient [8].

Pill count is a straightforward method which calculates the number of doses that have been taken between appointments and compares it with the total number of doses that the patient has received. An adherence ratio is then calculated. It can assess an average adherence, but does not give specific information about daily adherence or patterns of adherence [9].

Electronic monitoring devices, such as Medication Event Monitoring System (MEMS) are devices incorporated in the container that stores the dosing history of the patient's prescribed medication. It is commonly used in clinical trials though is more difficult to use in real-life settings and has been proven to be highly accurate in several studies. It may be used as a reference standard for validating other adherence methods [8].

Electronic databases are based on the assumption that prescription refilling patterns coincide with medication taking behaviour. Prescription refill data have the capacity to provide rough adherence estimations since they offer information on the possession of medication and not proof on actual intake of medicine, and in some cases could give overestimations. They gives the opportunity to assess non-adherence in a large population over an extensive period of time, including multi-drug non-adherence. However, they do not give information on individual patients' rates of adherence [8].

The overall measurement/calculation of adherence is commonly conducted using Medication Possession Ratio (MPR) and Proportion of Days Covered (PDC). MPR is usually defined as the sum of all days of medication supply received during a given time [7]. PDC is the number of days when the drug was available divided by the number of days in the study period [8]. A cut-off point is commonly advised (at least 80% adherent), which categorizes the patients as being adherent and non-adherent [10, 11].

Generally, electronic databases are the appropriate method to measure initiation and discontinuation of therapy while electronic monitoring is the preferred method for implementation, although they could be difficult to set up in real-life settings.

The use of self-reports or pill counts could be alternative methods [2].

Table 1. Measures of adherence [8]

Methods of measurement	Parameter measured	Advantages	Disadvantages
Direct			
Measurement of drug/metabolite levels	Concentration of the drug/metabolite	Accurate; Objective, proving the ingestion of the drug	Costly; Invasive; Inter individual differences
Indirect			
Self-reporting	A value that is interpreted in regards to a pre-established cut-off point	Easy to use; Inexpensive	Overestimate adherence; Subjective, influenced by recall or reporting bias
Pill counts	Number of doses missed	Simple Mostly used in clinical trials	No evidence of ingested medication
Electronic databases	Medication possession ration (MPR); Proportion of days covered (PDC)	Easy to use; Inexpensive; Non-invasive, patients not aware that they are being monitored; Especially specific to identify non-adherent patients	Evidence of the drug being dispensed but not ingested
Electronic monitoring devices	Overall percentage of doses taken; Dosing regime	Objective; Additional information on degree of adherence; One of the most accurate methods	The patient is aware of the evaluation; No actual evidence that the medication is being ingested

Adherence to Osteoporotic Medications: State of the Art

Osteoporosis medications have been shown to be effective in fracture risk reduction [12], however, as a chronic disease, non-adherence to pharmacological treatment in osteoporosis is a well-recognized problem [13] and reported in several studies. As discussed previously, bisphosphonates are the first line drugs for osteoporosis. In line with treatment initiation rates in other diseases [14], about 20–30% of patients do not initiate a treatment after a prescription for oral bisphosphonates [15] even when there is no cost to the patient of the medication. In addition, patients on bisphosphonates frequently miss doses [14]. Furthermore, multiple large observational studies from countries with different health systems have reported low rates of long-term adherence with oral bisphosphonates (daily

or weekly) [14]. In a recent review [16] including 89 studies published up to April 2018, the mean persistence of oral bisphosphonates for 6 months, 1 year and 2 years ranged from 34.8% to 71.3%, 17.7% to 74.8% and 12.9% to 72.0%, respectively. Although a number of studies reported high levels of persistence and adherence, patient persistence and adherence with oral bisphosphonates was poor and reduced notably over time. In a Belgian study [17], the rate of persistence was estimated at 39.5% for postmenopausal women at 1 year (without a gap of more than 5 weeks in treatment), while 48.1% of patients had a 12-month MPR ≥80% (patients as being adherent).

Apart from bisphosphonates, other osteoporosis medications are also commonly used. A recent systematic review and meta-analysis reported substantial heterogeneity in reports of persistence and adherence rates with parenteral osteoporosis therapies [18]. Twenty nine studies examined persistence to teriparatide, with persistence rates of 10–87% (median 55%) at 1 year and 10–69% (median 29.5%) at 2 years. A 2-year Japanese observational study [19] showed that once-daily teriparatide adherence and persistence rates were higher among patients who enrolled in a patient support program than among those who did not (54.2 vs. 48.3%). Although we expect greater persistence with treatment injected by a health care practitioner (e.g., denosumab), persistence remains suboptimal after 24 months. Median persistence rates of 46% were estimated at 2 years for denosumab [18].

Low adherence to osteoporotic medications is thus well recognized, and has been shown to reduce the potential benefits of osteoporosis therapy leading to increased risk of fractures and representing a substantial clinical and economic burden. Understanding the determinants of patient non-adherence and the potential effects of adherence-enhancing interventions are therefore crucial.

Determinants of Non-adherence

Adherence is a complex multidimensional phenomenon; profiles of non-adherence differ from patient to patient. Some patients never initiate a treatment, while others delay initiation of therapy. There are patients who frequently miss doses, and multi-week drug holiday periods have also been observed [20]. Several patients discontinue treatment earlier than prescribed and many patients are noted to have undergone multiple episodes of starting and stopping drugs [2].

The WHO has classified factors for non-adherence of medication into five main categories: socio-economic factors, health care team and system related factors, condition-related factors, therapy-related factors, and patient-related factors

[21]. Kardas et al. [22] conducted an umbrella review up to December 2009 on the determinants of patient adherence on the basis of a recently agreed European consensus taxonomy and terminology. Fifty one reviews were identified covering 771 individual factor items, of which most were determinants of implementation, and only 47 determinants of persistence with medication.

In the field of osteoporosis, Yeam et al. [23] performed a systematic review up to January 2018 and identified 24 factors with 139 sub-factors that influence patients' adherence to anti-osteoporotic therapy from 124 relevant studies. These factors were then grouped into categories as per the WHO recommendation [21]. Condition-related factors that were associated with poorer medication adherence included, among others, polypharmacy. Patients who had never taken a prescription medication also demonstrated poorer global adherence [15]. A history of falls was associated with higher medication adherence. Patient-related factors which were associated with poorer medication adherence included older age and misconceptions about osteoporosis, while therapy-related factors included higher dosing frequency and medication side effects. Both perceived and experienced side effects are reasons for non-adherence, and patients are easily influenced by information from social media or searching online. One study reported that rare yet serious harmful events through prescription of bisphosphonates have received wide coverage in the media and have resulted in perceived risks by the public that may be out of proportion to the absolute risks, leading patients to not fill or refill prescriptions for these drugs [24]. Health system-based factors associated with poorer medication adherence included care under different medical specialties and lack of patient education. Socio-economic-related factors associated with poorer medication adherence included current smoker and lack of medical insurance coverage. In general, patient-related factors were the most commonly studied domain across all studies, followed by therapy-related domains (e.g. convenience of administration, frequency of administration) and condition-related domains.

Additionally, patient perceptions and preferences with osteoporosis medications were also shown to impact adherence behaviour [25] and discontinuation rates [26]. A review investigated the preferences of patients for osteoporosis drug reporting that osteoporotic patients have preferences for medications and their attributes, in particular for less-frequent dosing regimens [27]. Furthermore, another study [28] reported that the low rate of osteoporosis medication initiation may stem from participants having difficulty trusting the content of the video vignettes included in the intervention, since these educational materials were not endorsed by a source familiar to the patient (e.g. their treating physician). As medication non-adherence is affected by multiple determinants, suitable measurement and multifaceted

interventions may be effective to enhance patient adherence to medication.

Consequences of Poor Adherence to Osteoporosis Medications

Poor adherence to osteoporosis medications has substantial clinical and economic consequences. Multiple studies have been conducted to investigate the impact of osteoporosis treatment adherence on fracture risk. Siris et al. [29] undertook a meta-analysis that indicated that adherence and persistence with osteoporosis medications are suboptimal, resulting in increased rates of fragility fractures. Similarly, Ross et al. [30] conducted a meta-analysis and reported that fracture risk increases by approximately 30% with non-adherence and by 30% to 40% with non-persistence. Imaz et al. [31] assessed the impact of adherence to oral bisphosphonates on fracture rate and provided a pooled 46% increased fracture risk in non-compliant patients compared with compliant patients. The increased fracture risk was higher for clinical vertebral fractures than non-vertebral and hip fractures. In addition, another study [32] indicated that among patients who received teriparatide, low-MPR was a significant risk factor for any fracture (OR = 1.64; $p < 0.01$), vertebral fracture (OR = 2.56; $p = 0.001$), and non-vertebral fracture (OR = 1.44; $p = 0.013$). Furthermore, persistence to generic formulations has been shown to be poorer than for branded formulations for some osteoporosis medications [33, 34].

These clinical consequences also lead to economic consequences. For example, an Irish study [35] indicated that poor adherence with osteoporosis medications resulted in around a 50% reduction in the potential benefits observed in clinical trials and a doubling of the cost per quality-adjusted life-years (QALY) gained from these medications. Similar results have been observed in other studies [36, 37]. Therefore, poor adherence and failure to persist with osteoporosis medications results not only in deteriorating health outcomes, but also in a decreased cost-effectiveness of pharmacotherapy [35]. The integration of medication adherence into pharmacoeconomic analyses has therefore been recommended in several studies [38, 39]. A recent published osteoporosis-specific guideline for the design and conduct of an economic evaluation in osteoporosis has suggested the use of real-world medication adherence in an alternative scenario, as well as sensitivity analyses varying adherence levels [37].

Interventions to Improve Adherence to Osteoporosis Medications

In recent years, several interventions and programs have been developed to improve medication adherence for osteoporosis (see Table 2). Hiligsmann et al. [40] systematically reviewed studies that evaluated interventions to improve medication adherence in osteoporosis. A total of 20 studies were included. The

most frequent intervention was education, followed by monitoring/supervision, suggested drug regimens, drug regimens and patient support, pharmacist intervention, and electronic prescription. In 2019, Cornelissen et al. [41] updated the previous review including recently published relevant studies up to December 2018. Interventions were classified as patient education, suggested drug regimens, monitoring and supervision, and interdisciplinary collaboration, with mixed results on medication adherence and persistence, though more positive effects were observed for multicomponent interventions with active patient involvement, counselling and shared decision-making.

Table 2. Interventions identified through previous systematic reviews

	Hiligsmann et al. [38]	Cornelissen et al. [41]
Time period	January 1999–June 2012	July 2012–December 2018
Total studies included	20	15
Types of interventions	Education (n = 11) Monitoring/supervision (n = 4) Drug regimens (n = 2) Drug regimens and patient support (n = 1) Pharmacist intervention (n = 1) Electronic prescription (n = 1)	Education (n = 9) Drug regimen (n = 3) Monitoring and supervision (n = 2) Interdisciplinary collaboration (n = 1)
Studies with positive effects (improved medication adherence)	Education (n = 4) Drug regimens (n = 2) Drug regimens and patient support (n = 1) Pharmacist intervention (n = 1) Electronic prescription (n = 1)	Education (n = 2) Monitoring and supervision (n = 1)

Specially, ***patient education*** is the most frequent intervention considered in both reviews [38, 39], which can be classified into different forms including group educational sessions (consisted of meetings with 4–6 patients and a psychologist), provision of education material (providing booklets or flyers with information or providing DVDs with visual information), the use of a decision aid, and motivational interviewing. In some cases, education was combined with counselling. The method of administration and the intensity of patient counselling varied from offering patients advice and recommendation concerning the educational material [42] up to four telephonic follow-up calls combined with four group sessions in 12 months [43]. One study [44] combining patient education, counselling, blood tests, BMD test prescription, and follow-up phone calls reported an increase in

adherence between 40 (minimal) and 53% (intensive) in the intervention groups, compared with 19% in usual care. In another study [45], an education program was combined with a referral to an endocrinologist by a nurse reporting significant improvement of implementation rates compared with usual care. In addition, a coordinator-based screening program was conducted in a study by Beaton et al. [42], reporting significant improvements in BMD testing and treatment initiation after the initiation of this program. Hence the initiation of patient education can improve patients' interaction/communication with doctors/coordinators and, therefore, their knowledge of osteoporosis and perception of future fracture risk.

Special ***drug regimen implementation*** is an important determinant of non-adherence, in particular for bisphosphonates. Several studies indicated that a flexible dosing regimen was associated with improved adherence. One study [46] reported that compared to common oral bisphosphonates, prescription of gastro-resistant (GR) risedronate tablets with less strict administration requirements was associated with improved persistence. Another study [47] indicated that a significant difference between the flexible and fixed regimens was seen in persistence in favour of the flexible regimen. In addition, longer dosing regimen (such as 6-month subcutaneous injection of denosumab or yearly intravenous injection of zoledronic acid) may improve adherence, although adherence levels have also been disappointing and far from optimal [2].

Monitoring and supervision such as phone calls and counselling may also improve medication adherence. One study [48] suggested that implementation of telephone monitoring (medical secretaries contacted the patients every 2 months by telephone) in the routine medical management of osteoporosis could contribute to a reduction of complications associated with treatment discontinuation compared with patients without telephone follow-up (67% vs. 30%,). In another study [49], the MeMo program consisted of initial structured counselling (regarding administration, effectiveness, and possible side-effects) and continuous actively monitoring after 2 weeks (focused on patients' first experiences with adverse effects and drug administration problems), and every 3 months, where pharmacists actively searched for patients who should have redeemed a new prescription for their osteoporosis medication. Compared with patients in usual care, non-adherence and discontinuation with osteoporosis medication were decreased for patients who participated in this program. Monitoring and supervision could enhance communication between patients and caregivers and further motivate patients to maintain good adherence to the treatment.

Fracture liaison services (FLSs) represent an ***interdisciplinary collaboration***

program which connects different physicians (institutional health care professionals (HCPs) with primary care physicians (PCPs) in outpatient settings) and facilitate communication between them and patients for secondary fracture prevention. A systematic review and meta-analysis [50] indicated that compared with patients receiving usual care (or those in the control arm), patients receiving care from an FLS program had higher treatment initiation (38.0% vs 17.2%) and greater adherence (57.0% vs 34.1%), significant FLS-associated with improvements in treatment (95% CI 0.16–0.25) and adherence (95% CI 0.13–0.31). In addition, multiple studies have also reported that FLSs have a potential to improve treatment initiation [51,52]. The FLS is described in detail in the next chapter.

Shared decision-making offers a structured way to incorporate evidence as well as patient values and preferences into medical decision making [53], and has been increasingly recommended in several recent guidelines for its potential of improving treatment initiation and medication adherence. Decision aids are frequently used to facilitate elements in shared decision making. In one study patients received a standard brochure, or a decision aid (a tailored pictographic 10-year fracture risk estimate, absolute risk reduction with bisphosphonates, side effects, and out-of-pocket cost) [54] with the group receiving the decision aid having higher adherence to medication. In addition, patients receiving the decision aid were 1.8 times more likely to correctly identify their 10-year fracture risk and 2.7 times more likely to identify their estimated risk reduction with bisphosphonates.

As discussed earlier in this book, Bone turnover marker response has been used as an intervention for improving treatment adherence [38, 55]. Low response may be detected shortly after treatment has been started and may indicate low adherence, low bioavailability, interactions with other drugs, or the presence of secondary osteoporosis [56]. The IOF and European Calcified Tissue Society Working Group has suggested monitoring the adherence of bisphosphonates by measuring Serum PINP (procollagen type I N-terminal propeptide) and CTX (collagen type I C-terminal telopeptide) at baseline and 3 months after starting therapy to check for a decrease above the least significant change (decrease of more than 38% for PINP and 56% for CTX). If a significant decrease is observed, the treatment should continue, but if no decrease occurs, the clinician should reassess to identify any problems with the treatment, specifically the possibility of low adherence [57]. In addition, a positive message that highlights a good bone turnover marker response can be associated with a significant improvement in persistence [55].
Interventions discussed above could facilitate interaction/communication between patients and doctors, and therefore help patients improve their knowledge of osteoporosis and understand risks and benefits, which would further improve

the quality of clinical decisions and motivate patients to maintain good adherence to osteoporotic-medications. Because well understood communication from healthcare professionals is the foundation of a patient's appropriate understanding of risks, we will now review recommendations and existing tools for effective communication of general health-related risks as well as effective communication of osteoporosis fracture risk.

EFFECTIVE RISK COMMUNICATION TO IMPROVE OSTEOPOROSIS MANAGEMENT

General Health Risk Communication

Bias in Patients-Doctors' Health Communication

Effective communication between a healthcare professional and patient is an important aspect of patient-centred care. Appropriate communication of health-related risks is essential to help patients make the best-informed health-related decisions that are in concordance with their personal values, experiences, and preferences. However, informing patients about their risk of developing a disease, the risk reduction or benefits associated with a drug intake or risk of side-effects associated with a treatment remains challenging. Different factors could (partially) explain difficulties encountered by patients in understanding information provided by their clinicians.

The perception by the patient of the risk that doctors communicate to them is based on the patient's understanding of the medical information provided to them. Patients usually do not understand the complete information provided by healthcare professionals but take the gist or essential message of the medical information. This gist is also influenced by the source of the information (e.g. physician, pharmacist, social media or media coverage). The information is also influenced by several different types of biases which patients often unconsciously use in their medical decision-making:

- ***Immediacy bias*:** A new or novel risk may be perceived differently [58]. If information was heard recently or easily remembered, it may be judged more likely to be true. A good example of this is the side effect osteonecrosis of the jaw (ONJ). Although exceptionally rare, when covered by the media in reports, patients fill fewer osteoporosis medications [15].
- ***Catastrophic bias*:** A side effect may be more easily remembered and feared if it is sensational or catastrophic. A jawbone dying (ONJ) or hip breaking spontaneously (atypical femoral fracture; AFF) is more likely to be remembered

than an upset stomach from an oral bisphosphonate.

- ***Optimism bias:*** People view risks as riskier for other people than themselves [59]. Post-menopausal women at increased risk of fracture tend to underestimate their risk of fracture [60].
- ***Pessimism bias*:** Some individuals overestimate their risk of side effects. They feel that side effects always happen to them when they take a medicine, no matter how low the risk.
- ***Categorical bias:*** Patients, when they hear of a risk, may simply consider the medicine as safe or dangerous. After they learned of the risk of ONJ and AFF, some patients first considered all bisphosphonate drugs as dangerous, then considered all osteoporosis medications as dangerous.

The way clinicians communicate about risk is therefore of primary importance. Rules, recommendations, and guidance for successful risk communication between clinicians and patients have been developed.

General Recommendations for an Effective Communication of Risks

In the report of the science of patient input program of the Medical Device Innovation Consortium (MDIC) published in September 2020 and entitled *"Best practices for communicating benefits, risks and uncertainty for medical devices"* [61], a comprehensive assessment of benefits and risks communication is provided. After providing an overview of the opportunities for communicating benefits, risks and uncertainty information throughout clinical research, direct-to consumer advertising, social media channels, patient decision aids, etc. and defining key concepts of benefits, risks, harm, patient preference, risk tolerance and uncertainty attitudes, authors presented evidence-based key factors and available tools for making an optimal communication. Among other [62–64], authors presented guidelines from the Food and Drug Administration (FDA) published in 2016 [65]. Within its **Guidance to Industry** *"Patient Preference Information – Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and De Novo Requests, and Inclusion in Decision Summaries and Device Labeling"*, the FDA concluded that no single format of risk communication from healthcare professionals to patients is universally superior to another format but developed the following overall recommendations:

1. Avoid solely verbal descriptions of uncertainty. Patients may interpret what "low" and "high" risks are differently;
2. Avoid fractions, decimals, and different denominators when presenting risks of multiple treatments. These are relatively difficult for cognitive processing and rely on numeracy skills;

3. If possible, describe the benefits and risks in absolute scales (e.g. 1 in 100) instead of relative terms, which better inform the actual benefits and risks;
4. If possible, use multiple formats simultaneously (e.g., verbal frequency, percent, and icon array/pictograph). Relative understanding of these formats varies from patient to patient. Moreover, one format may make the other formats easier to understand;
5. If possible, describe uncertainty in both positive and negative framing(e.g., 20% chance of adverse events or 80% chance of no adverse events) to avoid cognitive bias. Indeed, the way health care professionals frame the risk (e.g. 'Is a treatment 90% effective or 10% ineffective?') may influence whether the patient accepts the information;
6. Pre-test the communication format. Since patient populations vary, pre-testing the chosen format can improve the comprehension of the format by the study population of interest.

Since patients may immediately forget the information that doctors present to them [66], or simply choose to ignore this information, it is important to keep messages about risk simple. Simplified language (e.g. avoidance of clinical or statistical jargon, use of simple and well-structured sentences), is recommended so people with low literacy can read and understand the information [64]. A range of terms are commonly used in day-to-day life to describe risk. For example, risk may be categorized as "low", "moderate", "high" or "very high". A systematic review performed in 2014 [67], compared the use of numbers to the use of words in communicating risks. Results indicated that verbal descriptors including "common", "uncommon" and "rare" lead to an overestimation of the probability of adverse effects compared to numerical information. Interpretation of these terms varies widely from person to person and therefore authors have suggested using examples (i.e. comparison of medical risks to common nonmedical risks such as a risk of a traffic accident) or analogies to illustrate the meaning of such terms [68]. Another recent study pointed to a very considerable variation in the numerical translation of verbal probability by both patients and clinicians suggesting that verbal probability expression should not be used in isolation for communication between doctors and patients [69]. Nevertheless, "adding" a verbal description to a numeric data may be useful to better frame the information so a participant understands the risk.

Another important aspect in risk communication is the valence (negativity or positivity) of words used by clinicians. When talking about risk, it is possible to present either benefits or risks, or to communicate using positive/gain terms or using negative/loss terms. To illustrate that, researchers found that presenting adverse event information before benefits (compared to benefits before adverse

events) lowers the likelihood that subjects will perceive that the benefits outweigh the risks of a proposed new medication [70]. Warning patients of risks such as side-effects has also been shown to increase the incidence of these side-effects, (through the nocebo effect) while positively framing risk information did not [71]. It is also important for the clinician to build a trust-based relationship with patients. If patients have trust in their healthcare provider, they are more likely to understand and accept the information [72]. Nevertheless, it has been shown that information about risk sometimes needs to be heard and confirmed by other persons (e.g. a spouse, a child, a caregiver, or a friend) who may or may not be present before being accepted. Healthcare professionals should therefore try to understand the role of others in risk communication, particularly social media in decision making but also the perspective of peers, family, and friends.

Communication of Numeric Data

It has been shown that numerous patient-related factors such as advanced age [73] or low literacy [74] may impair understanding of evidence-based information such as numerical concepts. Lipkus et al. [75] showed that many patients cannot perform basic numeric tasks. Even among highly educated people, they found that 16% incorrectly answered a simple question about risk magnitude (e.g. Which represents the larger risk: 1%, 5% or 10%?). Highly numerate people are likely to pay more attention to numbers, better understand them, and ultimately use them more often in decisions. Lower numeracy has also been shown to be associated with overestimation of risk probabilities, being more susceptible to being influenced by factors other than numerical data (e.g., framing, mood states, feedback from others), and greater denominator neglect [76]. Denominator neglect is a classical bias met in ratio concepts understanding. People often pay too much attention to the number of times an event happens (numerator) without paying attention to the overall number of opportunities for it to happen (denominator). For example in a perfect example of denominator neglect Yamagishi et al. [77] showed in one study that people rated the likelihood of a cancer killing 1286 out of 10,000 people (i.e. 12.86%) as higher than 24.14 out of 100 people (i.e. 24.14%).

Communication of risks can be presented to the patient under different more or less complex numeric formats. First, it is recommended that clinicians present as simple frequencies rather than a percentage. Indeed, this format has been shown to be preferred by patients and improves understanding [62, 64, 78–81]. Second, it has been shown that numerical likelihoods presented as 1-in-X (e.g. 1 in 25) are processed fasted and are perceived as conveying larger likelihoods than the x-in-100 (e.g. 4 in 100) and percentage formats (e.g. 4%) [82, 83]. Pighin and al [84]. suggested that the 1-in-X format may increase the ability to identify oneself as

affected with the possible outcome. Third, there is also a general agreement that decimals (e.g. likelihood of 0.03) should not be used in risk communicates as they may lead to misunderstanding [85]. Fourth, it has been shown that the concept of number need to treat (NNT) may not be readily understood by patients and should be avoided in doctor-patient communication [62, 64, 79, 86]. Fifth, when presenting frequencies information, healthcare professionals should keep the dominator constant to reduce effort and increase comprehension of individuals (e.g. always keep the denominator as 1000 and avoid presenting one time the risk as x of 50 and a second time the risk as x of 1000).

Careful attention to information presentation allows everyone, including less numerate people, to better integrate numbers and use them more effectively in decision making. One solution could be to test the presentation of numeric information with target audiences whenever possible and adapt it as many times it is necessary to increase the comprehensibility and usability of the information; future research in this area is needed.

Communication Using Visual Aid Presentations

Presenting information visually as well as numerically may improve understanding [87–90] though interpretation of graphics have been shown to be dependent upon instructions provided [91] as visual displays can still misrepresent information.

It has been suggested that type and formatting of graphics seems to influence comprehension and behaviour (Fig. 1). Some studies have suggested that the formats that are perceived most accurately and easily by patients are bar graphs (Fig. 1c) and pictographs (Fig. 1c) [92, 93]. while areal presentations (e.g. pie charts (Fig. 1a)) seems less effective [94]. Pictographs (Fig. 1c)can be a useful way to highlight the number of people affected, or not affected, by a medical treatment [95]. In this type of graph, an icon display of symbols or figures shows the entire population at risk (the denominator) and highlighted icons show those in whom an event occurred (the numerator). Icon arrays may be an effective method for eliminating denominator neglect [96]. The performance of icon array however depends on the numerator size. When the outcome is less than 100/1000, for example, pictographs are better understood than bar charts. However, for more even outcomes (e.g. higher than 100/1000), icon array arrangement may be complicated and bar charts seems to work better [97]. Depending on the aim of the communication, pictograms, or pictures to illustrate the risk, can also be used (Fig. 1g). A recent study [98] explored the impact of different type of pictures (anatomical pictures, photos, cartoons and drawings) on health information perception. This study however failed to show the superiority of any type of picture in understanding risk. Finally, it also appears that

the combination of different graphic risk presentations formats seems preferable to a single presentation. In a preference study [99] that compared six types of graphical representations, an augmented bar chart combined with a flow diagram seemed to be the most preferred combined format of risk communication.

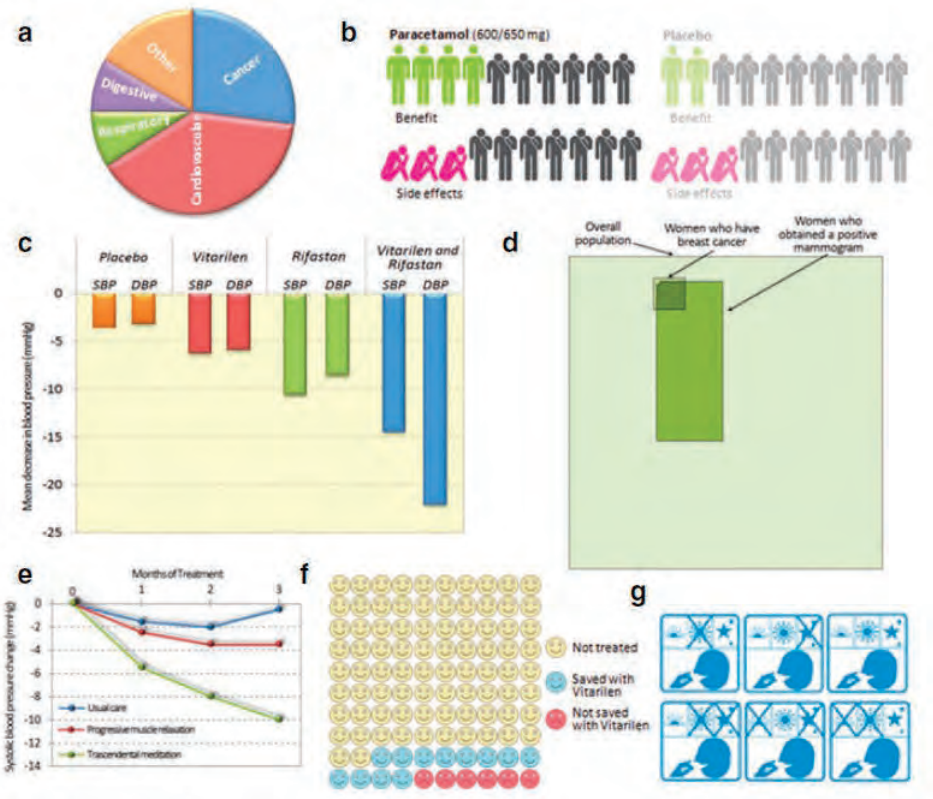

Figure 1. Examples of visual aids (Figure issued from Garcia-Retamero et al. [89], used with permission).
(**a**) A pie chart reporting the proportion of deaths by cause of death. (**b**) Icon arrays representing benefits and side effects of a medical treatment and a placebo. (**c**) A bar chart comparing the efficacy of two medical treatments (DBP = diastolic blood pressure; SBP = systolic blood pressure). (**d**) A visual grid to help infer the predictive value of mammography screening. (**e**) A line plot comparing the efficacy of several therapies. (**f**) Icon arrays to communicate treatment–risk reduction. (**g**) Pictograms reporting dosage, timing, and action information about prescribed medications

Communication Using Leaflets

In 2006, a study reviewing 50 leaflets of the most prescribed medicines in England and Wales highlighted substantial variation in the methods used to communicate risk to patients [100], and in which only 8% of leaflets provided any form of numerical indication of risk. Communication using patient information leaflets have shown variable results in regards to its efficacy. In a study including 1000 health practitioners, only a small minority of responders correctly stated the meaning of terms that are used to describe the risk presented in a communication leaflet [101]. Another study reported that patients who are provided with supplementary written information in the form of leaflets have a higher level of knowledge when compared with patients who received no written information [101].

It is also important to keep in mind that less information may be more effective. When designing leaflets or education materials, there is a natural tendency to present a lot of information to be sure not to miss any important data. However, presenting too much information can distract patients, prevent them focusing on the essential information and understanding the information that is needed for decision making [102]. Catching the essential is therefore one important feature in risk communication.

Conclusion on General Health Risk Communication

A considerable amount of data highlights the importance of well-build risk communication from clinicians to patients using adequate support tools. Different factors may improve the quality of communication between healthcare professionals and patients: the way the information is presented from clinicians, the capacity of the clinicians to adapt their language to the patient they have in from of them, the relationship between clinicians and patients, the way the information is understood by patients, the self-perception and understanding of their own disease, their perspective in regards of their own health, their health literacy, their numeracy, their own emotions and experiences, etc. The globality of these rules could be applied for communicating risk in various pathologies, including communication of fractures risk for osteoporosis population.

Risk Communication in the Context of Osteoporosis Medication

Importance of Risk Communication In Osteoporosis

Adequate risk communication is especially important in a disease like osteoporosis where fracture risk, treatments effects and risk of side-effects represent key information for an informed decision [103]. Current data reveals care gaps and limited communication about fracture risks between therapists and patients [104, 105]. Osteoporosis patients are often dissatisfied with the information they

received from health professionals. Studies also report difficulties of patients in interpreting the diagnosis of osteoporosis, the risk of fracture and the way they have to manage their disease in everyday life [104]. Moreover, poor quality of written materials available to communicate information about prevention and treatment of osteoporosis is also often observed, which limits informed decision making [106]. From a clinical and public health point of view, there is a huge need for a patient's understanding of the risk of fractures and their consequences. Research also shows that patients often do not consider themselves at risk of fracture, even if they have suffered a previous fracture, which is an important aspect to consider by clinicians in fracture risk communication [107]. It is not always necessary for doctors to calculate fracture risk and some may even consider fracture risk assessment as not necessary for certain categories of patients. Indeed, most countries accept the presence of a previous fracture or a very low BMD as being evidence of need for treatment alone without fracture risk assessment [108]. Nevertheless, even with those patients, the communication of fracture risk may be a good opportunity to involve the patients in the understanding and management of their own disease and also to motivate patients to be more adherent to treatment. Indeed, fractures in both men and women often precedes a cascade of declining mobility, physical activity, muscle strength, quality of life and balance contributing to the loss of independence in daily activities that could further lead to institutionalization, as well as falls and fall-related injuries including fractures and increased mortality risk [109–111].

Even if clinical indicators, performance measures, and educational tools to better understand and identify fracture risk are now available, realizing the full benefits of these advances is not always easy.

Key Elements for Optimal Communication of Fractures Risk

For effective fractures risk communication, healthcare professionals need to consider what is important to communicate to patients, what are the patient's needs (e.g. health and biopsychosocial needs) and what is the best way to communicate this information [112, 113]. Optimal fracture risk communication should ideally involve not only patients but also primary care physicians (PCPs). PCPs are often the first line in this risk communication since they have an important role in the care of osteoporosis patients. Healthcare professionals should be able to verify that patients understand the conversation and feel free to ask questions and express their concerns. The teach-back method could also be interesting to assess patients' understanding of their fracture risk [114, 115]. Key components of risk communication also include important communications skills with the use of terminology that is appropriate for the patient's level of health care education.

Moreover, clinicians that are best equipped to communicate risks and benefits are those that are familiar with the medical evidence, are statistically literate, have clinical experience with osteoporosis and its treatment options, and able to translate complex information to a form that is understood by the patient.

Communication can be achieved using written or electronic educational material such as clinical tools (e.g., brochures, graphs, videos, models) or visual graphs that underline the fracture risks (e.g. icon array, bar graph, etc.) [116]. Much more than risk numbers are needed, and, ideally, fracture risk tools should be integrated into bone densitometry reporting or placed into comprehensive, user-friendly, decision aids [117]. In the context of osteoporosis and risk of fractures, output from a fracture tool should ideally provide information in several different ways not all patients receive and digest information about treatment in the same way.

Communication of Fractures Risk Using Letters and Educational Brochures

The most investigated tool to communicate about fracture risk consists of an individual letter with patient's fracture risk and an educational brochure mailed or posted rapidly after a DXA scan [118–125]. This is considered as a rapid, low-cost, direct-to-patient risk of fracture communication tool. Pre-post interventional pilot studies [122, 123] have demonstrated that a personalized letter and an information brochure as a technique of risk communication improved osteoporosis knowledge, feelings of susceptibility regarding osteoporosis as well as the understanding of DXA results. However, this method of communication, tested through different randomized controlled trials [118–120, 125], using usual care as control, has failed to demonstrate the positive impact of this communication tool on change in bone health behaviour of participants (e.g. treatment initiation, calcium and vitamin D intake, enhancing preventive measures against risk of fractures, etc.). It is possible that many patients do not understand the written fracture risk information. Moreover, educational materials such as brochures about osteoporosis or internet websites are often inadequate in their display of evidence-based information and risk communication. Quality of understanding may therefore be limited using this written communication approach. Direct-to consumer conversation may improve disease-state and risk awareness. Counselling and decisions aids has been shown to be more effective [119]. Decision aids should nevertheless be accurate, unbiased, and effective at communicating the desired information.

Communication of Fractures Risk Using Pictures

The communication of fracture risk can be accompanied with a visual representation to allow a better patient's understanding and interpretation. In 2014, Edmonds et al. [126] provided preferences of 142 patients suffering from osteoporosis for four

different visual deceptions of fracture risk (Fig. 2):

1. "Faces array" (Fig. 2(1)), which is a pictogram comprising 100 faces. In the example provided in Fig. 8.2, 79 were smiling and 21 were coloured red and frowning, depicting a 21% risk of breaking a bone in the next 10 days.
2. "Arrow" (Fig. 2(2)), which is a horizontally oriented arrow-shaped, directional graph that integrates a red, yellow and green coloured "stoplight" system to indicate risk. Low risk is associated with green, moderate is associated with yellow and high risk is associated with red. All parts of the arrow are of equal widths.
3. "Stoplight" (Fig. 2(4)), which is an illustration that integrates stoplight colours using a rectangular depiction that does not imply a progression (unlike the arrow presentation) and is scaled to 100 risk.
4. "Bar" (Fig. 2(3)) which is an illustration employing a graduated stoplight colour system but is oriented vertically, similar to thermometers tools.

Of the four risk depictions investigated, the bar graph was the most preferred (selected by 37% of the participants) compared to stoplight (selected by 24%), faces (selected by 22%) or arrow (selected by 17%). The stoplight colour system was regarded as the most "clear," "clean," and "easy to read". Finally, the majority of subjects rated the pictogram as the most difficult to understand as this format does not allow people to quickly ascertain their individual risk category.

Up to now, no study has been able to rate the effectiveness of these visual presentations on patient's intentions of taking medication to prevent fractures [54, 127]. It has not been proven that one technique is superior to another to initiate treatment of patients. Moreover, sometimes the concept of "high risk" for future fracture, even when using a visual graph highlighting the "high risk" segment, can be confusing and can have varying levels of meaning to patients. Many patients believe that "high risk" has little relevance to their personal circumstances [104].

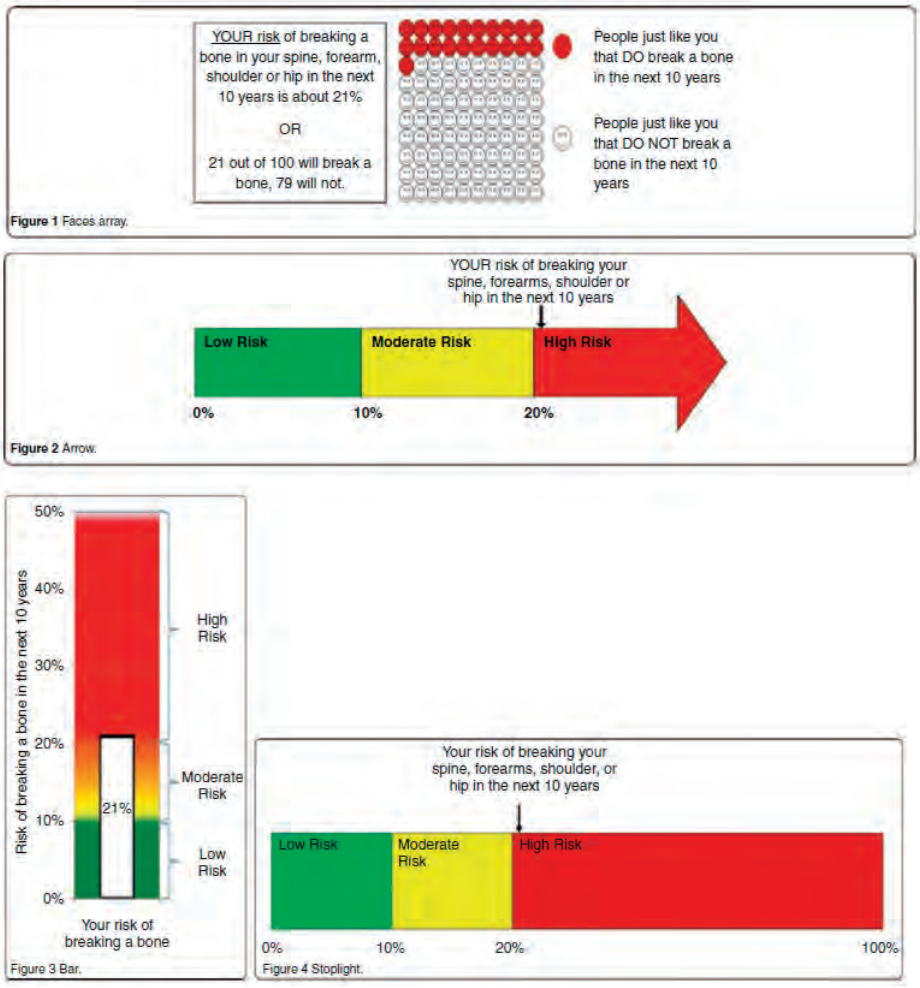

Figure 2. Four risk depictions (Figure issued from Edmonds et al. [126], used with permission)

New Techniques to Communicate Fractures Risk in Osteoporosis

Communication of fracture risk can also be achieved using other types of visual presentations. In 2016, Stephens et al. [128] tested the efficacy of a 3-D bone model (Fig. 3) to communicate fracture risk. In this study, patients received either a standard physician interview following their DXA or an interview augmented by the presentation of a 3-D bone model. This communication technique was shown to be effective in modifying cognitive and emotional representations relevant to treatment initiation among people with osteoporosis, which might facilitate commencement of treatment.

A study by Feldstein et al. [129] compared two interventions with a population receiving either patient-specific clinical guideline advice to the primary care provider delivered by electronic medical record (EMR) message or a second intervention consisting of EMR plus an educational letter mailed to the patient. The results indicated that this communication tool is highly effective at increasing the proportion of patients who receive a BMD measurement or an osteoporosis medication. No added value of the letter mailed to the patient was however noticed.

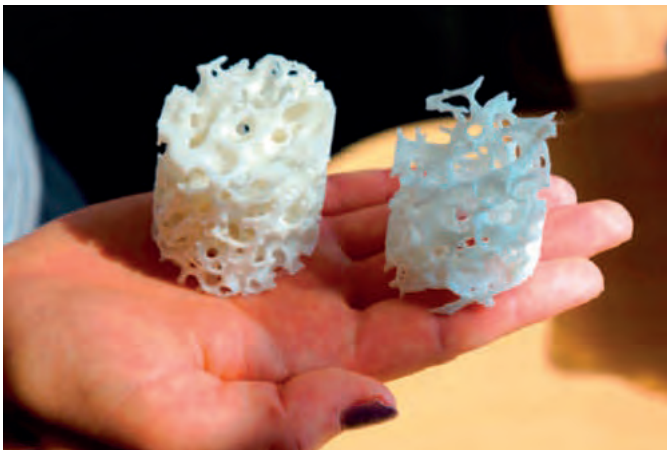

Figure 3. 3-D printed models used as intervention (Figure issued from Stephens et al. [128], used with permission)

CONCLUSION ON FRACTURES RISK COMMUNICATION

Several risk algorithms have been developed and are available for the assessment of individuals' risk of fractures. The FRAX® tool, for example, allows us to estimate the risk of fracture over 10 years. Developing online tools to convert output of those fracture risk algorithms into friendly and visual presentation could facilitate professionals communicating with patients about fracture risk, either at time if visit or later, by mail or email. Using available and effective educational materials in daily practice to communicate in a highly efficient manner about risk could be an important step in enhancing patient education, self-management of the disease, acceptation of treatment and, ultimately, adherence to treatment. Nevertheless, further studies are needed to offer a more comprehensive approach of optimal communication about fractures and osteoporosis risks. Cultural differences between patients, that may impact communication comprehension, are often not considered in studies and further investigation of the impact of these cultural

differences on the understanding of health information and fractures risks could be valuable.

Recommendations for Clinical Practice and Conclusion

Key Recommendations

1. Healthcare professionals need to optimize the doctor- patient relationship, in order to increase patients' trust in the healthcare provider and team.
2. Healthcare professionals need to better understand the individual perspective of the patient in front of them in terms of the patient's perceived risks and benefits for therapy. They need to be good listeners as patients are now more likely to suggest their own treatment plan.
3. Healthcare professionals need to understand the patient's self-perception of fracture risk.
4. Healthcare professionals need to understand the role of biases in decision-making by their patients.
5. Healthcare professionals need to optimise their communication with patients (e.g. framing effects). To do this they need to understand their patient's level of health literacy and numeracy.
6. Healthcare professionals need to better understand the role of other factors, particularly social media in decision making, but also the perspective of peers, family and friends.
7. Healthcare professionals need to understand cultural differences between patients (e.g. are decisions made only by the patient or by patient and family members?).
8. Healthcare professionals can help their patients by helping them understand the risk of no treatment versus risk of treatment explaining these risks to their spouse, child or caregiver as appropriate, and with consent.
9. The burden of nonadherence and poor implementation or compliance to osteoporosis therapies is large both in terms of societal costs of the burden of fractures but equally important in terms of the effects of fracture on quality of life of the individual with fractures.

CONCLUSION

Adherence or persistence to osteoporosis medications and to healthy behaviours such as calcium, vitamin D, exercise and balance training begins with effective communication of the risk of fractures and falls by the health care practitioner. Communication of risk is complex, potentially influenced by gender and cultural differences as well as unconscious biases. The ability to comprehend the information is also limited by differences in the way individual patients understand this information. To help patients understand this information, there is a need for tools to help communicate information about risk as patients have different levels of numeracy, literacy and different learning styles (verbal or visual).

REFERENCES

1. Borgström F, Karlsson L, Ortsäter G, et al (2020) Fragility fractures in Europe: burden, management and opportunities. *Arch Osteoporos*. doi: 10.1007/s11657-020-0706-y
2. Hiligsmann M, Cornelissen D, Vrijens B, et al (2019) Determinants, consequences and potential solutions to poor adherence to anti-osteoporosis treatment: results of an expert group meeting organized by the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal. *Osteoporos Int* 30:2155–2165. doi: 10.1007/s00198-019-05104-5
3. Lam WY, Fresco P (2015) Medication Adherence Measures: An Overview. *Biomed Res Int.* doi: 10.1155/2015/217047
4. World Health Organisation. Adherence to long-term therapies: evidence for action. Available from http://www.who.int/chp/knowledge/publications/adherence_report/ en/.
5. Dobbels F, Van Damme-Lombaert R, Vanhaecke J, De Geest S (2005) Growing pains: Non-adherence with the immunosuppressive regimen in adolescent transplant recipients. *Pediatr Transplant* 9:381–390. doi: 10.1111/j.1399-3046.2005.00356.x
6. Vrijens B, De Geest S, Hughes DA, et al (2012) A new taxonomy for describing and defining adherence to medications. *Br J Clin Pharmacol* 73:691–705. doi: 10.1111/j.1365-2125.2012.04167.x
7. Lekkerkerker F, Kanis JA, Alsayed N, et al (2007) Adherence to treatment of osteoporosis: A need for study. *Osteoporos Int* 18:1311–1317. doi: 10.1007/s00198-007-0410-4
8. Anghel LA, Farcas AM, Oprean RN (2019) An overview of the common methods used to measure treatment adherence. *Med Pharm Reports* 92:117–122. doi: 10.15386/mpr-1201
9. Vrijens B, Heidbuchel H (2015) Non-vitamin K antagonist oral anticoagulants: Considerations on once- vs. twice-daily regimens and their potential impact on medication adherence. *Europace* 17:514–523. doi: 10.1093/europace/euu311
10. Bonafede M, Johnson BH, Tang DH, et al (2015) Etanercept-Methotrexate Combination Therapy Initiators Have Greater Adherence and Persistence Than Triple Therapy Initiators with Rheumatoid Arthritis. *Arthritis Care Res* 67:1656–1663. doi: 10.1002/acr.22638
11. Chu LH, Kawatkar AA, Gabriel SE (2015) Medication Adherence and Attrition to Biologic Treatment in Rheumatoid Arthritis Patients. *Clin Ther* 37:660–666. doi: 10.1016/j.clinthera.2014.10.022
12. Kanis JA, Cooper C, Rizzoli R, et al (2019) European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Osteoporos Int* 30:235–238. doi: 10.1007/s00223-018-00512-x
13. Rabenda V, Reginster JY (2010) Overcoming problems with adherence to osteoporosis medication. Expert *Rev Pharmacoeconomics Outcomes Res* 10:677–689. doi: 10.1586/erp.10.76
14. Fischer MA, Stedman MR, Lii J, et al (2010) Primary medication non-adherence: Analysis of 195,930 electronic prescriptions. *J Gen Intern Med* 25:284–290. doi: 10.1007/s11606-010-1253-9
15. Reynolds K, Muntner P, Cheetham TC, et al (2013) Primary non-adherence to bisphosphonates in an integrated healthcare setting. *Osteoporos Int* 24:2509–2517. doi: 10.1007/s00198-013-2326-5
16. Fatoye F, Smith P, Gebrye T, Yeowell G (2019) Real-world persistence and adherence with oral bisphosphonates for osteoporosis: A systematic review. *BMJ Open* 9:1–18. doi: 10.1136/bmjopen-2018-027049

17. Rabenda V, Mertens R, Fabri V, et al (2008) Adherence to bisphosphonates therapy and hip fracture risk in osteoporotic women. *Osteoporos Int* 19:811–818. doi: 10.1007/s00198-007-0506-x
18. Koller G, Goetz V, Vandermeer B, et al (2020) Persistence and adherence to parenteral osteoporosis therapies: a systematic review. *Osteoporos Int* 31:2093–2102. doi: 10.1007/s00198-020-05507-9
19. Sato M, Tsujimoto M, Kajimoto K, et al (2018) Effect of a patient-support program on once-daily teriparatide adherence and persistence in the Japan Fracture Observational Study (JFOS). *Arch Osteoporos*. doi: 10.1007/s11657-018-0487-8
20. Blaschke TF, Osterberg L, Vrijens B, Urquhart J (2012) Adherence to medications: Insights arising from studies on the unreliable link between prescribed and actual drug dosing histories. *Annu Rev Pharmacol Toxicol* 52:275–301. doi: 10.1146/annurev-pharmtox-011711-113247
21. Sabate E (ed) (2003) Adherence to long-term therapies: evidence for action. *World Health Organization, Geneva.*
22. Kardas P, Lewek P, Matyjaszczyk M (2013) Determinants of patient adherence: A review of systematic reviews. *Front Pharmacol* 4 JUL:1–16. doi: 10.3389/fphar.2013.00091
23. Yeam CT, Chia S, Tan HCC, et al (2018) A systematic review of factors affecting medication adherence among patients with osteoporosis. *Osteoporos Int* 29:2623–2637. doi: 10.1007/s00198-018-4759-3
24. Adler R, El-Hajj Fuleihan G, Bauer DC, Camacho PM, Clarke BL, Clines GA, Compston JE, Drake MT, Edwards BJ, Favus MJ, Greespan SL, McKinney R Jr, Pignolo RJ S DE (2016) Managing osteoporosis patients after long-term bisphosphonate treatment. *J Bone Min Res* 31:16–35. doi: 10.1002/jbmr.2708.Managing
25. Kendler DL, Macarios D, Lillestol MJ, et al (2014) Influence of patient perceptions and preferences for osteoporosis medication on adherence behavior in the Denosumab Adherence Preference Satisfaction study. *Menopause* 21:25–32. doi: 10.1097/GME.0b013e31828f5e5d
26. Barrett-Connor E, Wade SW, Do TP, et al (2012) Treatment satisfaction and persistence among postmenopausal women on osteoporosis medications: 12-month results from POSSIBLE USTM. *Osteoporos Int* 23:733–741. doi: 10.1007/s00198-011-1620-3
27. Hiligsmann M, Bours SPG, Boonen A (2015) A Review of Patient Preferences for Osteoporosis Drug Treatment. *Curr Rheumatol Rep.* doi: 10.1007/S11926-015-0533-0
28. Danila MI, Outman RC, Rahn EJ, et al (2018) Evaluation of a Multimodal, Direct-to-Patient Educational Intervention Targeting Barriers to Osteoporosis Care: A Randomized Clinical Trial. *J Bone Miner Res* 33:763–772. doi: 10.1002/jbmr.3395
29. Siris ES, Selby PL, Saag KG, et al (2009) Impact of Osteoporosis Treatment Adherence on Fracture Rates in North America and Europe. *Am J Med* 122:S3. doi: 10.1016/j.amjmed.2008.12.002
30. Ross S, Samuels E, Gairy K, et al (2011) A meta-analysis of osteoporotic fracture risk with medication nonadherence. *Value Heal* 14:571–581. doi: 10.1016/j.jval.2010.11.010
31. Imaz I, Zegarra P, González-Enríquez J, et al (2010) Poor bisphosphonate adherence for treatment of osteoporosis increases fracture risk: Systematic review and meta-analysis. *Osteoporos Int* 21:1943–1951. doi: 10.1007/s00198-009-1134-4
32. Yu S, Burge RT, Foster SA, et al (2012) The impact of teriparatide adherence and persistence on fracture outcomes. *Osteoporos Int* 23:1103–1113. doi: 10.1007/s00198-011-1843-3
33. Ringe JD, Möller G (2009) Differences in persistence, safety and efficacy of generic and original branded

once weekly bisphosphonates in patients with postmenopausal osteoporosis: 1-year results of a retrospective patient chart review analysis. *Rheumatol Int* 30:213–221. doi: 10.1007/s00296-009-0940-5

34. Kanis JA, Reginster JY, Kaufman JM, et al (2012) A reappraisal of generic bisphosphonates in osteoporosis. *Osteoporos Int* 23:213–221. doi: 10.1007/s00198-011-1796-6
35. Hiligsmann M, McGowan B, Bennett K, et al (2012) The clinical and economic burden of poor adherence and persistence with osteoporosis medications in Ireland. *Value Health* 15:604–612. doi: 10.1016/j.jval.2012.02.001
36. Hiligsmann M, Rabenda V, Gathon HJ, et al (2010) Potential clinical and economic impact of nonadherence with osteoporosis medications. Calcif Tissue Int 86:202–210. doi: 10.1007/s00223-009-9329-4
37. Hiligsmann M, Rabenda V, Bruyère O, Reginster JY (2010) The clinical and economic burden of non-adherence with oral bisphosphonates in osteoporotic patients. *Health Policy (New York)* 96:170–177. doi: 10.1016/j.healthpol.2010.01.014
38. Hiligsmann M, Boonen A, Rabenda V, Reginster JY (2012) The importance of integrating medication adherence into pharmacoeconomic analyses: The example of osteoporosis. *Expert Rev Pharmacoeconomics Outcomes Res* 12:159–166. doi: 10.1586/erp.12.8
39. Hiligsmann M, Reginster JY, Tosteson ANA, et al (2019) Recommendations for the conduct of economic evaluations in osteoporosis: outcomes of an experts' consensus meeting organized by the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) and. *Osteoporos Int* 30:45–57. doi: 10.1007/s00198-018-4744-x
40. Hiligsmann M, Salas M, Hughes DA, et al (2013) Interventions to improve osteoporosis medication adherence and persistence: A systematic review and literature appraisal by the ISPOR Medication Adherence & Persistence Special Interest Group. *Osteoporos Int* 24:2907–2918. doi: 10.1007/s00198-013-2364-z
41. Cornelissen D, de Kunder S, Si L, et al (2020) Interventions to improve adherence to anti-osteoporosis medications: an updated systematic review. *Osteoporos Int* 31:1645–1669. doi: 10.1007/s00198-020-05378-0
42. Beaton DE, Mamdani M, Zheng H, et al (2017) Improvements in osteoporosis testing and care are found following the wide scale implementation of the Ontario Fracture Clinic Screening Program. *Med (United States)* 96:1–7. doi: 10.1097/MD.0000000000009012
43. Tüzün Ş, Akyüz G, Eskiyurt N, et al (2013) Impact of the training on the compliance and persistence of weekly bisphosphonate treatment in postmenopausal osteoporosis: A randomized controlled study. *Int J Med Sci* 10:1880–1887. doi: 10.7150/ijms.5359
44. Roux S, Beaulieu M, Beaulieu MC, et al (2013) Priming primary care physicians to treat osteoporosis after a fragility fracture: An integrated multidisciplinary approach. *J Rheumatol* 40:703–711. doi: 10.3899/jrheum.120908
45. Seuffert P, Sagebien CA, McDonnell M, O'Hara DA (2016) Evaluation of osteoporosis risk and initiation of a nurse practitioner intervention program in an orthopedic practice. *Arch Osteoporos* 11:1–6. doi: 10.1007/s11657-016-0262-7
46. Hiligsmann M, Reginster JY (2019) Cost-effectiveness of gastro-resistant risedronate tablets for the

treatment of postmenopausal women with osteoporosis in France. *Osteoporos Int* 30:649–658. doi: 10.1007/s00198-018-04821-7

47. Oral A, Lorenc R, Sindel D, et al (2015) Compliance, persistence, and preference outcomes of postmenopausal osteoporotic women receiving a flexible or fixed regimen of daily risedronate: A multicenter, prospective, parallel group study. *Acta Orthop Traumatol Turc* 49:67–74. doi: 10.3944/AOTT.2015.14.0082
48. Ducoulombier V, Luraschi H, Forzy G, et al (2015) Contribution of phone follow-up to improved adherence to oral osteoporosis treatment. Am J Pharm Benefits 7:e81–e89.
49. Stuurman-Bieze AGG, Hiddink EG, Van Boven JFM, Vegter S (2014) Proactive pharmaceutical care interventions decrease patients' nonadherence to osteoporosis medication. *Osteoporos Int* 25:1807–1812. doi: 10.1007/s00198-014-2659-8
50. Wu CH, Tu S Te, Chang YF, et al (2018) Fracture liaison services improve outcomes of patients with osteoporosis-related fractures: A systematic literature review and meta-analysis. *Bone* 111:92–100. doi: 10.1016/j.bone.2018.03.018
51. Bachour F, Rizkallah M, Sebaaly A, et al (2017) Fracture liaison service: report on the first successful experience from the Middle East. *Arch Osteoporos* 12:4–9. doi: 10.1007/s11657-017-0372-x
52. Axelsson KF, Jacobsson R, Lund D, Lorentzon M (2016) Effectiveness of a minimal resource fracture liaison service. *Osteoporos Int* 27:3165–3175. doi: 10.1007/s00198-016-3643-2
53. Grad R, Légaré F, Bell NR, et al (2017) Shared decision making in preventive health care: What it is; what it is not. *Can Fam Physician* 63:682–684.
54. Montori VM, Shah ND, Pencille LJ, et al (2011) Use of a decision aid to improve treatment decisions in osteoporosis: The osteoporosis choice randomized trial. *Am J Med* 124:549–556. doi: 10.1016/j.amjmed.2011.01.013
55. Delmas PD, Vrijens B, Eastell R, et al (2007) Effect of monitoring bone turnover markers on persistence with risedronate treatment of postmenopausal osteoporosis. *J Clin Endocrinol Metab* 92:1296–1304. doi: 10.1210/jc.2006-1526
56. Diez-Perez A, Adachi JD, Agnusdei D, et al (2012) Treatment failure in osteoporosis. *Osteoporos Int* 23:2769–2774. doi: 10.1007/s00198-012-2093-8
57. Diez-Perez A, Naylor KE, Abrahamsen B, et al (2017) International Osteoporosis Foundation and European Calcified Tissue Society Working Group. Recommendations for the screening of adherence to oral bisphosphonates. *Osteoporos Int* 28:767–774. doi: 10.1007/s00198-017-3906-6
58. Lloyd AJ (2001) The extent of patients' understanding of the risk of treatments. *Qual Saf Heal Care* 10:i14–i18. doi: 10.1136/qhc.0100014
59. Weinstein ND (1989) Optimistic biases about personal risks. Science (80-) 246:1232–1233. doi: 10.1126/science.2686031
60. Siris ES, Gehlbach S, Adachi JD, et al (2011) Failure to perceive increased risk of fracture in women 55 years and older: The Global Longitudinal Study of Osteoporosis in Women (GLOW). *Osteoporos Int* 22:27–35. doi: 10.1007/s00198-010-1211-8
61. Science of Patient Input Communication Working Group Consortium of the Medical Device Innovation. Best Practices for Communicating Benefit, Risk, and Uncertainty for Medical Devices. https//mdic.

org/resource/best-practices-for-communicating-benefit-risk-and-uncertainty-for-medical-devices/. Accessed Sept. 2020

62. Schrager S (2018) Five ways to communicate risks so that patients understand. *Fam Pract Manag* 25:28–31.
63. Fischhoff B, Brewer N, and Downs J E Communicating Risks and Benefits: An Evidence-Based User's Guide [Internet]. *Silver Spring, MD U.S. Dep. Heal. Hum. Serv. Food Drug Adm.* 2011 Aug [cited 2013 Feb 27]. Available fr
64. Fagerlin A, Zikmund-Fisher BJ, Ubel PA (2011) Helping patients decide: Ten steps to better risk communication. *J Natl Cancer Inst* 103:1436–1443. doi: 10.1093/jnci/djr318
65. FDA. Patient Preference Information – Voluntary Submission R in PAA, Humanitarian Device Exemption Applications, and De Novo Requests and I in DS and, Device Labeling. https://www.fda.gov/media/92593/download Published October 2016. Accessed September 2020. No Title.
66. Kessels RPC (2003) Patients' memory for medical information. *J R Soc Med* 96:219–222. doi: 10.1258/jrsm.96.5.219
67. Büchter RB, Fechtelpeter D, Knelangen M, et al (2014) Words or numbers? Communicating risk of adverse effects in written consumer health information: A systematic review and meta-analysis. *BMC Med Inform Decis Mak* 14:1–11. doi: 10.1186/1472-6947-14-76
68. Wilson R, Crouch WA. Risk assessment and comparisons: an introduction. *Sciences (New York)*. 1987;236:267–270.
69. Wiles MD, Duffy A, Neill K (2020) The numerical translation of verbal probability expressions by patients and clinicians in the context of peri-operative risk communication. *Anaesthesia* 75:e39–e45. doi: 10.1111/anae.14871
70. Fraenkel L, Stolar M, Swift S, et al (2017) Subjective Numeracy and the Influence of Order and Amount of Audible Information on Perceived Medication Value. *Med Decis Mak* 37:230–238. doi: 10.1177/0272989X16650665
71. Webster RK, Weinman J, Rubin GJ (2019) Explaining all without causing unnecessary harm: Is there scope for positively framing medical risk information? *Patient Educ Couns* 102:602–603. doi: 10.1016/j.pec.2018.09.014
72. Silverman S, Age Q, Curtis J Understanding physicians' perceptions of patients' barriers to osteoporosis medication initiation. Present. *ASBMR* 2014. Available http//www.asbmr.org/education/abstract detail?aid= 8F4Fc 96 a-8ef1-4f7b-8dda-fa7d2747da1c.
73. Park DC, Lautenschlager G, Hedden T, et al (2002) Models of Visuospatial and Verbal Memory Across the Adult Life Span. doi: 10.1037/0882-7974.17.2.299
74. Schwartz LM, Woloshin S, Black WC, Welch HG (1997) The role of numeracy in understanding the benefit of screening mammography. *Ann Intern Med* 127:966–972. doi: 10.7326/0003-4819-127-11-199712010-00003
75. Lipkus et al., "General Performance."
76. Peters E, Västfjäll D, Slovic P, et al (2006) Numeracy and decision making. *Psychol Sci* 17:407–413. doi: 10.1111/j.1467-9280.2006.01720.x
77. Yamagishi K (1997) When a 12 . 86 % Mortality is More Dangerous than 24 . 14 %: Implications for Risk

Communication. 11:495–506.

78. Schapira MM, Nattinger AB, McHorney CA (2001) Frequency or probability? A qualitative study of risk communication formats used in health care. *Med Decis Mak* 21:459–467. doi: 10.1177/0272989X0102100604
79. Zipkin DA, Umscheid CA, Keating NL, et al (2014) Evidence-based risk communication: A systematic review. *Ann Intern Med* 161:270–280. doi: 10.7326/M14-0295
80. Akl EA, Oxman AD, Herrin J, et al (2011) Using alternative statistical formats for presenting risks and risk reductions. *Cochrane Database Syst Rev.* doi: 10.1002/14651858.cd006776.pub2
81. Covey J (2007) A meta-analysis of the effects of presenting treatment benefits in different formats. *Med Decis Mak* 27:638–654. doi: 10.1177/0272989X07306783
82. Bodemer N, Meder B, Gigerenzer G (2014) Communicating relative risk changes with baseline risk: Presentation format and numeracy matter. *Med Decis Mak* 34:615–626. doi: 10.1177/0272989X14526305
83. Cheung YB, Wee HL, Thumboo J, et al (2010) Risk communication in clinical trials: A cognitive experiment and a survey. *BMC Med Inform Decis Mak.* doi: 10.1186/1472-6947-10-55
84. Pighin S, Savadori L, Barilli E, et al (2011) The 1-in-X effect on the subjective assessment of medical probabilities. *Med Decis Mak* 31:721–729. doi: 10.1177/0272989X11403490
85. Sheridan SL, Pignone MP, Lewis CL (2003) A Randomized Comparison of Patients' Understanding of Number Needed to Treat and Other Common Risk Reduction Formats. *J Gen Intern Med* 18:884–892. doi: 10.1046/j.1525-1497.2003.21102.x
86. Trevena LJ, Zikmund-Fisher BJ, Edwards A, et al (2013) Presenting quantitative information about decision outcomes: A risk communication primer for patient decision aid developers. *BMC Med Inform Decis Mak* 13:S7. doi: 10.1186/1472-6947-13-S2-S7
87. Sprague D, Russo JE, Lavallie DL, Buchwald DS (2012) Influence of framing and graphic format on comprehension of risk information among American Indian Tribal College Students. *J Cancer Educ* 27:752–758. doi: 10.1007/s13187-012-0372-x
88. Waters EA, Weinstein ND, Colditz GA, Emmons K (2006) Formats for improving risk communication in medical tradeoff decisions. *J Health Commun* 11:167–182. doi: 10.1080/10810730500526695
89. Garcia-Retamero R, Cokely ET (2017) Designing Visual AIDS That Promote Risk Literacy: A Systematic Review of Health Research and Evidence-Based Design Heuristics. *Hum Factors* 59:582–627. doi: 10.1177/0018720817690634
90. Oudhoff JP, Timmermans DRM (2015) The effect of different graphical and numerical likelihood formats on perception of likelihood and choice. *Med Decis Mak* 35:487–500. doi: 10.1177/0272989X15576487
91. Ancker JS, Senathirajah Y, Kukafka R, Starren JB (2006) Design Features of Graphs in Health Risk Communication: A Systematic Review. *J Am Med Informatics Assoc* 13:608–618. doi: 10.1197/jamia.M2115
92. Barnes AJ, Hanoch Y, Miron-Shatz T, Ozanne EM (2016) Tailoring risk communication to improve comprehension: Do patient preferences help or hurt? *Heal Psychol* 35:1007–1016. doi: 10.1037/hea0000367
93. Hawley ST, Zikmund-Fisher B, Ubel P, et al (2008) The impact of the format of graphical presentation on health-related knowledge and treatment choices. *Patient Educ Couns* 73:448–455. doi: 10.1016/j.

pec.2008.07.023

94. Feldman-Stewart D, Kocovski N, McConnell BA, et al (2000) Perception of quantitative information for treatment decisions. *Med Decis Mak* 20:228–238. doi: 10.1177/0272989X0002000208
95. Staff RC, Zwanziger L, Wiley J, Group NP (2003) Communicating risks and benefits. Pharm Pract 13:289.
96. Garcia-Retamero R, Galesic M (2009) Communicating treatment risk reduction to people with low numeracy skills: A cross-cultural comparison. *Am J Public Health* 99:2196–2202. doi: 10.2105/AJPH.2009.160234
97. McCaffery KJ, Dixon A, Hayen A, et al (2012) The influence of graphic display format on the interpretations of quantitative risk information among adults with lower education and literacy: A 1y. *Med Decis Mak* 32:532–544. doi: 10.1177/0272989X11424926
98. Lühnen J, Steckelberg A, Buhse S (2018) Pictures in health information and their pitfalls: Focus group study and systematic review. *Z Evid Fortbild Qual Gesundhwes* 137–138:77–89. doi: 10.1016/j.zefq.2018.08.002
99. Dolan JG, Iadarola S (2008) Risk communication formats for low probability events: An exploratory study of patient preferences. *BMC Med Inform Decis Mak.* doi: 10.1186/1472-6947-8-14
100. Carrigan N, Raynor DK, Knapp P (2008) Adequacy of patient information on adverse effects: An assessment of patient information leaflets in the UK. *Drug Saf* 31:305–312. doi: 10.2165/00002018-200831040-00004
101. Trevena LJ, Davey HM, Barratt A, et al (2006) A systematic review on communicating with patients about evidence. *J Eval Clin Pract* 12:13–23. doi: 10.1111/j.1365-2753.2005.00596.x
102. Zikmund-Fisher BJ, Fagerlin A, Ubel PA (2010) A demonstration of "less can be more" in risk graphics. *Med Decis Mak* 30:661–671. doi: 10.1177/0272989X10364244
103. Lewiecki EM (2011) The role of risk communication in the care of osteoporosis. *Curr Osteoporos Rep* 9:141–148. doi: 10.1007/s11914-011-0056-1
104. Sale JEM, Hawker G, Cameron C, et al (2015) Perceived messages about bone health after a fracture are not consistent across healthcare providers. *Rheumatol Int* 35:97–103. doi: 10.1007/s00296-014-3079-y
105. Dewan N, MacDermid JC, MacIntyre NJ, Grewal R (2019) Therapist's practice patterns for subsequent fall/osteoporotic fracture prevention for patients with a distal radius fracture. *J Hand Ther 3*2:497–506. doi: 10.1016/j.jht.2018.03.001
106. Meyer G, Steckelberg A, Mühlhauser I (2007) Analysis of consumer information brochures on osteoporosis prevention and treatment. *Ger Med Sci* 5:Doc01.
107. Litwic AE, Westbury LD, Carter S, et al (2020) Self-perceived Fracture Risk in the Global Longitudinal Study of Osteoporosis in Women: Its Correlates and Relationship with Bone Microarchitecture. *Calcif Tissue Int* 106:625–636. doi: 10.1007/s00223-020-00680-9
108. Kanis JA, Harvey NC, McCloskey E, et al (2020) Algorithm for the management of patients at low, high and very high risk of osteoporotic fractures. *Osteoporos Int* 31:1–12. doi: 10.1007/s00198-019-05176-3
109. Barrett-Connor E, Sajjan SG, Siris ES, et al (2008) Wrist fracture as a predictor of future fractures in younger versus older postmenopausal women: Results from the National Osteoporosis Risk Assessment (NORA). *Osteoporos Int* 19:607–613. doi: 10.1007/s00198-007-0508-8
110. O'Reilly C, Keogan F, Breen R, et al (2013) Falls risk factors and healthcare use in patients with a low-trauma wrist fracture attending a physiotherapy clinic. *Int J Ther Rehabil* 20:480–486. doi: 10.12968/

ijtr.2013.20.10.480

111. Hakestad KA, Nordsletten L, Torstveit MK, Risberg MA (2014) Postmenopausal women with osteopenia and a healed wrist fracture have reduced physical function and quality of life compared to a matched, healthy control group with no fracture. *BMC Womens Health* 14:92. doi: 10.1186/1472-6874-14-92
112. Hvas L, Reventlow S, Malterud K (2004) Women's needs and wants when seeing the GP in relation to menopausal issues. *Scand J Prim Health Care* 22:118–121. doi: 10.1080/02813430410005964
113. Kasper MJ, Peterson MG, Allegrante JP (2001) The need for comprehensive educational osteoporosis prevention programs for young women: results from a second osteoporosis prevention survey. *Arthritis Rheum* 45:28–34. doi: 10.1002/1529-0131(200102)45:1<28::AID-ANR80>3.0.CO;2-G
114. Yen PH, Leasure AR (2019) Use and Effectiveness of the Teach-Back Method in Patient Education and Health Outcomes. *Fed Pract 3*6:284–289.
115. Prochnow JA, Meiers SJ, Scheckel MM (2019) Improving Patient and Caregiver New Medication Education Using an Innovative Teach-back Toolkit. *J Nurs Care Qual* 34:101–106. doi: 10.1097/NCQ.0000000000000342
116. Lewiecki EM (2010) Risk communication and shared decision making in the care of patients with osteoporosis. *J Clin Densitom* 13:335–345. doi: 10.1016/j.jocd.2010.06.005
117. Ettinger B (2008) A personal perspective on fracture risk assessment tools. *Menopause* 15:1023–1026. doi: 10.1097/gme.0b013e31817f3e4d
118. Roblin DW, Cram P, Lou Y, et al (2018) Diet and exercise changes following bone densitometry in the Patient Activation After DXA Result Notification (PAADRN) study. *Arch Osteoporos.* doi: 10.1007/s11657-017-0402-8
119. Roblin DW, Zelman D, Plummer S, et al (2017) Evaluation of a "Just-in-Time" Nurse Consultation on Bone Health: A Pilot Randomized Controlled Trial. *Perm J* 21:1–12. doi: 10.7812/TPP/16-112
120. Wolinsky FD, Lou Y, Edmonds SW, et al (2017) Activating Patients With a Tailored Bone Density Test Results Letter and Educational Brochure: the PAADRN Randomized Controlled Trial. *J Clin Densitom* 20:464–471. doi: 10.1016/j.jocd.2016.08.012
121. Wu F, Wills K, Laslett LL, et al (2018) Individualized Fracture Risk Feedback and Long-term Benefits After 10 Years. *Am J Prev Med* 54:266–274. doi: 10.1016/j.amepre.2017.10.018
122. Nadler M, Alibhai S, Catton P, et al (2014) The impact of bone mineral density testing, fracture assessment, and osteoporosis education in men treated by androgen deprivation for prostate cancer: A pilot study. *Support Care Cancer* 22:2409–2415. doi: 10.1007/s00520-014-2183-6
123. Brask-Lindemann D, Cadarette SM, Eskildsen P, Abrahamsen B (2011) Osteoporosis pharmacotherapy following bone densitometry: Importance of patient beliefs and understanding of DXA results. *Osteoporos Int* 22:1493–1501. doi: 10.1007/s00198-010-1365-4
124. Dunniway DL, Camune B, Baldwin K, Crane JK (2012) FRAX® counseling for bone health behavior change in women 50 years of age and older. *J Am Acad Nurse Pract* 24:382–389. doi: 10.1111/j.1745-7599.2012.00700.x
125. Solomon DH, Finkelstein JS, Polinski JM, et al (2006) A randomized controlled trial of mailed osteoporosis education to older adults. *Osteoporos Int* 17:760–767. doi: 10.1007/s00198-005-0049-y
126. Edmonds SW, Cram P, Lu X, et al (2014) Improving bone mineral density reporting to patients with an

illustration of personal fracture risk. *BMC Med Inform Decis Mak* 14:1–12. doi: 10.1186/s12911-014-0101-y

127. Kalluru R, Petrie KJ, Grey A, et al (2017) Randomised trial assessing the impact of framing of fracture risk and osteoporosis treatment benefits in patients undergoing bone densitometry. *BMJ Open* 7:1–8. doi: 10.1136/bmjopen-2016-013703
128. Stephens MH, Grey A, Fernandez J, et al (2016) 3-D bone models to improve treatment initiation among patients with osteoporosis: A randomised controlled pilot trial. *Psychol Heal* 31:487–497. doi: 10.1080/08870446.2015.1112389
129. Feldstein A, Elmer PJ, Smith DH, et al (2006) Electronic medical record reminder improves osteoporosis management after a fracture: A randomized, controlled trial. *J Am Geriatr Soc* 54:450–457. doi: 10.1111/j.1532-5415.2005.00618.x


4

CHAPTER 5

The impact of fracture liaison services on subsequent fractures and mortality: a systematic literature review and meta-analysis

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Abstract

Summary This systematic review and meta-analysis suggests that fracture liaison service (FLS) is associated with a significantly lower probability of subsequent fractures and mortality although the latter was only found in studies comparing outcomes before and after the introduction of an FLS.

Introduction To systematically review and evaluate the impact of fracture liaison services (FLSs) on subsequent fractures and mortality using meta-analysis.

Methods A literature search was performed within PubMed and Embase to identify original articles published between January 1, 2010, and April 30, 2020, reporting the effect of FLSs on subsequent fractures and/or mortality. Only studies comparing FLS to no-FLS were included. A meta-analysis using random-effects models was conducted. The quality of studies was appraised after combining and modifying criteria of existing quality assessment tools.

Results The search retrieved 955 published studies, of which 16 studies fulfilled the inclusion criteria. Twelve studies compared outcomes before (pre-FLS) and after (post-FLS) FLS implementation, two studies compared outcomes between hospitals with and without FLS, and two other studies performed both comparisons. In total, 18 comparisons of FLS and no-FLS care were reported. Follow-up time varied from 6 months to 4 years. Sixteen comparisons reported on subsequent fractures and 12 on mortality. The quality assessment revealed methodological issues in several criteria. Excluding studies with very high selection bias, the meta-analysis of nine comparisons (in eight papers) revealed that the FLS care was associated with a significantly lower probability of subsequent fractures (odds ratio: 0.70, 95% CI: 0.52-0.93, P=0.01). In studies with a follow-up > 2 years, a significantly lower probability of subsequent fractures was captured for FLS care (odds ratio: 0.57, 95% CI: 0.34-0.94, P=0.03), while in studies ≤ 2 years, there was no difference in the odds of subsequent fractures. No significant difference in the odds of mortality was observed (odds ratio: 0.73, 95% CI: 0.49-1.09, P=0.12) in the meta-analysis of eight comparisons (in seven papers). However, a significantly lower probability of mortality was identified in the six pre-post FLS comparisons (odds ratio: 0.65, 95% CI: 0.44-0.95, P=0.03), but not in studies comparing hospitals with and without FLS. No difference was observed in mortality stratified by follow-up time.

Conclusion This systematic review and meta-analysis suggests that FLS care is associated with a significantly lower probability of subsequent fractures and mortality although the latter was only found in studies comparing outcomes

before and after the introduction of an FLS. The quality assessment revealed that some important methodological issues were unmet in the currently available studies. Recommendations to guide researchers to design high-quality studies for evaluation of FLS outcomes in the future were provided.

Keywords Fracture liaison service . Meta-analysis . Mortality . Subsequent fracture

INTRODUCTION

Osteoporotic fractures are associated with increased subsequent fracture risk, morbidity, and excess mortality, placing a large medical and economic burden on healthcare systems [1]. Subsequent fracture risk is not constant, but fluctuates over time, and is the highest immediately after initial fractures [2]. One-quarter of all subsequent fractures occur within 1 year after a first fracture, and one in two occur within 5 years [3]. Additionally, the majority of deaths following fractures occur within the first year, thereafter the excess mortality gradually declines [4]. Mortality risk in the first 5 years is increased approximately twofold in women and two- to threefold in men [5]. Of note, the absolute impact on mortality is higher for non-hip non-vertebral (NHNV) fractures, since these account for three-quarters of the number of fractures in the population [6].

Despite the availability of various effective pharmacologic interventions and well-established guidelines for fracture prevention, the majority of patients sustaining a fragility fracture do not receive anti-osteoporosis drugs (AOD) [1]. This treatment gap is more pronounced in men than in women, and worsened in recent years [7]. The magnitude of the treatment gap is reported to be highly variable throughout Europe, ranging between 25 and 95%[8]. An Australian study showed that even less than 20% of postmenopausal women with a fracture received specific treatment for osteoporosis in primary care [9]. The low prescription rate of AOD is attributed to inadequate clinical management, including inadequate communication between physicians, disconnected care between healthcare settings, and knowledge gaps by both patients and physicians [10, 11]. These factors represent missed opportunities to actively manage osteoporosis and the prevention of subsequent fractures [12].

In response to this care gap, the International Osteoporosis Foundation (IOF) launched the Capture the Fracture (CTF) Campaign in 2012 to facilitate the implementation of coordinator- based, multi-disciplinary models of care for secondary fracture prevention. Fracture liaison services (FLSs) are nowadays widely advocated as the most appropriate approach to cover all aspects of secondary fracture prevention, including patient identification, education, risk evaluation, treatment, and long-term monitoring. Until November 2020, more than 550 FLSs (registered in CTF) have been implemented, leading to an increasing number of studies investigating the effectiveness of FLS. A previous review [13] including studies reporting the impact of FLS on subsequent fractures up to 2016 concluded that the observed reduction in subsequent fracture risk after the introduction of a FLS should be further quantified in better-designed studies. Especially the follow-up duration and the comparability of groups with or without FLS care were the

main methodological issues. As new studies have been conducted recently, and considering the fact that FLS could also have an impact on mortality, it is worthwhile to update the search, summarize results, and critically appraise studies. This systematic review and meta-analysis was therefore designed to summarize the effectiveness of FLS on subsequent fractures and mortality.

METHODS

A systematic literature search was undertaken according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline to identify eligible studies comparing FLS to no-FLS care with subsequent fractures and/or mortality as outcomes [14].

Literature search

The search was conducted in PubMed and Embase (Ovid) and restricted to English articles published between January 1, 2010, and April 30, 2020. The search strategy was designed to retrieve records addressing the following PICO research question: population (patients with a fracture), intervention (FLS care), comparator (no-FLS care), and outcome (subsequent fractures and/or mortality). Details on the complete search strategy based on the PICO criteria are provided in Supplementary 1.

Study selection

After removing duplicates, titles and abstracts were screened by one reviewer (NL). Then, full-text screening was performed for eligible studies by two independent reviewers (NL, RB), and discrepancies were resolved by consensus with the consultation of additional reviewers (MH and JB). Finally, reference lists and citations of included articles were manually screened for additional relevant studies using Web of Science. Studies were included if they reported the effectiveness of FLS care in terms of subsequent fractures and/or mortality compared to no-FLS care. Therefore, studies comparing the outcomes of FLS to historical data (post-FLS vs. pre-FLS) or studies comparing the outcomes of a hospital with FLS to a hospital without FLS were included. Studies comparing FLS attenders to non-attenders were excluded. Of note, during study selection, alternative names for FLS included fracture prevention service, orthogeriatric service/care or active osteoporosis care, etc. Non-original articles (e.g., editorials, review) and abstracts were excluded.

Data extraction

Study characteristics were extracted including publication characteristics (author, year of publication), study design (e.g., experimental or (type of) semi-experimental

design, prospective or retrospective data collection), population characteristics (country, inclusion and exclusion criteria for FLS and no-FLS populations, number of participants in each group, percentage of female participants, follow-up time, attendance proportion of FLS care), and outcomes (cumulative incidence of subsequent fractures and mortality, and corresponding Pvalue). Initiation of anti-osteoporosis treatment and bone mineral density (BMD) measurement were extracted as secondary outcomes when reported within the selected studies.

Study quality

Currently available quality assessment/risk of bias tools (such as ROBINS-I, Newcastle–Ottawa scale, and NIH tool) [15–17] did not address all potential methodological issues which we pre-identified. Therefore, concepts and items of the available checklists were combined and adjusted forming our quality assessment checklist, which better aligned to our needs. Overall, ten criteria were identified covering the traditional four domains (selection of participants and completeness of follow-up, exposure to post-fracture care, outcome, and statistical accuracy and analyses) for both intervention (FLS) and control (no-FLS) group. Supplementary 2 shows the checklist and indicates the source of the criteria.

Specifically, patients' selection was considered a key methodological issue in the study of evaluating the outcomes of FLS. All patients with a fracture should be included in the analysis regardless of whether they attended FLS clinic. Failing this principle could result in spurious associations due to large prognostic dissimilarity between groups. Besides, osteoporotic fracture is more prevalent in the geriatric population. In such population, competition between risk of subsequent fracture and risk of death is particularly high, which would hinder or modify the chance that the event of interest (subsequent fractures) occurs.

Each of the final ten criteria was scored using "Yes" (fulfilled the requirement), "No" (not fulfilled the requirement), "Part"(partially fulfilled the requirement), or "Not reported". To estimate a total quality score, we assigned a score of 1 for "Yes", 0.5 for "Part", and 0 for "No". Two researchers (NL and MO) independently evaluated the eligible studies; discrepancies were resolved by consensus through discussion.

Meta-analysis

A meta-analysis was performed to synthesize the results of included studies. Pooled results of subsequent fractures and mortality between the FLS and the no-FLS group were reported as odds ratio (OR) with associated 95% confidence interval (CI). Of note, in the meta-analysis, crude events data (how many patients had subsequent fracture/mortality) rather than cumulative incidence of subsequent fracture/

mortality were entered, and the OR were calculated based on these data. Statistical heterogeneity was assessed using the I^2 test. A fixed-effects model was used in case of small heterogeneity (I^2<50%), and a random-effects model was applied if the analysis showed to have high heterogeneity (I^2≥50%) [18]. In addition, subgroup analysis by study design (pre-post-FLS vs. hospitals with or without FLS care) and by follow-up time (follow-up ≤ 1 year vs. 1 year < follow-up ≤ 2 years vs. follow-up > 2 years) were conducted.

Of note, studies that did not include all patients with a fracture in both FLS and no-FLS cohorts (only inclusion of FLS attenders, or patient selection by consent procedure for both groups) were regarded as very high selection bias and were excluded from the main meta-analysis. However, to investigate the impact of studies with selection bias, these studies (patients' selection by consent) were additionally included into the model in the sensitivity analysis.

Given the number of studies included in the main meta-analysis for both subsequent fractures and mortality was less than ten, investigation of publication bias through computation of funnel plot is not meaningful.

All statistical analyses were performed in Review Manager (RevMan 5.4; The Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark, 2020).

RESULTS

Study selection

From the initial search, 955 records were retrieved (Fig. 1), of which 199 duplicates were removed. Following screening of titles and abstracts, 709 of the remaining 756 studies were excluded since they did not meet inclusion criteria. Upon review of the full text of the remaining 47 studies, 31 articles were excluded for reasons such as non-original articles (n=3), related to FLS organization (n=3), capturing other clinical outcomes (n=5), no control group (n=11), the intervention was not FLS care (n=3), and other reasons (n=6). In total 16 articles were thus eligible for inclusion.

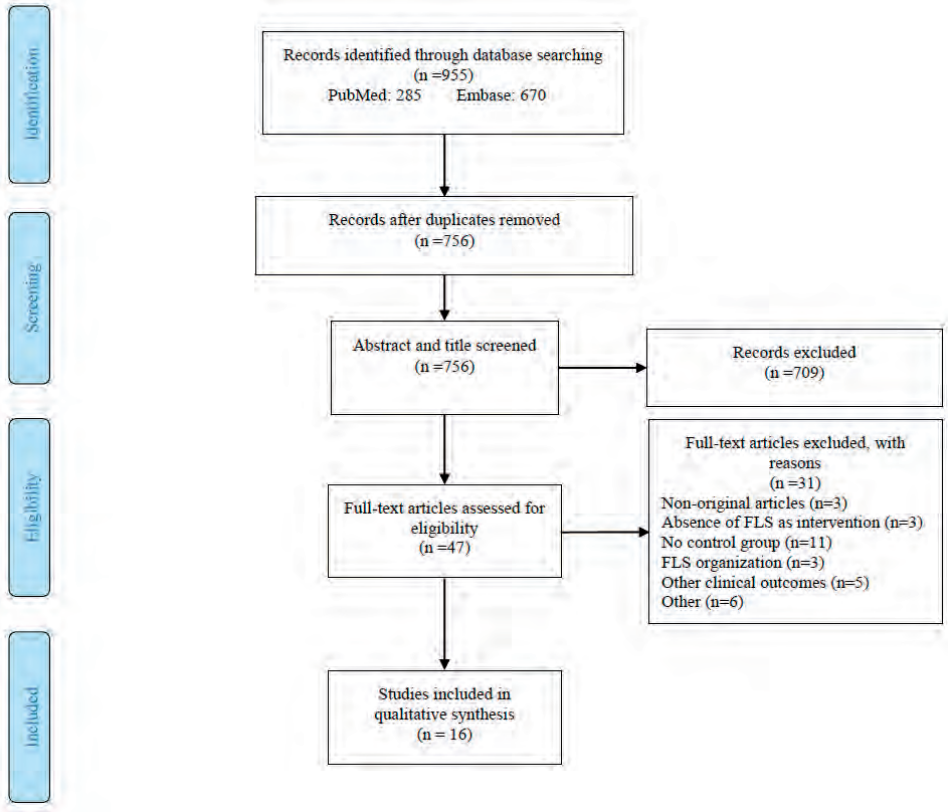

Figure 1. PRISMA flowchart of the study selection process

Characteristics of included studies

The characteristics of the included studies are reported in Table 1. Most studies (n=8) were conducted in Europe (the Netherlands, Sweden, Italy, UK, Ireland, and Spain), followed by Australia (n=3) and Asia (n=3), and the remaining two studies were performed in Canada and the USA. All studies were designed as cohort studies. Data for the FLS cohort were prospectively collected in ten [12, 19–22, 24–26, 28, 30] and retrospectively collected in six studies [1, 23, 27, 29, 31, 32]. The mean and median duration of follow-up for both FLS and no-FLS groups was 1.8 (2) years, varying from 6 months to 4 years. Of note, Inderjeeth et al. [12] presented the outcomes at 3 and 12 months. Considering 3-month follow-up was quite short, we reported the result of 12 months in our study. The sample size of individual studies varied from 47 to 33,152, and all studies included both genders, with 66 to 89% women.

Twelve studies [1, 19–29] compared the outcomes of FLS to historical data (post-FLS vs. pre-FLS). Two studies [30, 31] compared the outcomes of the FLS with data from a hospital without FLS, and two other studies [12, 32] performed both comparisons (pre-FLS vs. post-FLS, hospital with FLS vs. hospital without FLS).

When stratified by FLS outcome, 14 studies (16 comparisons) [1, 12, 19, 21-24, 26-32] reported subsequent fractures, and eleven studies (12 comparisons) [1, 19-22, 24-26, 28, 30, 32] reported mortality. Interestingly, Hawley et al. [23] reported the results from a post-hip care model in 11 hospitals, where each hospital was analyzed separately and acted as its own control in a before-and-after time series design. However, given specific data for both FLS and no-FLS cohorts were not available, this study was therefore excluded from the meta-analysis. In addition, within selected studies, eight studies [1, 12, 20-22, 24, 26, 29] reported BMD measurement, and nine studies [1, 12, 20-22, 24, 28, 29, 32] reported initiation of anti-osteoporosis treatment as secondary outcome.

When stratified by type of secondary fracture prevention care, 13 studies reported the outcomes of a typical FLS clinic. In these studies, case finding was conducted by an FLS coordinator such as a fracture nurse, secretaries at the emergency department (ED), or a physician champion, followed by BMD assessment, patients' education, and treatment initiation. The remaining three studies provided care to patients with fractures in the context of orthogeriatric care/service (OG), fracture prevention service (FPS), and active osteoporosis care, which resemble the model of FLS care and were regarded as FLS care [20, 25, 29].

The proportion of patients who attend the FLS defined as the number of patients actually attending the FLS divided by the total number of patients eligible or invited for the FLS (and thus assuming all patients with fractures are invited), which were available in six studies [1, 12, 19, 28, 30, 31] varying from 20 [31] to 86% [28]. The other ten studies did not report the proportion of FLS attenders.

Table 1. Characteristics of included studies that assessed the effect of fracture liaison service care

References (year)	Country	Data collection (FLS)	Follow-up (both groups)	Comparator	Inclusion and exclusion criteria (both group)		Number of participants		Female		Attendance proportion % (FLS)
					Inclusion	Exclusion	No-FLS	FLS	No-FLS (%)	FLS (%)	
Pre-FLS vs. post-FLS											
Huntjens et al. (2011) [19]	The Netherlands	Prospective	2 years	Pre-FLS vs. post-FLS	Patients ≥ 50 years presenting with a NVF at ED	Patients with a pathological, a clinical vertebral, or a skull fracture. For FLS group, patients were also excluded if they were selected to the no-FLS group	1920	1335	74.6	72.5	68
Ruggiero et al. (2015) [20]	Italy	Prospective	1 year	Pre-FPS vs. post-FPS	Patients ≥ 65 years with proximal hip fracture at orthopedic or traumatology department	NR	172	210	78.5	71.9	NR
Amphansap et al. (2016) [21]	Thailand	Prospective	1 year	Pre-FLS vs. post-FLS	Patients ≥50 years with hip fracture due to low energy trauma	Patients with a fracture due to high energy trauma, secondary osteoporosis, and bone tumors	120	75	73	84	NR
Axelsson et al. (2016) [22]	Sweden	Prospective	344 days	Pre-FLS vs. post-FLS	Patients ≥50 years with a hip, vertebra, shoulder, wrist, or pelvis fracture at the ED or orthopedic department	Patients with pathological fractures or who deceased prior to DXA referral	2713	2616	73	74	NR
Hawley et al. (2016) [23]	UK	Retrospective	2 years	Pre- vs. post-FLS (OG)	Patients ≥ 60 years with a primary hip fracture	NR	NR	33,152	NR	75	NR
Bachour et al. (2017) [1]	Lebanon	Retrospective	2 years	Pre-FLS vs. post-FLS	Patients ≥50 years with a MTF at ED	NR	100	98	69	80	82
Davidson et al. (2017) [24]	Australia	Prospective	3 years	Pre-FLS vs. post-FLS	Patients ≥45 years with a MTF (femur, tibia and fibula, ankle, pelvis, humerus, and wrist)	Patients with a pathological fracture (vertebral, clavicle, and rib) or if they were deceased	47	93	80.9	75.3	NR
Henderson et al. (2017) [25]	Ireland	Prospective	1 year	Pre-OG vs. post-OG	Patients with hip fracture (fractured neck of femur)	NR	248	206	66	73	NR
Singh et al. (2019) [26]	Canada	Prospective	6 months	Pre-FLS vs. post-FLS	Patients ≥50 years with a MTF (wrist, humerus, pelvis, hip, or vertebrae) at orthopedic department	Patients with a significant trauma or an underlying disease other than osteoporosis that leads to increased bone fragility, and patients had cognitive dysfunction or insufficient English language skills	65	130	85	84	NR
Wasfie et al. (2019) [27]	USA	Retrospective	2 years	Pre-FLS vs. post-FLS	Patients with a vertebral compression fracture with follow-up at the neurosurgery department	NR	150	215	69	71	NR
	Spain	Prospective	1 year	Pre-FLS vs. post-FLS	Patients ≥60 years with a hip fracture	Patients with pathological fractures	357	367	80	79	86

Table 1 (continued).

References (year)	Country	Data collection (FLS)	Follow-up (both groups)	Comparator	Inclusion and exclusion criteria (both group)		Number of participants		Female		Attendance proportion % (FLS)
					Inclusion	Exclusion	No-FLS	FLS	No-FLS (%)	FLS (%)	
González-Quevedo et al. (2020) [28]											
Shin et al. (2020) [29]	Korea	Retrospective	4 years	Pre- vs. post-active osteoporosis care	Patients ≥60 years with DRF caused by minor trauma	Patients with high energy trauma, multiple fractures, or injuries caused by motor vehicle accident or fall	205	852	80.9	85.6	NR
Hospital with FLS vs. hospital without FLS											
Huntjens et al. (2014) [30]	The Netherlands	Prospective	2 years	Without FLS vs. with FLS	Patients ≥50 years with a NVF	Patients with pathological or vertebral fractures	1910	1412	70	73	68
Nakayama et al. (2016) [31]	Australia	Retrospective	3 years	Without FLS vs. with FLS	Patients ≥50 years with MTF at ED	Patients without MTF and patients diagnosed as having a fracture but their imaging reported no fracture	416	515	73.6	75.3	20
Pre-FLS vs. post-FLS and hospital with FLS vs. hospital without FLS											
(a) Inderjeeth et al. (2018) [12]	Australia	Prospective	3 months and 12 months	Pre-FLS vs. post-FLS	Patients ≥50 years with MTF at ED	Patients without MTF but with fractures of the hands, feet or skull, and patients in high-level residential aged care facilities	105	241	72	82	69
(b) Inderjeeth et al. (2018) [12]	Australia	Prospective	3 months and 12 months	Without FLS vs. with FLS	Patients ≥50 years with MTF at ED	Patients without MTF but with fractures of the hands, feet or skull, and patients in high-level residential aged care facilities	55	241	89	82	69
(a) Axelsson et al. (2020) [32]	Sweden	Retrospective	2.2 years	Pre-FLS vs. post-FLS	Patients ≥50 years with a major osteoporotic fracture	Patients with malignancies and obvious high-energy fractures	4828	10,621	76	77	NR
(b) Axelsson et al. (2020) [32]	Sweden	Retrospective	2.2 years	Without FLS vs. with FLS	Patients ≥50 years with a major osteoporotic fracture	Patients with malignancies and obvious high-energy fractures	5634	15,449	76	76	NR

BMD bone mineral density, *FLS* fracture liaison service, *NVF* non-vertebral fracture, *FPS* fracture prevention service, *ED* emergency department, *MTF* minimal trauma fracture, *DRF* distal radius fracture, *OG* orthogeriatric service, *DXA* dual-energy X-ray absorptiometry, *NR* not reported, *vs.* versus

Quality assessment and recommendations

Table 4 presents the results of quality assessment of the included studies. The average score was 5.4 out of 10 (range 3-8.5). Only 50% of studies fulfilled more than half of the criteria, and room for improvement was thus identified for most studies. For patients' selection, most studies (n=11) made the comparison between all patients in both FLS and no-FLS groups. However, five studies [1, 12, 21, 24, 26] did not include all patients with fractures in the FLS or no-FLS cohort and were regarded with very high selection bias. Specifically, one study [21] compared FLS attenders to all patients with fractures in the no-FLS cohort, and four other studies [1, 12, 24, 26] only included and compared consenting subjects in both FLS and no-FLS groups. In addition, the quality was especially suboptimal for other criteria including "analyses of outcomes account for competing risk of death", "sample size is described based on power calculation", "loss to follow-up rate ≤20% in FLS/no-FLS group", and "at least 50% eligible patients attend FLS". Recommendations for each criterion were formulated given that they are the most important methodological issues for studies evaluating the outcomes of FLS (Table 4). Except for criteria mentioned in Table 4, the length of follow-up duration was also crucial to capture the effect of FLS care on subsequent fracture and mortality, and future studies should consider a longer duration of follow-up (at least 2 years).

Table 4. Quality of included studies assessed using self-designed tool

Quality criteria		Reference																Author's recommendations
		[19]	[20]	[21]	[22]	[23]	[1]	[24]	[25]	[26]	[27]	[28]	[29]	[30]	[31]	[12]	[32]	
Selection and completeness of follow-up	Patient baseline characteristics with no/minor significant differences between FLS and no-FLS group	No	Yes	Yes	Yes	No	Yes	Yes	NR	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Participants in two groups should be carefully selected with no/minor significant differences in characteristics to avoid selection bias
	All patients were included and analyzed in both FLS and no-FLS cohorts	Yes	Yes	No	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	All patients should be included and analyzed regardless of whether they were seen in the FLS clinic
	Inclusion/exclusion criteria are clearly described for FLS and no-FLS group	Yes	Part	Part	Part	Part	Part	Yes	Part	Yes	Part	Yes	Yes	Yes	Yes	Yes	Yes	Inclusion/exclusion criteria should be clearly described for completeness of reporting reason
	At least 50% eligible patients attend FLS	Yes	NR	NR	NR	NR	Yes	NR	NR	NR	NR	Yes	NR	Yes	No	Yes	NR	The proportion of FLS attending is expected to be at least 50% to provide confidence of the results
	Loss to follow-up ≤20% in FLS and no-FLS group	Yes	Yes	Part	NR	NR	NR	NR	NR	Part	NR	Yes	NR	NR	NR	Yes	NR	The loss of follow-up for both groups is expected to be less than 20% to guarantee statistical power for the results
Exposure	Clear description of care for FLS and no-FLS group	Yes	Part	Part	Yes	No	Part	No	Part	Part	Part	Yes	Part	Part	Part	Part	Part	Fracture care including BMD testing, treatment, education, long-term adherence, etc. should be clearly described for both groups
Outcome	Outcomes assessed in FLS and no-FLS groups using similar method	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	The same statistical methods should be used in both groups to assess the outcomes
Statistical accuracy and analyses	Analyses of outcomes accounted for relevant confounders	Yes	No	No	Yes	Yes	No	Yes	No	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Relevant confounders should be fully adjusted using statistical models, such as multivariable cox regression model
	Sample size is based on power calculation	No	No	No	Yes	No	No	No	No	Yes	No	No	No	No	No	Yes	No	To avoid insufficient statistical power for the results, sample size should be based on power calculation
	Analyses of outcomes account for competing risk of death	No	No	No	No	Yes	No	Yes	No	No	No	No	No	No	Yes	No	Yes	Competing risk analysis should be included in studies designed to evaluate risk of subsequent fracture
Total score		7	5	3.5	6.5	4.5	4	5	3	6	4	8	4.5	5.5	5.5	8.5	6.5	

Yes, fully fulfilled the criteria; No, not fulfilled the criteria; Part, partially fulfilled the criteria

NR not reported, *BMD* bone mineral density, *FLS* fracture liaison service

Subsequent fracture

As shown in Table 2, 10 out of 16 comparisons reported that the reduction of subsequent fractures in the FLS group was significant. Excluding five studies with very high selection bias, the mean cumulative incidence of subsequent fractures was 7.7% (SD 3.9%) and 10.9% (SD 6.5%) (median 6.7% and 9.1%) in the FLS versus no-FLS group. Of note, since Wasfie et al. [27] included patients with vertebral fractures (VFs) that were treated with vertebral augmentation, we did not use the data of VFs and only reported the data of other fractures (hip, ribs, and extremities) in our study. The result of meta-analysis on subsequent fractures of nine comparisons (eight studies) is presented in Fig. 2. Overall, FLS care was associated with a significantly lower probability of subsequent fractures (OR: 0.70, 95% CI: 0.52-0.93, P=0.01; heterogeneity: I^2=92%).

The first subgroup analysis by study design (Fig. 2) revealed that the OR of subsequent fractures in post versus pre-FLS group was 0.62 (95% CI: 0.42-0.91, P=0.01; heterogeneity: I^2=90%) and the OR for hospitals with versus without FLS care was 0.87 (95% CI: 0.77-0.99, P=0.03; heterogeneity: I^2=16%), both indicating a significant lower probability of subsequent fractures with FLS. The second subgroup analysis by follow-up duration (Fig. 3) revealed that in studies with a follow-up > 2 years, a significantly lower probability of subsequent fractures was captured for FLS care (odds ratio: 0.57, 95% CI: 0.34-0.94, P=0.03), while in studies ≤ 2 years, there was no difference in the odds of subsequent fractures.

Sensitivity analyses (Supplementary 3, Figure 1) including studies with very high selection bias also indicated that the FLS care was associated with a lower probability of subsequent fractures (OR: 0.70, 95% CI: 0.54-0.91, P=0.007). Subgroup analyses by study design remained overall similar.

Table 2. Results from cohort studies reporting cumulative incidence of subsequent fracture

Comparison	Cumulative incidence of subsequent fracture		P-value
	no-FLS	FLS	
Pre-FLS vs. post-FLS			
Huntjens et al. [19]	9.9%	6.7%	P=0.001*
Amphansap et al. [21]	30.0%	0.0%	P<0.0001*
Axelsson et al. [22]	8.4%	8.3%	P=0.85
Hawley et al. [23]	NA	4.2%	NA
Bachour et al. [1]	18%	8.2%	P=0.004*
Davidson et al. [24]	19.1%	10.5%	P=0.013*
Singh et al. [26]	1.8%	3.0%	P=0.667
Wasfie et al. [27]	25.0%	15.0%	P=0.01*
González-Quevedo et al. [28]	3.6%	4.6%	P=0.50
Shin et al. [29]	5.4%	1.9%	P=0.004*
Hospital with FLS vs. hospital without FLS			
Huntjens et al. [30]	6.8%	6.7%	time-dependent**
Nakayama et al. [31]	16.8%	12.2%	P=0.025*
Pre-FLS vs. post-FLS & hospital with FLS vs. hospital without FLS			
(a) Inderjeeth et al. [12]	18.3%	8.1%	P<0.05*
(b) Inderjeeth et al. [12]	17.3%	8.1%	NS
(a) Axelsson et al. [32]	12.9%	5.9%	P<0.001*
(b) Axelsson et al. [32]	9.0%#	8.0%#	NR

NA not applicable, NR not reported, NS not significant, FLS fracture liaison service, vs. versus
* Statistical significant P<0.05
**Significantly lower subsequent fracture from fifteen months onward
(a) Study compared pre-FLS to post-FLS care
(b) Study compared hospitals with and without FLS
Calculated based on available data

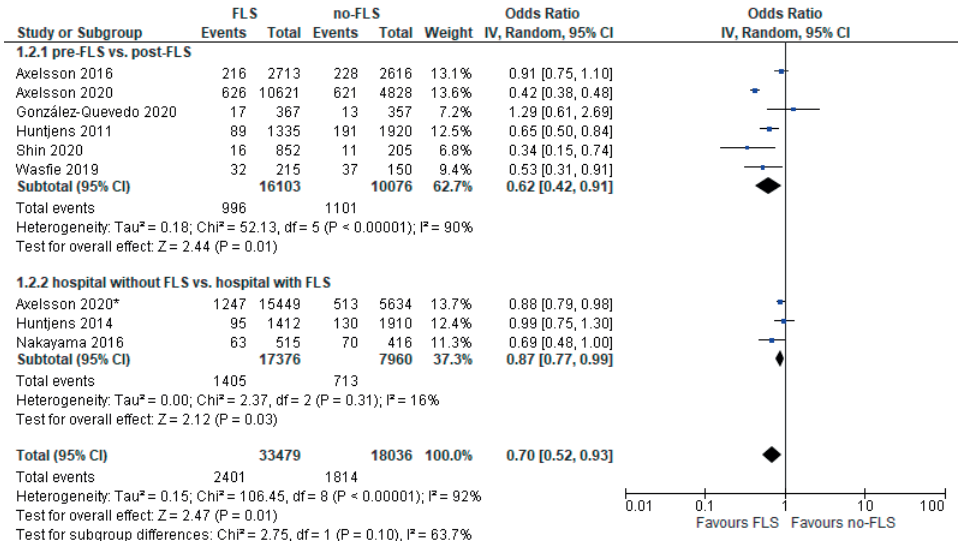

Figure 2. FLS versus no-FLS for subsequent fracture: overall and subgroup analysis by study design
CI confidence interval, IV inverse variance, FLS fracture liaison service
Asterisk indicates comparison between hospitals with and without FLS

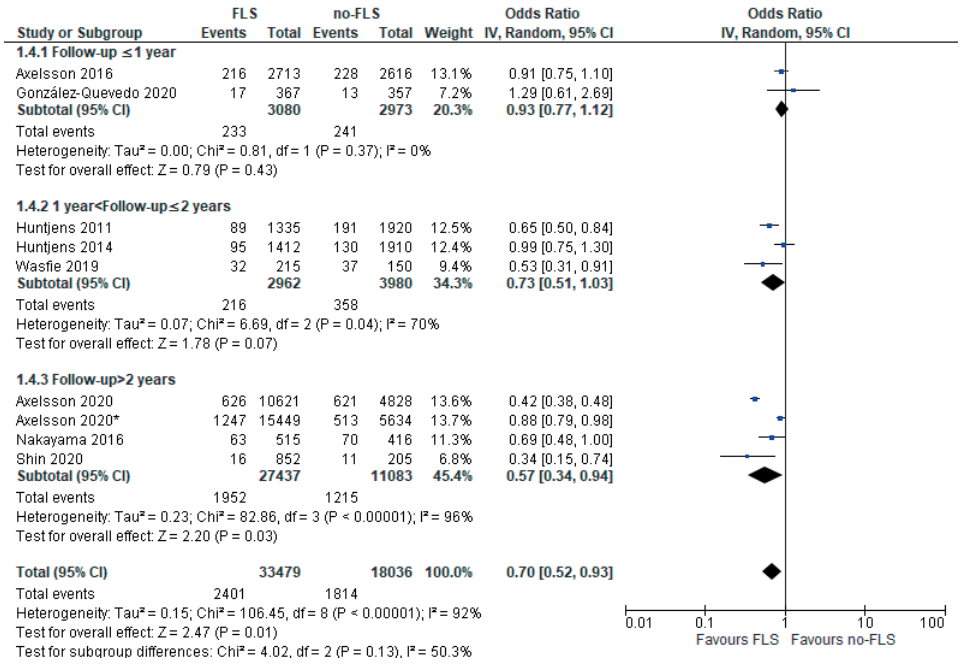

Figure 3. FLS versus no-FLS for subsequent fracture: subgroup analysis by follow-up duration
CI confidence interval, IV inverse variance, FLS fracture liaison service
Asterisk indicates comparison between hospitals with and without FLS

Mortality

As shown in Tables 3, 4 out of 12 comparisons indicated a significantly lower cumulative mortality incidence in the FLS group. Excluding five studies with very high selection bias, the mean cumulative incidence of mortality was 15.1% (SD 4.7%) and 22.8% (SD 7.8%) (median 13.8% and 18.4%) in the FLS versus no-FLS group. The result of meta-analysis on mortality of eight comparisons (seven studies) is presented in Fig. 4. Overall, FLS care was not significantly associated with lower mortality (OR: 0.73, 95% CI: 0.49-1.09, P=0.12; heterogeneity: I^2=98%).

The first subgroup analysis by study design (Fig. 4) revealed a lower probability of mortality in the pre- versus post-FLS studies (OR: 0.65, 95% CI: 0.44-0.95, P=0.03; heterogeneity: I^2=95%) but not for studies that compared two different hospitals (OR: 1.03, 95% CI: 0.92-1.15, P=0.57; heterogeneity: I^2=29%). In the second subgroup analysis by follow-up duration (Fig. 5), we found no significant influence by duration of follow-up.

Sensitivity analyses (Supplementary 3, Figure 2) including studies with very high selection bias also indicated that the FLS care was not associated with a lower

probability of mortality (OR: 0.81, 95% CI: 0.56-1.17, P=0.27). Subgroup analyses showed that the reduced probability of mortality in pre-post studies was not significant (OR: 0.76, 95% CI: 0.52-1.10, P=0.15).

Table 3. Results from cohort studies reporting cumulative incidence of mortality

Comparison	Cumulative incidence of mortality		P-value
	no-FLS	FLS	
Pre-FLS vs. post-FLS			
Huntjens et al. [19]	17.9%	11.6%	P<0.001*
Ruggiero et al. [20]	12.7%	15.7%	P=0.50
Amphansap et al. [21]	9.2%	10.7%	P=0.731
Axelsson et al. [22]	13.3%	12.2%	P=0.24
Hawley et al. [23]	NA	29.8%	NA
Bachour et al. [1]	16.0%	16.3%	P=0.950
Davidson et al. [24]	12.2%	20.6%	P=0.035*
Henderson et al. [25]	19.0%	9.7%	P<0.001*
González-Quevedo et al. [28]	25.8%	20.2%	P=0.07
Hospital with FLS vs. hospital without FLS			
Huntjens et al. [30]	12.3%	11.5%	P<0.05*
Pre-FLS vs. post-FLS & hospital with FLS vs. hospital without FLS			
(a) Axelsson et al. [32]	35.2%	17.2%	P=0.11
(b) Axelsson et al. [32]	21.8%#	22.9%#	NR

NA not applicable, NR not reported, FLS fracture liaison service, vs. versus
* Statistical significant P<0.05
(a) Study compared pre-FLS to post-FLS care
(b) Study compared hospitals with and without FLS
Calculated based on available data

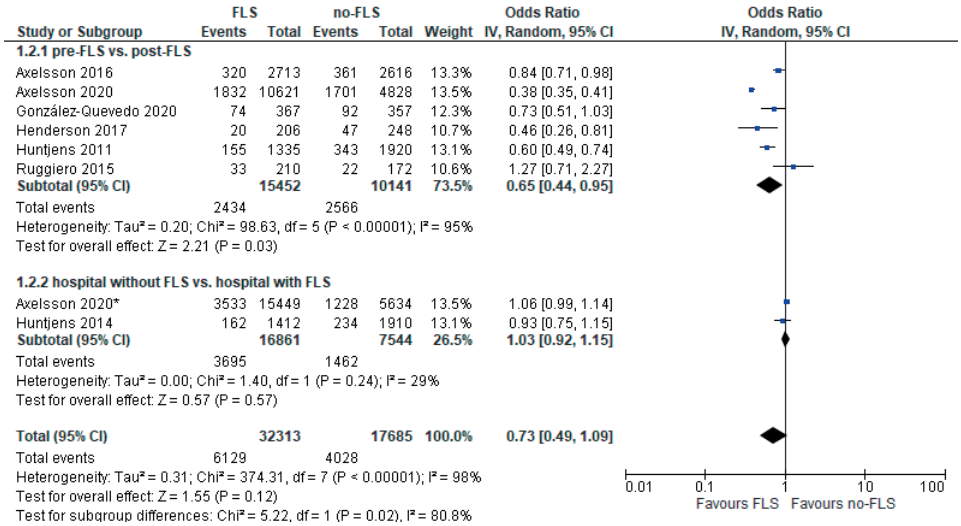

Figure 4. FLS versus no-FLS for mortality: overall and subgroup analysis by study design
CI confidence interval, IV inverse variance, FLS fracture liaison service
Asterisk indicates comparison between hospitals with and without FLS

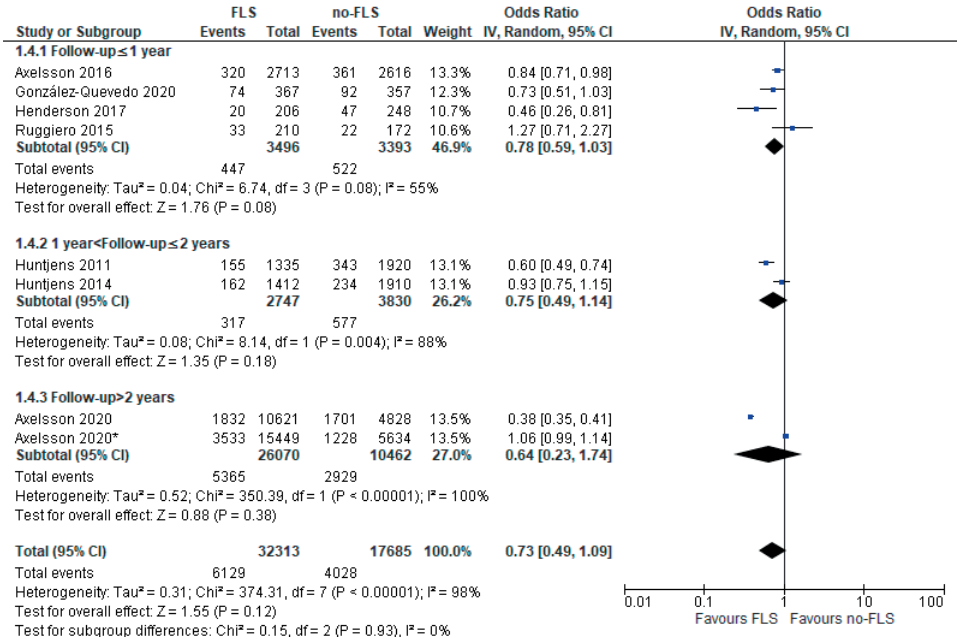

Figure 5. FLS versus no-FLS for mortality: subgroup analysis by follow-up duration
CI confidence interval, IV inverse variance, FLS fracture liaison service
Asterisk indicates comparison between hospitals with and without FLS

Secondary outcomes

Within selected studies, nine studies (11 comparisons) [1, 12, 20-22, 24, 28, 29, 32] reported the initiation of anti-osteoporosis treatment, and 9 out of 11 comparisons showed a significantly higher treatment proportion in post-FLS group. In addition, of the eight studies (9 comparisons) reported BMD measurement [1, 12, 20-22, 26, 29], and 8 out of 9 comparisons indicated that FLS was associated with a significant increase of BMD measurement proportion (Supplementary 4).

DISCUSSION

This systematic review and meta-analysis was performed to evaluate and summarize the evidence regarding the effectiveness of the FLS on subsequent fractures and mortality. The pooled overall results indicated that FLS care is associated with a significantly lower probability of subsequent fractures (30%) and mortality although the latter was only found in studies comparing outcomes before and after the introduction of an FLS. Overall, the effects of FLS care on both outcomes were larger in studies with a pre-post design compared to studies addressing hospitals with and without an FLS. Since only two studies were available for the analysis of mortality in hospitals with or without FLS, this may be insufficient to capture a significant impact. It is difficult to conclude that these study designs provide the most valid estimates. Each study design has some potential limitations. For the pre-post study design, changes in patients' lifestyles or the effectiveness of healthcare could happen over time. For (two) hospitals' study design, bias could result from differences in content of care and patients groups regarding lifestyle, comorbidities, or other confounders. Of note, high heterogeneity was revealed, especially for pre-post comparisons, even when the random-effects model and subgroup analysis were applied, which may limit the reliability of the analysis and could be recognized as a limitation.

Subgroup analysis by follow-up duration revealed that studies with relatively longer follow-up duration (more than 2 years) were associated with significantly lower probability of subsequent fractures; however, it was not the case for mortality. The potential reason could be that the impact of the FLS intervention on mortality may require a longer follow-up time to capture, while the studies included in the meta-analysis for mortality had a relatively short follow-up time (the longest was 2.2 years). Therefore, future studies should consider a follow-up duration of at least 2 years to adequately capture the effect of FLS care on subsequent fractures and mortality.

For quality appraisal, several methodology issues were identified among the included studies. Firstly, given it was difficult to design randomized controlled trials (RCTs) to evaluate the outcomes of FLS, some patients' characteristics could be considered potential confounders and available for adjustment through statistical methods (e.g., the multivariable cox regression model). However, due to the retrospective nature of some studies, several potential variables such as family fracture history, smoking/alcohol consumption, and physical activity that might impact the results were unable to be taken into account. Besides, avoiding selection bias during patients' enrollment is crucial to guarantee the comparability of two cohorts. As indicated by Huntjens et al. [19, 30], patients who were unable or not

willing to visit the FLS should be included in the FLS group and in all analyses although the level of health is not known in non-attenders and the effect of FLS care can only be achieved in the attenders. Sensitivity analysis additionally included studies with very high selection bias suggesting that these studies had no impact on overall results of meta-analysis; however, the impact on subgroups (by study design) was revealed. Future studies should avoid selection bias in the process of designing a study. Moreover, we recommend that some other criteria including "sample size is based on power calculation", "loss to follow-up ≤20%", and "at least 50% eligible patients attend the FLS" should be taken into account in future studies to provide sufficient statistical power.

Furthermore, when analyzing subsequent fracture risk, competing mortality risk may be an important methodological issue, which may particularly be the case in the geriatric population. Ignoring the competing risk of subsequent fractures and mortality could bias the results of studies on FLS care. Berry et al. [33] performed a simulation study comparing standard survival analysis versus a competing risk approach in a study of second hip fracture, indicating that standard survival analysis overestimated the 5-year risk of second hip fracture by 37% and the 10-year risk by 75% compared with competing risk estimates. Out of the 16 included studies, four reported a competing risk survival regression analysis [23, 24, 31, 32] (Supplementary 5). Three studies [23, 31, 32] used the method of Fine and Gray [34], which deals with the competing risk of mortality by retaining participants in the risk set with a diminishing weight when they die, rather than simply censoring them at the time of death [31]. Similar results were identified in three studies before and after accounting for competing risk of mortality, which allowed to evaluate (partly) the effect of competing risk (of mortality) on subsequent fractures. However, considering especially major fractures are associated with excess mortality [4], competing risk analyses should be taken into account in future studies to accurately estimate cumulative incidence of subsequent fracture.

The findings of this systematic review and meta-analysis is partially consistent with the study of Wu et al. [35], which included studies up to February 2017 suggesting that FLS programs improved outcomes of osteoporosis-related fractures, with significant increases in BMD testing, treatment initiation, and adherence to treatment and reductions in re-fracture incidence. Given more outcomes of interest were investigated and a wider search strategy was applied, more studies (n=159, including studies before CTF) were included in this previous study. By contrast, our study had a specific focus on effectiveness defined as subsequent fractures and mortality, and restricted inclusion of studies comparing FLS to no-FLS. Further, more precise meta-analyses (exclude studies with selection bias) were

conducted. Besides, subgroup and sensitivity analysis could also add value to our review. Compared to other previous reviews [13, 36], our study provides a quality assessment, recommendations for patients' selection, outcome measurement, and statistical analysis provided for future studies, which would guide researchers to design high-quality studies and further help to reduce inter-study heterogeneity, thereby facilitating inter-study comparisons.

This systematic review and meta-analysis has certain limitations. First, we did not conduct a systematic literature search for additional outcomes (initiation of anti-osteoporosis treatment and BMD measurement) since they were not the outcomes of interest in this review. The results of secondary outcomes should thus be interpreted with caution. Second, the quality assessment tool used in our study was generated through combining and modifying available quality assessment tools to fit several methodological issues, and each criterion was treated equally in scoring, the inter-validity of this tool was not verified.

CONCLUSION

This systematic review and meta-analysis suggests that FLS care is associated with a significantly lower probability of subsequent fractures and mortality although the latter was only found in studies comparing outcomes before and after the introduction of an FLS. The quality assessment revealed that some important methodological issues were unmet in the currently available studies. We therefore provided recommendations to guide researchers to design high-quality studies for evaluation of FLS outcomes in the future.

ELECTRONIC SUPPLEMENTARY MATERIAL

Supplementary 1 Search strategy of the systematic review (based on PICO criteria)

Databse	Population	Intervention	Outcome
PubMed	"Bone Diseases, Metabolic"[Mesh:NoExp] OR "Osteoporosis"[Mesh] OR "Bone Demineralization, Pathologic"[Mesh] OR "Bone Density"[MeSH] OR "Osteoporotic Fractures"[Mesh] OR metabolic bone disease*[tiab] OR osteoporo*[tiab] OR bone demineralization[tiab] OR bone demineralisation[tiab] OR pathologic decalcification*[tiab] OR bone densit*[tiab] OR bone mineral densit*[tiab] OR bone mineral content*[tiab] OR bone loss*[tiab] OR bone decreas*[tiab] OR bone deterioration*[tiab] OR osteoporotic fracture*[tiab] OR fragility fracture*[tiab]	"Secondary Prevention"[Mesh] OR Fracture liaison service*[tiab] OR FLS[tiab] OR fracture liaison program*[tiab] OR "Capture the fracture"[tiab] OR nurse-led liaison[tiab] OR osteoporosis liaison service*[tiab] OR secondary fracture prevention[tiab] OR fracture liaison service*[tiab] OR fracture liaison program*[tiab]	Re-fracture*[tiab] OR future fracture*[tiab] OR subsequent fracture*[tiab] OR secondary fracture*[tiab] OR treatment outcome*[tiab] OR treatment effect*[tiab] OR effectiveness[tiab] OR patient outcome*[tiab] OR recurrence[MeSH] OR recurrenc*[tiab] OR mortality[MeSH:NoExp] OR mortality*[tiab] OR "Mortality, Premature" [MeSH] OR premature mortality[tiab] OR
Embase	exp metabolic bone disease/ OR metabolic bone disease. ti,ab,kw. OR exp osteoporosis/ OR Osteoporosis.ti,ab,kw. OR exp bone demineralization/ OR bone demineralization.ti,ab,kw. OR exp bone density/ OR bone density.ti,ab,kw. OR exp fragility fracture/ OR fragility fracture. ti,ab,kw.	exp secondary prevention/ OR secondary prevention.ti,ab,kw. OR Fracture liaison service. ti,ab,kw. OR FLS.ti,ab,kw. OR fracture liaison program. ti,ab,kw. OR Capture the fracture.ti,ab,kw. OR nurse-led liaison.ti,ab,kw. OR osteoporosis liaison service.ti,ab,kw. OR fracture liaison program. ti,ab,kw.	Re-fracture.ti,ab,kw. OR future fracture.ti,ab,kw. OR subsequent fracture. ti,ab,kw. OR secondary fracture.ti,ab,kw. OR exp treatment outcome/ OR treatment outcome.ti,ab,kw. OR treatment effect.ti,ab,kw. OR patient outcome.ti,ab,kw. OR effectiveness.ti,ab,kw. OR recurrence.ti,ab,kw. OR exp mortality/ OR mortality. ti,ab,kw. OR exp mortality rate/ OR mortality rate. ti,ab,kw. OR mortality risk/ OR mortality risk. ti,ab,kw. OR exp premature mortality/ OR premature mortality.ti,ab,kw. OR exp death/ OR death.ti,ab,kw.

Supplementary 2 Quality assessment checklist and the source of each criteria

	Criteria	Source
Selection & completeness of follow-up	Patient baseline characteristics with no/minor significant differences between FLS and no-FLS group	NIH (criteria 4)
	All patients were included and analyzed in both FLS and no-FLS cohorts	Self-designed
	Inclusion/exclusion criteria are clearly described for FLS and no-FLS group	NIH (criteria 4)
	At least 50% eligible patients attend FLS	NIH (criteria 3)
	Loss to follow-up ≤20% in FLS and no-FLS group	NIH (criteria 13)
		Newcastle-Ottawa (Outcome section)
Exposure	Clear description of care for FLS and no-FLS group	NIH (criteria 9)
Outcome	Outcomes assessed in FLS and no-FLS groups using similar method	NIH (criteria 11)
Statistical accuracy and analyses	Analyses of outcomes accounted for relevant confounders	NIH (criteria 14);
		Newcastle-Ottawa (Comparability section)
	Sample size is based on power calculation	NIH (criteria 5)
	Analyses of outcomes account for competing risk of death	Self-designed

NIH: NIH quality assessment tool for observational cohort and cross-sectional studies
Newcastle-Ottawa: Newcastle-Ottawa quality assessment tool for cohort studies

Supplementary 3 Sensitivity analysis

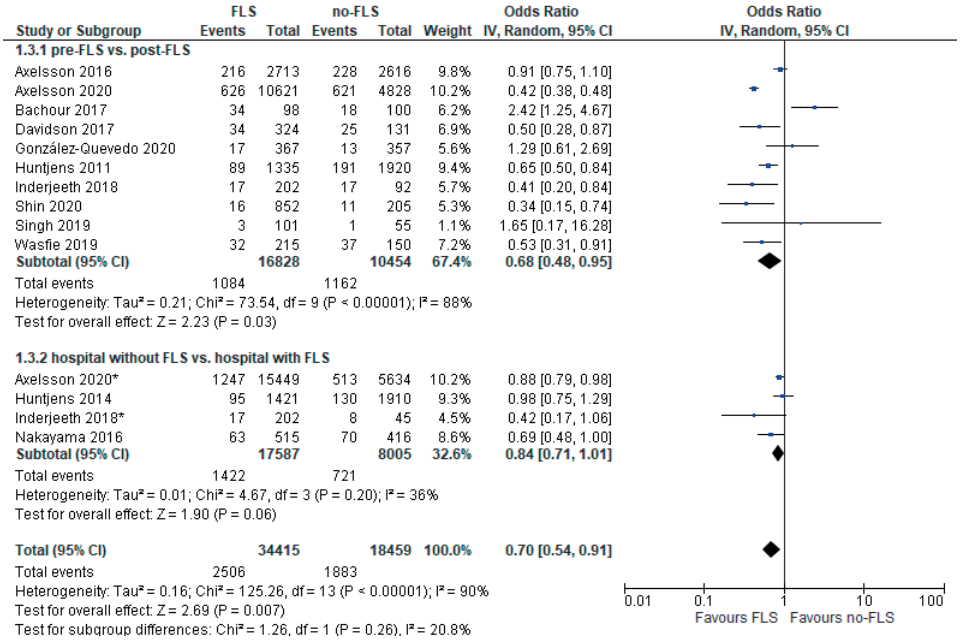

Figure 1. FLS versus no-FLS for subsequent fracture: sensitivity analysis
CI confidence interval, IV inverse variance, FLS fracture liaison service

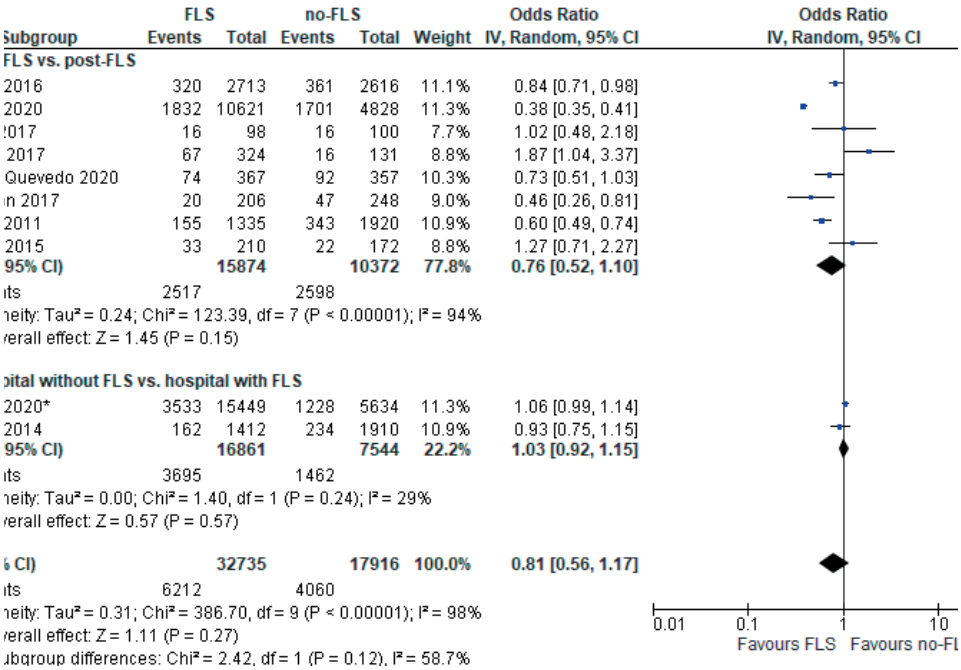

Figure 2. FLS versus no-FLS for mortality: sensitivity analysis
CI confidence interval, IV inverse variance, FLS fracture liaison service

Supplementary 4 Secondary outcomes (probability of medical treatment and BMD testing)

Comparison	Medical treatment		P-value	BMD testing		P-value
	no-FLS	FLS		no-FLS	FLS	
Pre-FLS vs. post-FLS						
Ruggiero et al. [20]	17.2%	48.5%	P<0.0001*	14.5%	47.6%	P<0.0001*
Amphansap et al. [21]	40.8%	80%	P=0.0148*	28.3%	48%	P=0.0053*
Axelsson et al. [22]	12.6%	31.8%	P<0.001*	7.6%	39.6%	P<0.001*
Bachour et al. [1]	26.0%	54.1%	P<0.001*	28.0%	65.3%	P<0.001*
Davidson et al. [24]	25.5%	42.6%	P=0.048*	40.9%	40.5%	NS
Singh et al. [26]	NA	NA	NA	23.6%	53.0%	P<0.001*
González-Quevedo et al. [28]	12.3%	74.9%	P<0.01*	NA	NA	NA
Shin et al. [29]	5.6%	20.2%	P<0.001*	12.6%	56.1%	P<0.001*
Pre-FLS vs. post-FLS & hospital with FLS vs. hospital without FLS						
(a) Inderjeeth et al. [12]	16.0%	46.9%	P<0.05*	37.4%	78%	P<0.05*
(b) Inderjeeth et al. [12]	41.5%	46.9%	NS	51.0%	78.0%	P<0.05*
(a) Axelsson et al. [32]	22.9%	26.6%	P<0.001*	NA	NA	NA
(b) Axelsson et al. [32]	14.0%#	25.0%#	NR	NA	NA	NA

NR not reported, NS not significant, NA not applicable, FLS fracture liaison service, BMD bone mineral density
* Statistical significant P<0.05
(a) Study compared pre-FLS to post-FLS care
(b) Study compared hospitals with and without FLS
Calculated based on available data

REFERENCES

1. Bachour F, Rizkallah M, Sebaaly A, et al. Fracture liaison service: report on the first successful experience from the Middle East. *Arch Osteoporos*. 2017;12(1):4-9. doi:10.1007/s11657-017-0372-x
2. Van Geel TACM, Huntjens KMB, Van Den Bergh JPW, Dinant GJ, Geusens PP. Timing of subsequent fractures after an initial fracture. *Curr Osteoporos Rep*. 2010;8(3):118-122. doi:10.1007/s11914-010-0023-2
3. Van Geel TACM, Van Helden S, Geusens PP, Winkens B, Dinant GJ. Clinical subsequent fractures cluster in time after first fractures. *Ann Rheum Dis*. 2009;68(1):99-102. doi:10.1136/ard.2008.092775
4. Tran T, Bliuc D, Hansen L, et al. Persistence of Excess Mortality Following Individual Nonhip Fractures: A Relative Survival Analysis. *J Clin Endocrinol Metab*. 2018;103(9):3205-3214. doi:10.1210/jc.2017-02656
5. P G, JA E, A S, J van den B. *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism, Ninth Edition*.; 2019.
6. Schousboe JT. Mortality After Osteoporotic Fractures: What Proportion Is Caused by Fracture and Is Preventable? *J Bone Miner Res*. 2017;32(9):1783-1788. doi:10.1002/jbmr.3216
7. Skjødt MK, Khalid S, Ernst M, et al. Secular trends in the initiation of therapy in secondary fracture prevention in Europe: a multi-national cohort study including data from Denmark, Catalonia, and the United Kingdom. *Osteoporos Int*. 2020;31(8):1535-1544. doi:10.1007/s00198-020-05358-4
8. Solomon DH, Johnston SS, Boytsov NN, McMorrow D, Lane JM, Krohn KD. Osteoporosis medication use after hip fracture in U.S. patients between 2002 and 2011. *J Bone Miner Res*. 2014;29(9):1929-1937. doi:10.1002/jbmr.2202
9. Eisman J, Clapham S, Kehoe L. Osteoporosis prevalence and levels of treatment in primary care: The Australian bonecare study. *J Bone Miner Res*. 2004;19(12):1969-1975. doi:10.1359/JBMR.040905
10. Geusens P, Bours SPG, Wyers CE, van den Bergh JP. Fracture liaison programs. *Best Pract Res Clin Rheumatol*. 2019;33(2):278-289. doi:10.1016/j.berh.2019.03.016
11. Inderjeeth CA, Glennon D, Petta A. Study of osteoporosis awareness, investigation and treatment of patients discharged from a tertiary public teaching hospital. *Intern Med J*. 2006;36(9):547-551. doi:10.1111/j.1445-5994.2006.01146.x
12. Inderjeeth CA, Raymond WD, Briggs AM, Geelhoed E, Oldham D, Mountain D. Implementation of the Western Australian Osteoporosis Model of Care: a fracture liaison service utilising emergency department information systems to identify patients with fragility fracture to improve current practice and reduce re-fracture rates: a 12-. *Osteoporos Int*. 2018;29(8):1759-1770. doi:10.1007/s00198-018-4526-5
13. Soiza RL, Donaldson AIC, Myint PK. Fracture liaison services: do they reduce fracture rates? *Ther Adv Vaccines*. 2018;9(6):259-261. doi:10.1177/https
14. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Med*. 2009;6(7). doi:10.1371/journal.pmed.1000097
15. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: A tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016;355:1-7. doi:10.1136/bmj.i4919
16. GA Wells, B Shea, D O'Connell, J Peterson, V Welch, M Losos PT. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

17. National Institutes of Health. Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. Published 2014. https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools
18. Grant J, Hunter A. Measuring inconsistency in knowledgebases. *J Intell Inf Syst*. 2006;27(2):159-184. doi:10.1007/s10844-006-2974-4
19. Amphansap T, Stitkitti N, Dumrongwanich P. Evaluation of Police General Hospital's Fracture Liaison Service (PGH's FLS): The first study of a Fracture Liaison Service in Thailand. *Osteoporos Sarcopenia*. 2016;2(4):238-243. doi:10.1016/j.afos.2016.09.002
20. Singh S, Whitehurst DG, Funnell L, et al. Breaking the cycle of recurrent fracture: implementing the first fracture liaison service (FLS) in British Columbia, Canada. *Arch Osteoporos*. 2019;14(1). doi:10.1007/s11657-019-0662-6
21. González-Quevedo D, Bautista-Enrique D, Pérez-del-Río V, Bravo-Bardají M, García-de-Quevedo D, Tamimi I. Fracture liaison service and mortality in elderly hip fracture patients: a prospective cohort study. *Osteoporos Int*. 2020;31(1):77-84. doi:10.1007/s00198-019-05153-w
22. Axelsson KF, Jacobsson R, Lund D, Lorentzon M. Effectiveness of a minimal resource fracture liaison service. *Osteoporos Int*. 2016;27(11):3165-3175. doi:10.1007/s00198-016-3643-2
23. Davidson E, Seal A, Doyle Z, Fielding K, McGirr J. Prevention of osteoporotic refractures in regional Australia. *Aust J Rural Health*. 2017;25(6):362-368. doi:10.1111/ajr.12355
24. Huntjens KMB, Van Geel TCM, Geusens PP, et al. Impact of guideline implementation by a fracture nurse on subsequent fractures and mortality in patients presenting with non-vertebral fractures. *Injury*. 2011;42(SUPPL. 4):S39-S43. doi:10.1016/S0020-1383(11)70011-0
25. Huntjens KMB, Van Geel TACM, Van Den Bergh JPW, et al. Fracture liaison service: Impact on subsequent nonvertebral fracture incidence and mortality. *J Bone Jt Surg - Ser A*. 2014;96(4):1-8. doi:10.2106/JBJS.L.00223
26. Henderson CY, Shanahan E, Butler A, et al. Dedicated orthogeriatric service reduces hip fracture mortality. *Ir J Med Sci*. 2017;186(1):179-184. doi:10.1007/s11845-016-1453-3
27. Ruggiero C, Zampi E, Rinonapoli G, et al. Fracture prevention service to bridge the osteoporosis care gap. *Clin Interv Aging*. 2015;10:1035-1042. doi:10.2147/CIA.S76695
28. Wasfie T, Jackson A, Brock C, Galovska S, McCullough JR, Burgess JA. Does a fracture liaison service program minimize recurrent fragility fractures in the elderly with osteoporotic vertebral compression fractures? *Am J Surg*. 2019;217(3):557-560. doi:10.1016/j.amjsurg.2018.09.027
29. Axelsson KF, Johansson H, Lundh D, Möller M, Lorentzon M. Association Between Recurrent Fracture Risk and Implementation of Fracture Liaison Services in Four Swedish Hospitals: A Cohort Study. *J Bone Miner Res*. 2020;35(7):1216-1223. doi:10.1002/jbmr.3990
30. Hawley S, Kassim Javaid M, Prieto-Alhambra D, et al. Clinical effectiveness of orthogeriatric and fracture liaison service models of care for hip fracture patients: Population-based longitudinal study. *Age Ageing*. 2016;45(2):236-242. doi:10.1093/ageing/afv204
31. Nakayama A, Major G, Holliday E, Attia J, Bogduk N. Evidence of effectiveness of a fracture liaison service to reduce the re-fracture rate. *Osteoporos Int*. 2016;27(3):873-879. doi:10.1007/s00198-015-3443-0
32. Shin YH, Hong WK, Kim J, Gong HS. Osteoporosis care after distal radius fracture reduces subsequent hip or spine fractures: a 4-year longitudinal study. *Osteoporos Int*. 2020;31(8):1471-1476. doi:10.1007/

s00198-020-05410-3

33. Stark S, Landsbaum A, Palmer JL, Somerville EK, Morris JC. of Older Adults. 2009;58(4):235-246. doi:10.1111/j.1532-5415.2010.02767.x
34. Wolkewitz M, Cooper BS, Bonten MJM, Barnett AG, Schumacher M. Interpreting and comparing risks in the presence of competing events. *BMJ*. 2014;349(August):1-5. doi:10.1136/bmj.g5060
35. Wu CH, Tu S Te, Chang YF, et al. Fracture liaison services improve outcomes of patients with osteoporosis-related fractures: A systematic literature review and meta-analysis. *Bone*. 2018;111(138):92-100. doi:10.1016/j.bone.2018.03.018
36. Briot K. Fracture Liaison Services. *Curr Opin Rheumatol*. 2017;29(4):416-421. doi:10.1097/BOR.0000000000000401


5

CHAPTER 6

Health-related quality of life of patients with a recent fracture attending a fracture liaison service: a 3-year follow-up study

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Li N, van Oostwaard M, van den Bergh JP, Hiligsmann M, Boonen A, van Kuijk SM, Vranken L, Bours SP, Wyers CE. Health-related quality of life of patients with a recent fracture attending a fracture liaison service: a 3-year follow-up study. Osteoporos Int. 2022 Mar;33(3):577-588. doi: 10.1007/s00198-021-06204-x.

ABSTRACT

Summary This study explored the course of health state utility value over 3 years in patients with a recent fracture attending a Fracture Liaison Service and suggested that the overall change in health-related quality of life was not significant, although significant improvements were observed at 6 and 12 months compared to baseline.

Introduction To estimate the 3-year health-related quality of life (HRQoL) of patients with a recent fracture presenting at a Fracture Liaison Service (FLS) and to explore factors associated with health state utility value (HSUV).

Methods Patients' HSUVs were derived from the EQ-5D-5L and SF-6D and calculated at six time points. Multiple imputation was applied for missing data. Linear mixed-effects regression analysis with random intercept and slope was applied to explore the course of HSUV over 3 years. The impact of subsequent fracture and the length of time between FLS visit and patients' index fracture on HSUV were also investigated. A backward stepwise elimination was applied to identify factors associated with HSUV.

Results A total of 499 patients were included. The change of EQ-5D HSUV was not significant over 3-year follow-up (P = 0.52), although slightly but significantly higher HSUV was captured at 6 months (mean difference (MD): 0.015, P = 0.02) and 12 months (MD: 0.018, P = 0.01). There was no significant difference in the course of EQ-5D HSUV between fracture locations (P = 0.86). A significant increase in HSUV was only captured for patients had shorter time period (< 107 days)

between FLS visit and their index fracture. Suffering a subsequent fracture was associated with significant QoL loss (MD: − 0.078, P < 0.001). Subsequent fracture, previous treatment with anti-osteoporosis medication, a prevalent vertebral fracture (grade 2 or 3), use of a walking aid, previous falls, and higher BMI were negatively associated with mean EQ-5D HSUV over 3 years. Comparable results were found using SF-6D HSUV. The lack of HRQoL data immediately after fracture and selection bias were two main limitations.

Conclusion The 3-year change in HSUV was not statistically significant, although significant improvements were observed at 6 and 12 months in comparison with baseline. Six factors were negatively associated with EQ-5D HSUV.

Keywords EQ-5D-5L • Health utility • Longitudinal analysis • SF-6D

INTRODUCTION

The increasing prevalence of osteoporosis is associated with increased risk of a bone fracture [1]. A Dutch study based on claims data from all Dutch healthcare insurers reported an annual average of 114,116 patients with a fracture was identified between 2009 and 2011, of which 32% were attributed to osteoporosis [2]. Patients with a recent fracture after the age of 50 years have an increased risk of subsequent fractures. This risk, which is referred to as imminent subsequent fracture risk [3], is highest immediately after the initial fracture and then declines. In addition, the majority of deaths following fractures occur within the first year; thereafter, the excess mortality gradually declines [4]. From the perspective of caregivers, morbidity and mortality following a fracture are important clinical considerations, along with substantial loss of patients' quality of life.

To improve secondary fracture prevention, Fracture Liaison Services (FLSs) are advocated as the most appropriate and effective approach to identify, investigate, and treat patients at risk of new fractures. The first FLS was introduced in 1999 by McLellan and colleagues in the UK [5]; since then, awareness of initiating FLSs worldwide has increased through the Capture the Fracture (CTF) campaign in 2012 by the International Osteoporosis Foundation (IOF) [6] and by other professional organizations [7,8]. Until May 2021, 644 FLSs (registered in CTF) have been implemented in 48 countries; nearly half of these are in Europe.

To capture the full burden of fractures for a society, it is essential to assess their impact on health. Insight into the loss of healthy life years can facilitate rational decision-making when allocating resources across fracture types or diseases [9]. Health state utility value (HSUV) measures are a specified type of health-related quality of life (HRQoL) instruments that reveal the society's preference or value for specific health states. HSUV is an essential component in economic evaluations, used to establish whether the cost of a new intervention can be justified in terms of expected health benefits [10]; it can help decision-makers in prioritizing health interventions.

In fracture research, a large number of studies were conducted to investigate HSUV in patients not attending an FLS. For example, the large ICUROS study [9] reported that fractures resulted in substantial HRQoL loss directly after fracture, and the HRQoL improved after 4 months but did not return to pre-fracture levels. In 2014, a meta-analysis identified 62 studies that reported HSUVs after hip, vertebral, or distal forearm fracture [13]; the study populations were heterogeneous (e.g., pre-fracture, posthip/vertebral/wrist fracture), and most studies had a small sample

size and were limited by short follow-up periods, indicating that fracture events were associated with decrements in HSUVs which differed between fracture types. Very few studies were conducted to investigate HRQoL in patients with fractures attending an FLS [14, 15], especially the course of HSUV in the long term. Therefore, the main objective of this study was to investigate the course of HSUV in patients with a recent fracture presenting at an FLS in the Netherlands, as measured by two generic preference-based instruments: the EuroQol (EQ-5D-5L) and the Short Form Health Survey (SF-36), over a 3-year follow-up. In addition, considering previous studies [9, 11, 16, 17] indicated that demographics and fracture-related characteristics such as age, previous fracture, hospitalization, and treatment initiation were significantly associated with patients' HSUV, our secondary objective was to identify factors associated with HSUV in patients at the FLS.

MATERIALS AND METHODS

Subject and study procedures

This study used data from the "FX MoVie Study," which is a 3-year prospective observational study conducted at the FLS of VieCuri Medical Center in Venlo, the Netherlands [18]. The study protocol (registration number NL45707.072.13) was approved by an independent Medical Ethics Committee and complied with the Declaration of Helsinki. All patients gave written informed consent prior to participation and after receiving oral and written information on the study.

According to standard care, a nurse specialized in osteoporosis invited all patients aged 50 years and older, who visited the emergency department (ED) because of a recent clinical vertebral or non-vertebral fracture, to the FLS. All patients attending the FLS between October 2014 and June 2016 were screened for participation in the "FX MoVie Study." A total of 1380 FLS attenders were screened for eligibility, of whom 990 were eligible to participate and a total of 500 patients aged between 50 and 90 years with a recent, radiologically confirmed fracture participated. We excluded non-Caucasian patients, patients with a fracture due to high-energy trauma, bone metastasis, failure of prosthesis, or osteomyelitis, and patients with cognitive impairment.

All participants received a detailed questionnaire for evaluating clinical risk factors for fractures, such as medical history, medication, previous fractures, and calcium and vitamin D intake, and were scheduled for dual X-ray absorptiometry (DXA) measurement, vertebral fracture assessment (VFA), and a blood test. In addition to the questionnaire for evaluating risk factors, HRQoL questionnaires (EQ-5D-

5L and SF-36) were filled out at 3, 6, 12, 24, and 36 months after inclusion. Of note, the patients' first visits at the FLS were scheduled 3–4 months after their fracture, so HRQoL data immediately after their fracture were not available. Three and 6 months after inclusion, patients received the HRQoL questionnaires and a fall diary. Furthermore, they received a telephone call from the research assistant to verify whether they sustained a fall or a subsequent fracture and to complete the questionnaires in case of missing data. At 12, 24, and 36 months after inclusion, patients came to the hospital for a study visit and the questionnaires were repeated. Bone mineral density (BMD) in the left or right hip and the lumbar spine was determined using DXA with the Hologic QDR 4500 (Hologic, Bedford, MA, USA). Diagnosis of osteoporosis was based on the World Health Organization criteria for BMD [19] according to the lowest value of T-score in femoral neck, total hip, or lumbar spine: osteoporosis as a T-score of − 2.5 or less, osteopenia as a T-score between − 2.5 and − 1.0, and normal BMD as a T-score of − 1.0 or higher.

Assessment of vertebral fractures (VFs) was performed via vertebral fracture assessment (VFA). VFs were graded according to the grading of Genant et al. [20] as mild (grade 1, 20–24% reduction in vertebral body height at the anterior, mid, or posterior location), moderate (grade 2, 25–39% reduction), or severe (grade 3, ≥ 40% reduction), respectively.

If laboratory results were abnormal, additional investigations were performed for detailed evaluation of newly diagnosed contributors to secondary osteoporosis or other metabolic bone disorders and treatment was initiated when necessary.

Demographics and disease-related characteristics

The socio-demographics included age (years at time of fracture), gender, and body mass index (BMI). Baseline fracture-related characteristics were collected through (1) questionnaire (and further verified during FLS visit): smoking, fracture site, previous fracture, previous falls (last year), parental hip fracture, use of a walking aid, visual and hearing impairment, previous treatment with anti-osteoporosis medication (AOM), and medical history (which is classified based on International Classification of Diseases version 10), and (2) laboratory tests: BMD, prevalent VFs, secondary osteoporosis, and vitamin D deficiency. In addition, the specific times of new falls and subsequent fractures were recorded for each patient during 3-year follow-up, and we assumed that none of the patients had a fall or a subsequent fracture between their baseline fracture (i.e., the fracture for which they were invited to attend the FLS) and the time they attended the FLS.

Fracture classification

Patients' index fractures were recorded in electronic Case Report Forms. For purpose of analyses, these fractures were grouped into ten categories according to their location as clavicle/scapula, humerus, radius/ulna, hand/foot, vertebra, rib/sternum, pelvis, femur, tibia/fibula/patella, and multiple fractures (if patients had more than one index fracture). In addition, based on visual inspection, patients with femoral, vertebral, or multiple fractures had a strikingly lower baseline HSUV in comparison with patients with other fractures; the pre-defined ten categories were further divided into two groups (femoral/vertebral/multiple fractures vs. other fractures) to investigate between-group differences.

Health state utility value (outcome)

HRQoL is expressed in the form of HSUV, which is scored on a scale that assigns a value of 1 to a state equivalent to full health and 0 to a state equivalent to death. In our study, HSUVs were calculated according to EQ-5D-5L and SF-36 data. The EQ-5D-5L quantifies health status in terms of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Patients score each dimension on a five-level Likert scale (no problem, slight problem, moderate problem, severe problem, and extreme problem). To translate the EQ-5D profiles to societal HSUVs, a value set based on population preferences in the Netherlands was used [21]. The predicted values for the EQ-5D-5L range from – 0.446 to 1, where HSUV below 0 represents health states considered worse than death. The SF-6D was derived from the SF-36 health status measure (version 1, UK Programme) including 6 dimensions of health: physical functioning, social functioning, role limitations, pain, mental health, and vitality, with each dimension having four to six levels. The societal HSUVs were computed using the algorithm developed by Brazier et al. [22]. The predicted values for the SF-6D range from + 0.291 to + 1.

Statistical analysis

For baseline characteristics, descriptives are provided as means and standard deviations (SD) for continuous variables, number, and percentage (%) for categorical variables. Comparisons between groups (different fracture sites) were conducted using the independent samples t-tests or one-way analysis of variance (ANOVA) for continuous variables, and Pearson's chi-square test or Fisher's exact test for categorical variables.

Multiple imputation (MI) with fully conditional specification was employed to impute missing EQ-5D and SF-6D data. The number of imputations was set to 18, given that approximately 18% of incomplete cases were identified. Patients' missing index values were drawn at six time points, using predictive mean matching. Details

of missing data and MI were reported in Supplement 1.

Linear mixed-effects regression with random intercept and slope for patients was applied to compare the mean HSUV between baseline and each time point, to explore the course of the HSUV for all sites of fracture over the 3-year follow-up, and to investigate the impact of fracture site on the course of HSUV over time by including an interaction term of time and baseline fracture group (categorical variable with ten pre-defined categories) in the model.

Additionally, given that the time period between index fracture and FLS visit varied among patients, a subgroup analysis was conducted to explore the difference in the change of HSUV. Since this time period was normally distributed, we used the mean (107 days) as a cut-off to categorize our patients into two groups (i.e., time between index fracture and FLS visit < 107 days vs. ≥ 107 days). A clustered line graph was used to visually display the difference in HSUV change over time and the mean difference (MD) was calculated between baseline and each time point. Besides, considering patients' characteristics might influence the results, we also investigated the difference in five most relevant baseline characteristics, i.e., age, gender, BMD, index fracture (femoral/vertebral/multiple fracture, other fractures), and medical history (ICD-10 coded diseases) between two groups using previous mentioned statistical method to further validate our results.

Moreover, the impact of subsequent fracture on HSUV was also investigated. Of note, 20 patients already had a subsequent fracture before the first FLS visit and were therefore excluded for the following analyses. First, the subsequent fracture was treated as a time-varying variable to explore the overall association with HSUV, both between-subjects and within-subjects interpretation were provided. Second, for patients who had a subsequent fracture (during follow-up), the HSUVs before and after a subsequent fracture were compared for these patients. To capture the maximum impact of a subsequent fracture, the HSUV just before and immediately after the subsequent fracture was treated as pre- and post-HSUV, respectively (i.e., if one patient had a subsequent fracture at 6 months, the HSUV at 3 months was treated as pre-HSUV and the HSUV at 6 months as post-HSUV). Third, the impact of different locations of subsequent fracture was also investigated. Patients were subdivided into two groups (subsequent femoral/vertebral/multiple fractures vs. subsequent other fractures), the HSUVs before and after a corresponding subsequent fracture were compared for each subgroup. Fourth, we subsequently compared the HSUVs in the group of patients without subsequent fracture to those with a subsequent fracture and applied the median time to subsequent fracture (which was 354 days) to both groups in order to compare HSUVs in the time period

before and after subsequent fracture (period 1: 0–364 days vs. period 2: 365–1095 days) in both groups. Given the HSUVs were estimated at discrete time points, and the median time to subsequent fracture was 364 days, the mean HSUV of baseline, 3 months, 6 months, and 12 months was therefore treated as pre-HSUV, and the mean HSUV of 24 months and 36 months was treated as post-HSUV for both groups. Through pre-testing, normal distribution was indicated for the difference (in mean HSUV) between period 1 and 2 for both groups, and given the HSUV of each patient was repeated measured, mean difference was therefore calculated through paired-samples T-test.

Furthermore, the identification of factors associated with the average HSUV (over 3 years) was also conducted, using the linear mixed-effect regression model. The abovementioned demographics and disease-related characteristics (16 baseline and two longitudinally assessed variables) were considered potential factors and therefore included in the model. A backward stepwise elimination was applied to omit insignificant factors from the model.

The above-mentioned longitudinal analyses for EQ-5D HSUV were included as the main analysis, and the analyses based on SF-6D HSUV were included as sensitivity analysis. All mixed-effects regression analyses were adjusted for age, gender, and baseline BMD. All analyses were conducted using SPSS (version 26.0, IBM Statistics), and a P-value of ≤ 0.05 was considered statistically significant.

RESULT

Baseline characteristics

After multiple imputations, 499 patients with one or more recent fractures were included in our analyses. Of note, one patient did not complete any questionnaire at all, so no imputation was conducted for this patient, who was therefore excluded from the whole analysis. Baseline characteristics according to fracture site are presented in Table 1. Patients were on average 64.6 ± 8.6 years, and 71.3% were females. One hundred ten (22.0%) patients were diagnosed with osteoporosis, 133 (26.7%) had at least one VF, and 54 (10.8%) patients reported that they have ever used AOM, at the time of FLS visit, treatment was initiated or continued in 175 (35%) of patients. More than 90% of patients had one or more comorbidities (ICD-10 coded disease). On average, patients attended the FLS 107 days after their index fracture.

Table 1. Baseline characteristics of participants by fracture site

Characteristic		Clavicle/ scapula	Humerus	Radius/ulna	Hand/foot	Vertebra	Rib/sternum	Pelvis	Femur	Tibia/fibula/ patella	Multiple fractures	Total group
Number of patients with fractures		13	47	125	140	25	17	11	21	80	20	499
Mean age, years (SD)*		65.8 (10.9)	67.9 (8.6)	65.2 (8.2)	62.1 (8.4)	68.8 (9.2)	64.9 (9.5)	71.7 (6.5)	68.6 (8.9)	61.9 (7.0)	67.8 (7.4)	64.6 (8.6)
Female (%)*		6 (46.2%)	34 (72.3%)	101 (80.8%)	95 (67.9%)	17 (68.0%)	4 (23.5%)	11 (100.0%)	14 (66.7%)	58 (72.5%)	16 (80.0%)	356 (71.3%)
BMI, kg/m2 (SD)*		26.6 (2.9)	28.8 (4.2)	27.4 (4.4)	27.6 (4.7)	28.4 (4.6)	27.6 (3.8)	25.3 (2.7)	25.2 (4.7)	28.3 (4.1)	28.3 (5.3)	27.7 (4.4)
BMD (%) *	Normal	3 (23.1%)	12 (25.5%)	39 (31.2%)	39 (27.9%)	3 (12.0%)	5 (29.4%)	2 (18.2%)	1 (4.8%)	26 (32.5%)	5 (25.0%)	135 (27.1%)
	Osteopenia	9 (69.2%)	23 (48.9%)	51 (40.8%)	80 (57.1%)	11 (44.0%)	9 (52.9%)	5 (45.5%)	10 (47.6%)	46 (57.5%)	10 (50.0%)	254 (50.9%)
	Osteoporosis	1 (7.7%)	12 (25.5%)	35 (28.0%)	21 (15.0%)	11 (44.0%)	3 (17.6%)	4 (36.4%)	10 (47.6%)	8 (10.0%)	5 (25.0%)	110 (22.0%)
Prevalent VF (%)*	No VF	11 (84.6%)	35 (74.5%)	97 (77.6%)	112 (80.0%)	2 (8.0%)	15 (88.2%)	5 (45.5%)	11 (52.4%)	64 (80.0%)	14 (70.0%)	366 (73.3%)
	Only grade 1	0 (0%)	6 (12.8%)	17 (13.6%)	16 (11.4%)	4 (16.0%)	2 (11.8%)	3 (27.3%)	3 (14.3%)	12 (15.0%)	2 (10.0%)	65 (13.0%)
	Grade 2 or 3	2 (15.4%)	6 (12.8%)	11 (8.8%)	12 (8.6%)	19 (76.0%)	0 (0%)	3 (27.3%)	7 (33.3%)	4 (5.0%)	4 (20.0%)	68 (13.6%)
Currently smoking (%)		2 (15.4%)	4 (8.5%)	16 (12.8%)	23 (16.4%)	5 (20.0%)	2 (11.8%)	2 (18.2%)	1 (4.8%)	13 (16.3%)	1 (5.0%)	69 (13.8%)
Secondary osteoporosis (%)		3 (23.1%)	11(23.4%)	20 (16.0%)	19 (13.6%)	2 (8.0%)	1 (5.9%)	3 (27.3%)	5 (23.8%)	13 (16.3%)	6 (30.0%)	83 (16.6%)
Medical history (ICD-10 coded diseases) (%)		12 (92.3%)	46 (97.9%)	122 (97.6%)	129 (92.1%)	24 (96.0%)	17 (100%)	11 (100%)	21 (100%)	70 (87.5%)	19 (95.0%)	471 (94.4%)
Vitamin D deficiency (%)		3 (23.1%)	20 (42.6%)	40 (32.0%)	53 (37.9%)	11 (44.0%)	7 (41.2%)	5 (45.5%)	6 (28.6%)	30 (37.5%)	4 (20.0%)	179 (35.9%)
Use of a walking aid (%)*		2 (15.4%)	2 (4.3%)	5 (4.0%)	3 (2.1%)	3 (12.0%)	0 (0%)	3 (27.3%)	3 (14.3%)	5 (6.3%)	0 (0%)	26 (5.2%)
Visual impairment (%)		13 (100%)	44 (93.6%)	116 (92.8%)	128 (91.4%)	22 (88.0%)	15 (88.2%)	10 (90.9%)	20 (95.2%)	72 (90.0%)	19 (95.0%)	459 (92.0%)
Hearing impairment (%)*		1 (7.7%)	3 (6.4%)	10 (8.0%)	7 (5.0%)	2 (8.0%)	5 (29.4%)	2 (18.2%)	3 (14.3%)	6 (7.5%)	5 (25.0%)	44 (8.8%)
Parental hip fracture (%)		0 (0%)	0 (0%)	7 (5.6%)	10 (7.1%)	0 (0%)	0 (0%)	1 (9.1%)	1 (4.8%)	4 (5.0%)	0 (0%)	23 (4.6%)
Previous fracture (%)		8 (61.5%)	27 (57.4%)	67 (53.6%)	66 (47.1%)	12 (48.0%)	9 (52.9%)	4 (36.4%)	10 (47.6%)	46 (57.5%)	12 (60.0%)	261 (52.3%)
Previous treatment with AOM (%)*		2 (15.4%)	7 (14.9%)	11 (8.8%)	10 (7.6%)	4 (16.0%)	1 (5.9%)	1 (9.1%)	4 (19.0%)	7 (8.8%)	7 (35.0%)	54 (10.8%)
Falls in past year (%)		3 (23.1%)	13 (27.7%)	42 (33.6%)	33 (23.6%)	8 (32.0%)	5 (29.4%)	4 (36.4%)	2 (9.5%)	28 (35.0%)	4 (20.0%)	142 (28.5%)
Mean time length between fracture and FLS visit, days (SD)		115.2 (19.1)	110.3 (28.3)	104.9 (29.1)	106.6 (31.1)	95.5 (37.5)	102.3 (28.5)	115.5 (40.2)	120.2 (33.3)	107.9 (29.5)	113.2 (27.3)	107.3 (30.4)

BMI body mass index, *SD* standard deviation, *BMD* bone mineral density, *VF* vertebral fracture, *AOM* anti-osteoporosis medication, *FLS* fracture liaison service, *ICD-10* International Classification of Diseases (version 10)

*Statistically significant among ten pre-defined fracture categories

EQ-5D health state utility value

The estimated EQ-5D utility scores of patients with a recent fracture attending the FLS had an average HSUV of 0.813 (0.187), 0.822 (0.180), 0.829 (0.176), 0.833 (0.180), 0.825 (0.196), and 0.825 (0.202) at baseline, 3, 6, 12, 24, and 36 months, respectively (Supplement 2, Table 1). In comparison with baseline (reference), the mean HSUV of the FLS patients was slightly but significantly higher at 6 months (MD: 0.015, 95% CI: 0.002–0.029; P = 0.02) and 12 months (MD: 0.018, 95% CI: 0.004–0.032; P = 0.01), but not at 24 and 36 months (Table 2). When grouping patients further, significant improvement in HSUV was observed for patients with femoral, vertebral, or multiple fractures later during follow-up (i.e., at 12 and 24 months) than for patients with other fractures (significant improvement in HSUV was shown at 6 months).

Figure 1 shows the change in the HSUV over 3 years by the pre-defined ten categories based on fracture site. The linear mixed-effects model (Supplement 2, Table 2) showed that there was no association between HSUV and time regardless of the baseline fracture location, and also significant difference was not observed (interaction term: P = 0.86) between these ten fracture categories in terms of the overall HSUV change. When patients were further grouped (femoral/vertebral/multiple fractures vs. other fractures), a higher yearly increase (0.011 vs. < 0.001 units) was observed for patients with femoral/vertebral/multiple fractures (though which was not statistically significant).

Table 2. The mean difference in EQ-5D HSUV between each time point and baseline by fracture location (adjusted)

Time point	Reference	Total group		Femoral/vertebral/multiple fractures		Other fractures	
		Mean difference (95% CI)	*P*-value	Mean difference (95% CI)	*P*-value	Mean difference (95% CI)	*P*-value
3 months	Baseline	0.008 (−0.005, 0.021)	0.218	0.018 (−0.021, 0.057)	0.352	0.006 (−0.005, 0.017)	0.251
6 months		0.015 (0.002, 0.029)	0.024*	0.032 (−0.007, 0.071)	0.103	0.013 (0.001, 0.025)	0.039*
12 months		0.018 (0.004, 0.032)	0.011*	0.054 (0.007, 0.102)	0.024*	0.012 (0.001, 0.025)	0.056
24 months		0.011 (−0.004, 0.026)	0.160	0.046 (0.002, 0.090)	0.041*	0.006 (−0.010, 0.021)	0.465
36 months		0.010 (−0.005, 0.026)	0.193	0.042 (−0.012, 0.096)	0.122	0.006 (−0.009, 0.021)	0.448

CI confidence interval, *HSUV* health state utility value

*Statistically significant (*P*-value ≤ 0.05)

Adjusted: the regression analysis was adjusted for age, gender, and bone mineral density (BMD)

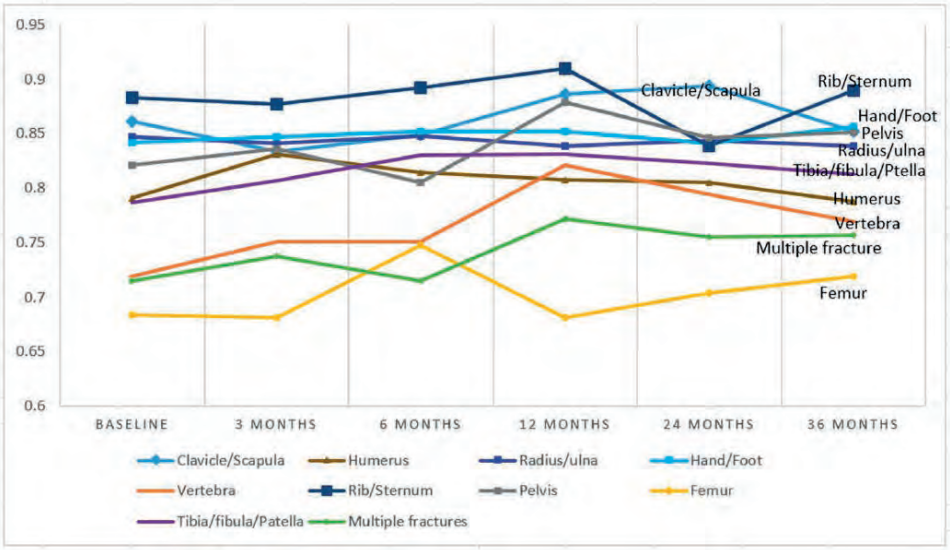

Figure 1. The development of EQ-5D HSUV over time by fracture site

When patients were categorized into two groups according to the length of time between index fracture and FLS visit, 258 patients had the first FLS visit < 107 days and 241 patients ≥ 107 days after their index fracture. As seen in Table 3 and Supplement 2 (Fig. 1), a significant increase of QoL was captured at 6, 12, and 24 months for patients who had FLS visit less than 107 days, which was not the case for the group with longer time period for FLS visit. No significant differences between these two groups were observed for age, gender, BMD, index fracture, and medical history.

Table 3. The mean difference in EQ-5D HSUV between each time point and baseline by the time period between index fracture and FLS visit (adjusted)

Time point	Time between fracture and baseline < 107 days (n=258)			Time between fracture and baseline ≥ 107 days (n=241)		
	Mean (SD)	Mean difference (95% CI)	P-value	Mean (SD)	Mean difference (95% CI)	P-value
Baseline	0.805 (0.195)	Reference		0.822 (0.178)	Reference	
3 months	0.820 (0.189)	0.014 (−0.005, 0.033)	0.156	0.823 (0.170)	0.002 (−0.016, 0.020)	0.806
6 months	0.832 (0.176)	0.026 (0.006, 0.045)	0.010*	0.826 (0.176)	0.005 (−0.014, 0.024)	0.620
12 months	0.836 (0.172)	0.028 (0.009, 0.048)	0.005*	0.829 (0.187)	0.007 (−0.012, 0.027)	0.464
24 months	0.833 (0.183)	0.025 (0.006, 0.045)	0.012*	0.817 (0.208)	−0.004 (−0.025, 0.017)	0.692
36 months	0.826 (0.210)	0.018 (−0.001, 0.038)	0.069	0.825 (0.194)	0.003 (−0.019, 0.024)	0.790

CI confidence interval, *HSUV* health state utility value

*Statistically significant (P-value ≤ 0.05)

Adjusted: the regression analysis was adjusted for age, gender, and bone mineral density (BMD)

With regard to the impact of subsequent fracture on EQ-5D HSUV, the analyses were performed in 479 patients of whom 50 had a subsequent fracture during follow-up. The association between EQ-5D HSUV and subsequent fracture was displayed in Supplement 2 (Table 3). The between subjects interpretation indicates that the mean HSUV of patients with subsequent fracture was significantly lower (– 0.078 units) than of patients without subsequent fracture; and the within-subject interpretation indicates that a new subsequent fracture during follow-up was associated with a significant 0.078 units decrease in the mean HSUV (3 years). In addition, for patients had a subsequent fracture (n = 50), as seen in Fig. 2 and Supplement 2 (Table 4), both mean and median HSUV of post-subsequent fracture was lower than pre-subsequent fracture. The MD was – 0.078 (SD: 0.147), indicating that the suffering of a subsequent fracture resulted in significant 0.078 units decrease (P < 0.001) in HSUV for these patients. Moreover, when patients were subdivided into two groups, 15 patients had subsequent femoral/vertebral/multiple fractures, and 35 had subsequent other fractures. Similar results were indicated for both groups (i.e., significantly lower HSUV for post-subsequent fracture) besides, compared to patients with subsequent other fractures, greater (but not significant) HSUV decrease was observed for patients with subsequent femoral/vertebral/multiple fractures (MD: – 0.102 vs. – 0.068, P = 0.46).

Furthermore, when median time to subsequent fracture (364 days) was applied to compare the HSUVs in the group of patients without subsequent fracture (n = 429) to those with a subsequent fracture (n = 50), as seen in Supplement 2 (Table 5 and Fig. 2), the median and mean HSUV (in both period 1 and 2) for patients with subsequent fracture was lower than patients without subsequent fracture. For patients who suffered a subsequent fracture, the decrease in mean HSUV (MD: – 0.015) was observed in period 2 compared to period 1 whereas the increase (MD: 0.001) was captured for patients without subsequent fracture during the follow-up, both were not statistically significant.

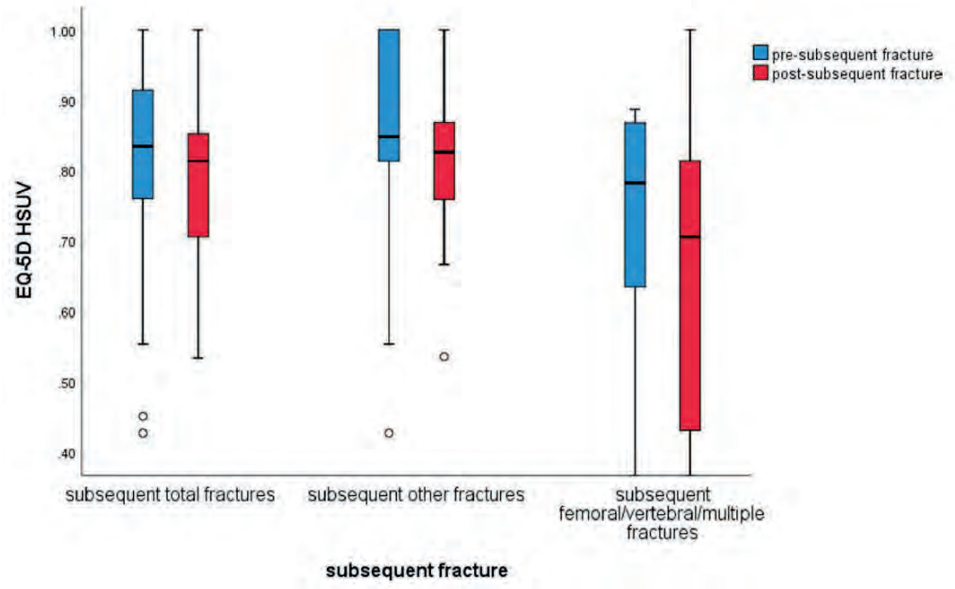

Figure 2. The comparison of EQ-5D HSUV before and after a subsequent fracture by the location of subsequent fracture

SF-6D health utility (sensitivity analysis)

The above-mentioned analyses were also conducted using SF-6D HSUV; the statistical results are shown in Supplement 3. In comparison with baseline HSUV, a statistically significant increase was also captured at 6 months (Supplement 3, Table 2). Besides, the longitudinal regression also indicated that the change in HSUV over time was not significant for the total cohort, and the course of SF-6D HSUV was also not significantly different between pre-defined ten fracture categories. In addition, when patients were categorized into two groups according to the length of time between index fracture and FLS visit, compared to baseline HSUV, a significant increase was also captured at 6 and 12 months for patients had FLS visit less than 107 days, which was not the case for the group with longer time period for FLS visit (Supplement 3, Table 3). Moreover, for patients who had a subsequent fracture, both mean and median HSUV of post-subsequent fracture was also lower than pre-subsequent fracture, and the suffering of a subsequent fracture resulted in significant decrease in HSUV for these patients. The results remained when patients were subdivided by subsequent fracture location (Supplement 3, Table 4 and Fig. 2). Furthermore, when median time to subsequent fracture (364 days) was applied to compared the HSUVs in the group of patients without subsequent fracture to those with a subsequent fracture, the median and mean HSUV (in both

period 1 and 2) for patients with subsequent fracture was also lower than patients without subsequent fracture (Supplement 3, Fig. 3).

Factors associated with EQ-5D and SF-6D HSUV

The stepwise regression analysis (Table 4) indicated the effect of covariates on patients' mean HSUV over 3 years (six time point). BMI, use of a walking aid, AOM treatment, previous falls, prevalent VF (grade 2 or 3), and subsequent fracture were identified as factors associated with mean EQ-5D HSUV. With regard to time-varying covariates, a negative predictive relationship between subsequent fracture and HSUV was indicated (the between- and within-subject interpretations were similar to previously described). As for time-invariant covariates, patients using a walking aid, taking AOM, and having experienced previous falls had significantly lower HSUV in comparison to their counterparts. To investigate the association between prevalent vertebral fractures (VFs) and HSUV, patients without prevalent VFs were set as the reference; it can be seen from Table 4 that only prevalent VFs grade 2 or 3 was identified as a factor associated with HSUV. The effect size can be interpreted that patients with prevalent VFs grade 2 or 3 had significantly 0.050 units lower EQ-5D HSUV on average (mean HSUV of 3 years) than patients without prevalent VFs. Other covariates like age and smoking were excluded through the process of backward stepwise elimination based on P-value, but we found that the increasing in patients' age was associated with decreasing in mean HSUV (1-year age increase was associated with 0.001 units decrease in mean HSUV), and smokers had (0.030 units) lower HSUV than non-smokers.

In addition to the above-mentioned factors (by EQ-5D), SF-6D indicated another two factors (gender and smoking). In comparison with males, females had a significantly lower HSUV on average, and smokers reported significantly lower utility in comparison with non-smokers.

Table 4. Factors associated with HSUV

Covariate	EQ-5D		SF-6D	
	Coefficient	*P*-value	Coefficient	*P*-value
Female	Exc		−0.037	<0.001
Age	Exc		Exc	
BMI	−0.006	<0.001	−0.004	<0.001
Osteopenia BMD	Exc		Exc	
Osteoporotic BMD	Exc		Exc	
Prevalent VFs grade 1	Exc		Exc	
Prevalent VFs grade 2 or 3	−0.050	0.009	−0.041	0.003
Smoking	Exc		−0.033	0.016
Medical history (ICD-10 coded diseases)	Exc		Exc	
Secondary osteoporosis	Exc		Exc	
Vitamin D deficiency	Exc		Exc	
Use of a walking aid	−0.279	<0.001	−0.138	<0.001
Visual impairment	Exc		Exc	
Hearing impairment	Exc		Exc	
Parental hip fracture	−0.060	0.047	Exc	
Previous fracture	Exc		Exc	
Previous treatment with AOM	−0.046	0.030	Exc	
Falls past year	−0.038	0.007	−0.028	0.007
Falls during follow-up	Exc		Exc	
Subsequent fractures during follow-up	−0.068	<0.001	−0.044	<0.001

BMI body mass index, *BMD* bone mineral density, *VF* vertebral fracture, *AOM* anti-osteoporosis medication, *ICD-10* international classification of disease (version 10), *HSUV* health state utility value

For BMD, patients with normal BMD was the reference, for prevalent VFs, patients without VF was the reference

Exc = covariate was excluded in stepwise selection process

DISCUSSION

This study, to our knowledge, is the first longitudinal study using prospective data over 3 years, with the objective of estimating the HRQoL of patients following visits to a FLS because of a recent fracture. With regard to EQ-5D HSUV, no significant change was captured over 3 years, although a small but statistically significant improvement was observed at 6 and 12 months in comparison with baseline HSUV. This short-term improvement is more likely due to natural healing of the fracture rather than the effect of attending an FLS or having a fracture risk evaluation at the FLS. When patients were stratified by baseline fracture (femoral/vertebral/multiple fractures vs. other fractures), our results remained (i.e., there was no significant overall change). We did not find any previous study investigating the long-term HRQoL of patients attending a FLS. In contrast, two studies [14, 15] compared the

HSUV of patients with a recent fracture before and after the introduction of a FLS; no significant difference between two groups was identified at the 6 or 12 months follow-up.

The primary potential reason for a non-significant change in HSUV over 3 years is that the patients included in our study attended the FLS 3–4 months after their index fracture; thus, their HRQoL might have already improved through natural fracture recovery and/or through treatment in the emergency department before attending the FLS, resulting in non-striking change after attending FLS. This was also found in the ICUROS studies [9, 11, 12]: although substantial loss of HRQoL was captured in the short term after fracture, patients' HRQoL was largely improved at 4 months. Except for ICUROS studies, the improvement was also identified in patients who did not attend a FLS in recent studies [14, 15], which can also be attributable to natural healing (recovery) of the fracture. The second potential reason for lack of significant change may be selection bias; it is likely that patients with more severe fractures, older patients, or patients who were hospitalized did not attend the FLS. Furthermore, approximately half of FLS attenders did not consent to participate in this study. In this study, the average baseline HSUV was 0.81, which is a bit lower but still comparable to the HSUV of community-dwelling Dutch residents aged 65 years and older as reported by Mangen et al. [23]. Therefore, our study included relatively healthy patients, which may have resulted in a relatively good HRQOL after the index fracture, without a significant change over time.

Additionally, the greater increase in QOL in patients with a shorter time period (< 107 days) between index fracture and FLS visit may be attributed to the earlier stage of the fracture healing process, and by the timely treatment from FLS clinic compared to patients with a longer time period to FLS visit.

Of note, although patients' baseline HRQoL was measured 3–4 months after their index fracture, patients with femoral, vertebral, or multiple fractures still had a lower HSUV in comparison with patients with other fractures. Also, significant improvement in HRQoL takes a longer time to capture (baseline HSUV as the reference) as reported in our study. Fisher et al. [24] assessed the timeline of functional recovery after hip fracture in seniors (aged 65 years and older) and reported that objective functional recovery (lower extremity function) was largely complete in the first 6 months, whereas subjective recovery (HRQoL) improved up to 9 months after hip fracture. In addition, we also identified that the number of baseline fractures impacted patients' HRQoL. Patients with multiple fractures had a significantly lower HSUV in comparison with patients with only one index fracture such as clavicle/scapula, radius/ulna, hand/foot, rib/sternum fracture.

This finding is supported by a previous study showing that patients with multiple clinical fractures would experience an additive effect, resulting in disability similar to a single hip or vertebral fracture [25] which is in line with our finding that the absolute average HSUV (over 3 years) difference between femoral, vertebral, and multiple fractures was not significant.

Suffering a subsequent fracture was associated with a decrease in HSUV; this finding is supported by several previous studies [26–28] reporting that subsequent fractures have a significantly negative impact on the QoL, greater loss of function, and increased mortality. However, whether the effect of FLS is larger immediately after subsequent fracture, and whether the cost-effectiveness of FLS is somewhat better, it remains unknown based on our data and recently published studies.

Furthermore, to accurately estimate the effect of FLS on QoL is even difficult given QoL is determined by multiple factors such as lifestyle, aging, and comorbidities; however, it would be interesting for future studies. Also, the presence of a moderate or severe prevalent VF was associated with a lower HSUV, which is in line with recent findings of Shah et al. [29]. Besides, patients who previously received treatment with AOM reported lower utility in comparison with their counterparts. The lower HSUV might be explained by two aspects: first, since the indication for treatment (according to the Dutch guideline) is osteoporosis and/or a moderate or severe VF, patients' awareness of having osteoporosis and/or VFs and increased future fracture risk might result in over cautiousness and limiting daily activities; second, the potential side effects of oral AOM including bone, joint, or muscle pain, as well as nausea, difficulty swallowing, and heartburn might affect patients' HRQoL, and the rare side effects such as osteonecrosis of the jaw and atypical femoral fracture actually scare many patients away from taking AOM, with the result that suboptimal persistence and adherence lead to an increased rate of fracture and to worse HRQoL [30]. Moreover, patients' HSUVs following a fracture are clearly negatively associated with high BMI since excessive body fat produces inflammatory cytokines which may stimulate bone resorption and reduce bone strength [31]. Several recent studies reported that both low and high BMI are risk factors for fragility fracture. The study of Yan et al. [32] investigated the relationships of BMI with HRQoL in adults 65 years and older and revealed that compared with normal-weight people, both underweight and obese older adults reported impaired QoL, particularly worse physical functioning and physical well-being. Furthermore, some previous studies identified that gender [13, 16] and previous fracture [9] are important factors; these were not captured by EQ-5D in our study.

In a sensitivity analysis using another HRQoL measure, namely the SF-6D,

comparable results were identified and our main message remained, though there were small differences. For example, the mean SF-6D HSUV was generally lower than the EQ-5D HSUV, and only SF-6D indicated that the course of HSUV for patients with hand/foot fracture was significant. Besides, when the median time to subsequent fracture (364 days) was applied to compare the HSUVs patients without subsequent fracture to those with a subsequent fracture, a higher median EQ-5D HSUV was captured in period 2 for both groups, however, which was only observed for patients without subsequent fracture by SF-6D HSUV. These discrepancies between the two instruments might result from differences in the content of the descriptive systems and in the variation of scoring algorithms [33]; a further head-to-head comparison will be conducted to explore the equivalency of EQ-5D-5L and SF-6D cross-sectionally, including scoring distribution, domain content, and longitudinal validity.

This study has some limitations. First, relatively healthy patients were included in this study (selection bias), so the generalizability of the findings of this study to patients with a fracture could therefore be questionable. Second, our patients attended the FLS approximately 3–4 months after their index fracture; we therefore lacked HRQoL data immediately after fracture, which might limit our capturing an overall significant change of HRQoL in the first several weeks of recovery from a fracture. Finally, 18 patients scored an item of EQ-5D twice; we calculated their two utility scores and used the average value for further analyses, which might affect the results.

CONCLUSION

In patients at the FLS, subsequent fracture, previous treatment with AOM, a prevalent VF (grade 2 or 3), use of a walking aid, previous falls, and higher BMI were negatively associated with EQ-5D HSUV. The change in HSUV over the total course of 3 years was not statistically significant, although significant improvements were observed at 6- and 12-month time points compared to baseline. There was no significant difference in the course of HSUV between the pre-defined ten fracture categories. A significant increase in HSUV was only captured for patients had shorter time period (< 107 days) between FLS visit and their index fracture. Suffering a subsequent fracture was associated with significant QoL loss.

ELECTRONIC SUPPLEMENTARY MATERIAL

Supplement 1: Missing data and multiple imputation (MI)

The number of missing utility data at each time point were shown in Table 1; given a few patients had missing data, MI was applicable. In addition, 18% of incomplete cases were identified; the number of imputations was therefore set to 18. The overall missing data were in a random pattern. Considering that some patients died or stopped participation during the follow-up, different strategies of imputation were applied. For patients who died during the follow-up period (n=5), their HSUVs were set at 0 from that time point, and MI was applied for the period of their participation. MI was conducted for patients who withdrew their consent or stopped the study during the follow-up (n=15); however, for these patients, imputed index values remained only for the period before they quit. For patients providing two answers to one single question, a mean HSUV was calculated from the two responses.

Table 1. The number of missing utility data at each time point

	Baseline	3 months	6 months	1 year	2 years	3 years
EQ-5D	3	11	19	15	17	16
SF-6D	14	22	26	26	19	17

Supplement 2: EQ-5D HSUV by fracture site during 3-year follow-up

Table 1. EQ-5D mean HSUV and median HSUV by fracture site for patients attending the FLS during 3 years

Index Fracture	Baseline		3 months		6 months		12 months		24 months		36 months	
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
Total fracture	0.813 (0.187)	0.852 (0.113)	0.822 (0.180)	0.852 (0.123)	0.829 (0.176)	0.852 (0.218)	0.833 (0.180)	0.879 (0.213)	0.825 (0.196)	0.852 (0.213)	0.825 (0.202)	0.879 (0.213)
Clavicle/Scapula	0.861 (0.117)	0.887 (0.259)	0.834 (0.183)	0.852 (0.201)	0.849 (0.139)	0.887 (0.302)	0.886 (0.098)	0.887 (0.187)	0.894 (0.093)	0.887 (0.188)	0.852 (0.233)	1.000 (0.252)
Humerus	0.791 (0.188)	0.822 (0.182)	0.831 (0.167)	0.852 (0.257)	0.814 (0.189)	0.852 (0.266)	0.808 (0.206)	0.852 (0.135)	0.805 (0.215)	0.848 (0.286)	0.788 (0.246)	0.848 (0.280)
Radius/ulna	0.847 (0.165)	0.887 (0.201)	0.841 (0.166)	0.881 (0.187)	0.848 (0.166)	0.887 (0.204)	0.839 (0.189)	0.887 (0.213)	0.844 (0.202)	0.887 (0.187)	0.839 (0.210)	0.883 (0.189)
Hand/Foot	0.842 (0.159)	0.885 (0.213)	0.847 (0.144)	0.852 (0.213)	0.852 (0.153)	0.883 (0.108)	0.852 (0.160)	0.883 (0.194)	0.841 (0.171)	0.861 (0.220)	0.856 (0.154)	0.887 (0.196)
Vertebra	0.719 (0.220)	0.787 (0.223)	0.751 (0.197)	0.817 (0.217)	0.751 (0.203)	0.797 (0.201)	0.821 (0.137)	0.852 (0.185)	0.794 (0.181)	0.848 (0.159)	0.769 (0.203)	0.813 (0.144)
Rib/Sternum	0.883 (0.062)	0.887 (0.050)	0.877 (0.096)	0.887 (0.153)	0.892 (0.086)	0.887 (0.099)	0.910 (0.086)	0.887 (0.139)	0.839 (0.231)	0.870 (0.187)	0.890 (0.082)	0.849 (0.182)
Pelvis	0.821 (0.153)	0.830 (0.217)	0.836 (0.125)	0.830 (0.222)	0.805 (0.159)	0.830 (0.135)	0.879 (0.072)	0.852 (0.116)	0.846 (0.071)	0.850 (0.051)	0.851 (0.091)	0.841 (0.129)
Femur	0.684 (0.270)	0.787 (0.291)	0.681 (0.269)	0.813 (0.331)	0.747 (0.214)	0.791 (0.185)	0.681 (0.290)	0.772 (0.285)	0.704 (0.282)	0.825 (0.372)	0.719 (0.287)	0.834 (0.138)
Tibia/fibula/Patella	0.787 (0.223)	0.833 (0.119)	0.807 (0.222)	0.852 (0.096)	0.830 (0.189)	0.861 (0.128)	0.831 (0.181)	0.887 (0.109)	0.823 (0.200)	0.857 (0.126)	0.813 (0.231)	0.887 (0.082)
Multiple fractures	0.715 (0.194)	0.778 (0.122)	0.737 (0.191)	0.779 (0.167)	0.715 (0.223)	0.730 (0.248)	0.772 (0.127)	0.783 (0.146)	0.755 (0.186)	0.804 (0.145)	0.757 (0.146)	0.788 (0.170)

SD standard deviation, IQR interquartile range, HSUV health state utility value

Table 2. The association between time and the HSUV measured by EQ-5D (adjusted)

Fracture site	Parameter	Regression coefficient	P-value
Total group (n=499)	Intercept	0.979	0.519
	Time (year)	0.002	
Femoral/vertebral/multiple fractures (n=66)	Intercept	0.718	0.206
	Time (year)	0.011	
Femur	Intercept	1.014	0.605
	Time (year)	0.007	
Vertebra	Intercept	0.636	0.376
	Time (year)	0.014	
Multiple fractures	Intercept	0.830	0.369
	Time (year)	0.014	
Other fractures (n=433)	Intercept	0.972	0.975
	Time (year)	<0.001	
Clavicle/Scapula	Intercept	0.861	0.778
	Time (year)	0.004	
Humerus	Intercept	1.198	0.473
	Time (year)	-0.006	
Radius/ulna	Intercept	1.066	0.551
	Time (year)	-0.003	
Hand/Foot	Intercept	0.972	0.697
	Time (year)	0.001	
Rib/Sternum	Intercept	1.044	0.610
	Time (year)	-0.005	
Pelvis	Intercept	0.880	0.413
	Time (year)	0.009	
Tibia/fibula/Patella	Intercept	0.578	0.520
	Time (year)	0.004	

HSUV health state utility value
Adjusted: the regression analysis was adjusted for age, gender and bone mineral density (BMD)

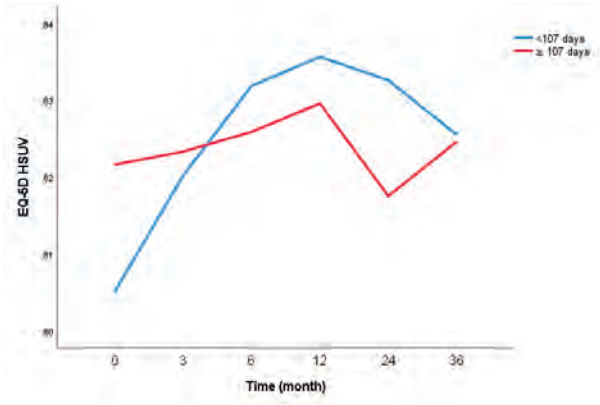

Figure 1. The EQ-5D HSUV by the length of time period between index fracture and FLS visit

Table 3. The association between subsequent fracture and the EQ-5D HSUV (adjusted)

Parameter	Regression coefficient	P-value
Intercept	0.993	**<0.001***
Subsequent fracture	**-0.078**	

HSUV health state utility value
Adjusted: the regression analysis was adjusted for age, gender and BMD

Table 4. The comparison of EQ-5D HSUV before and after a subsequent fracture

Estimates	Subsequent total fractures (n=50)		Subsequent femoral/ vertebral/multiple fractures (n=15)		Subsequent femoral/ vertebral/multiple fractures (n=15)	
	Pre-subsequent fx	Post-subsequent fx	Pre-subsequent fx	Post-subsequent fx	Pre-subsequent fx	Post-subsequent fx
Mean (SD)	0.803 (0.202)	0.725 (0.248)	0.707 (0.211)	0.605 (0.302)	0.845 (0.186)	0.777 (0.205)
Median (IQR)	0.835 (0.178)	0.813 (0.150)	0.782 (0.274)	0.705 (0.485)	0.848 (0.187)	0.826 (0.136)
Mean difference (SD) -0.078 (0.147) -0.102 (0.136) -0.068 (0.152)						
P-value	**<0.001**		**0.011**		**0.012**	

fx fracture, SD standard deviation, IQR interquartile range

Table 5. The comparison of EQ-5D HSUV between patients with and without subsequent fracture by different time periods

	Subsequent fracture (n=50)		No subsequent fracture (n=429)	
	period 1 (0-364 days)	period 2 (365-1095 days)	period 1 (0-364 days)	period 2 (365-1095 days)
Mean (SD)	0.789 (0.180)	0.774 (0.237)	0.831 (0.159)	0.835 (0.180)
Median (IQR)	0.835 (0.163)	0.845 (0.163)	0.863 (0.145)	0.870 (0.163)
Mean difference (SD) -0.015 (0.125) 0.001 (0.111)				
P-value	0.392		0.888	

SD standard deviation, IQR interquartile range

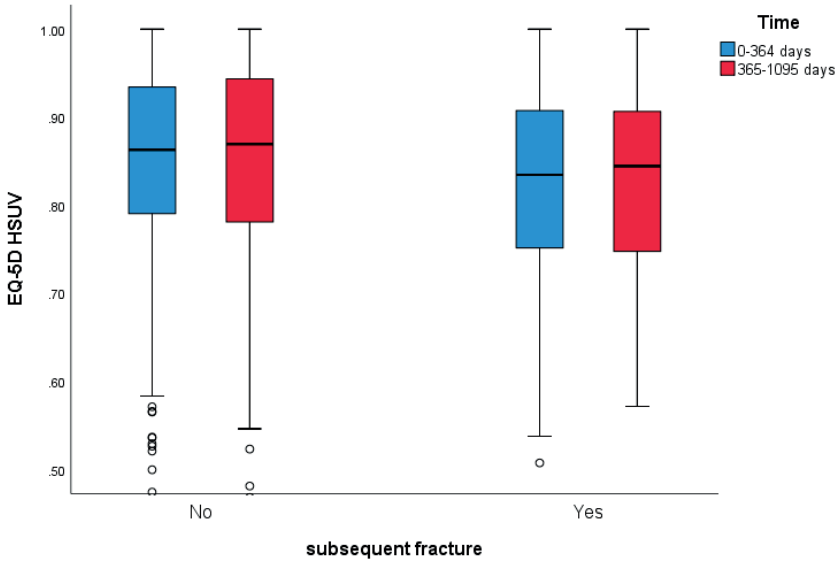

Figure 2. The The comparison of EQ-5D HSUV for patients with and without subsequent fracture by different time periods

Supplement 3: Sensitivity analysis (SF-6D HSUV over time by fracture site)

Table 1. SF-6D mean HSUV and median HSUV by fracture site for patients attending the FLS during 3 years

Index Fracture	Baseline		3 months		6 months		12 months		24 months		36 months	
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
Total fracture	0.766 (0.121)	0.793 (0.154)	0.773 (0.128)	0.810 (0.152)	0.779 (0.124)	0.810 (0.140)	0.773 (0.134)	0.810 (0.153)	0.767 (0.139)	0.810 (0.173)	0.765 (0.142)	0.810 (0.175)
Clavicle/Scapula	0.796 (0.114)	0.810 (0.170)	0.806 (0.134)	0.845 (0.230)	0.789 (0.133)	0.830 (0.153)	0.776 (0.121)	0.845 (0.207)	0.764 (0.114)	0.791 (0.130)	0.769 (0.140)	0.845 (0.189)
Humerus	0.739 (0.129)	0.762 (0.182)	0.760 (0.125)	0.755 (0.203)	0.770 (0.115)	0.801 (0.165)	0.757 (0.122)	0.774 (0.181)	0.751 (0.134)	0.792 (0.187)	0.744 (0.124)	0.764 (0.213)
Radius/ulna	0.788 (0.113)	0.810 (0.128)	0.784 (0.121)	0.810 (0.140)	0.800 (0.111)	0.810 (0.124)	0.779 (0.146)	0.810 (0.124)	0.780 (0.148)	0.810 (0.122)	0.779 (0.161)	0.810 (0.109)
Hand/Foot	0.789 (0.107)	0.810 (0.138)	0.796 (0.111)	0.810 (0.138)	0.795 (0.107)	0.810 (0.136)	0.785 (0.108)	0.810 (0.142)	0.777 (0.122)	0.810 (0.177)	0.777 (0.122)	0.799 (0.173)
Vertebra	0.688 (0.116)	0.687 (0.148)	0.719 (0.136)	0.700 (0.176)	0.702 (0.110)	0.707 (0.167)	0.754 (0.115)	0.755 (0.176)	0.743 (0.102)	0.753 (0.155)	0.709 (0.107)	0.693 (0.189)
Rib/Sternum	0.805 (0.096)	0.810 (0.153)	0.806 (0.110)	0.810 (0.168)	0.832 (0.084)	0.810 (0.135)	0.831 (0.072)	0.817 (0.098)	0.815 (0.120)	0.820 (0.171)	0.777 (0.114)	0.799 (0.194)
Pelvis	0.754 (0.136)	0.789 (0.209)	0.800 (0.103)	0.810 (0.138)	0.775 (0.108)	0.755 (0.117)	0.779 (0.082)	0.753 (0.141)	0.803 (0.078)	0.810 (0.065)	0.771 (0.105)	0.761 (0.159)
Femur	0.690 (0.117)	0.721 (0.202)	0.680 (0.119)	0.684 (0.195)	0.706 (0.150)	0.741 (0.185)	0.696 (0.220)	0.770 (0.297)	0.686 (0.209)	0.741 (0.271)	0.682 (0.201)	0.747 (0.187)
Tibia/fibula/Patella	0.749 (0.127)	0.755 (0.181)	0.768 (0.148)	0.810 (0.138)	0.777 (0.148)	0.802 (0.169)	0.776 (0.151)	0.810 (0.115)	0.763 (0.156)	0.810 (0.215)	0.771 (0.150)	0.810 (0.159)
Multiple fractures	0.717 (0.152)	0.731 (0.185)	0.701 (0.167)	0.713 (0.270)	0.702 (0.168)	0.705 (0.257)	0.716 (0.126)	0.707 (0.200)	0.735 (0.111)	0.735 (0.204)	0.749 (0.122)	0.752 (0.206)

SD standard deviation, IQR interquartile range, HSUV health state utility value

Table 2. The mean difference in SF-6D HSUV between each time point and baseline (adjusted)

Time point	Reference	Total group		Femoral/vertebral/multiple fractures		Other fractures	
		Mean difference (95% CI)	P-value	Mean difference (95% CI)	P-value	Mean difference (95% CI)	P-value
3 months	Baseline	0.007 (-0.001, 0.016)	0.103	0.004 (-0.021, 0.028)	0.745	0.008 (-0.002, 0.017)	0.103
6 months		**0.013 (0.004, 0.022)**	**0.004***	0.006 (-0.019, 0.030)	0.636	**0.014 (0.005, 0.024)**	**0.003**
12 months		0.006 (-0.004, 0.016)	0.275	0.025 (-0.005, 0.055)	0.096	0.003 (-0.008, 0.013)	0.631
24 months		<0.001 (-0.010, 0.011)	0.951	0.024 (-0.007, 0.055)	0.125	-0.003 (-0.014, 0.008)	0.540
36 months		-0.002 (-0.013, 0.009)	0.697	0.015 (-0.022, 0.051)	0.402	-0.005 (-0.016, 0.007)	0.431

CI confidence interval; HSUV health state utility value
* statistically significant (P-value ≤ 0.05)
Adjusted: the regression analysis was adjusted for age, gender and bone mineral density (BMD).

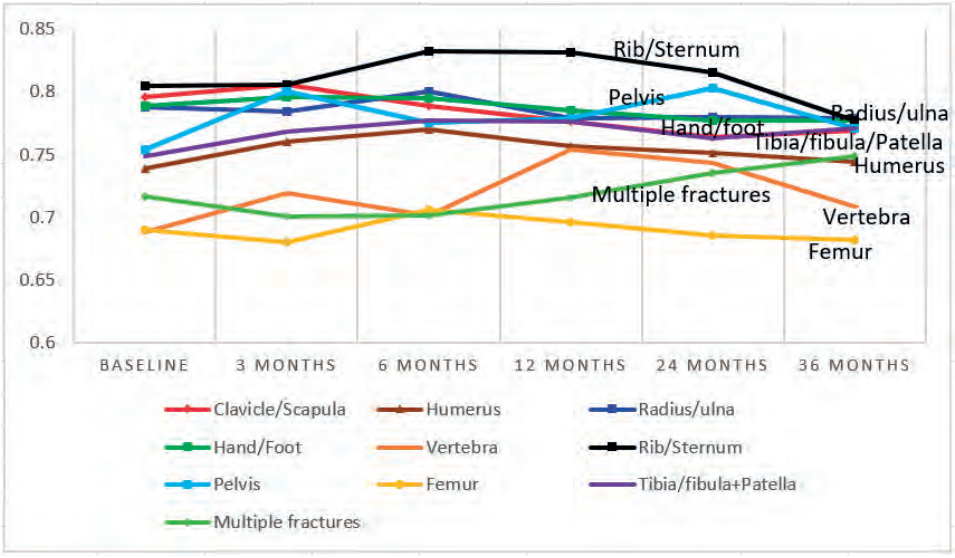

Figure 1. The development of SF-6D HSUV over time by fracture site

Table 3. The mean difference in SF-6D HSUV between each time point and baseline by the time period between index fracture and FLS visit (adjusted)

Time point	Time between fracture and baseline < 107 days (n=258)			Time between fracture and baseline ≥ 107 days (n=241)		
	Mean (SD)	Mean difference (95% CI)	P-value	Mean (SD)	Mean difference (95% CI)	P-value
Baseline	0.758 (0.124)	Reference		0.773 (0.118)	Reference	
3 months	0.777 (0.130)	**0.017** (0.006, 0.028)	**0.002***	0.769 (0.127)	-0.004 (-0.018, 0.010)	0.600
6 months	0.778 (0.124)	**0.018** (0.005, 0.031)	**0.005***	0.781 (0.125)	0.008 (-0.007, 0.022)	0.287
12 months	0.778 (0.134)	**0.017** (0.003, 0.031)	**0.018***	0.767 (0.134)	-0.006 (-0.021, 0.008)	0.390
24 months	0.771 (0.134)	0.011 (-0.004, 0.026)	0.168	0.763 (0.144)	-0.010 (-0.025, 0.004)	0.161
36 months	0.770 (0.135)	0.010 (-0.006, 0.026)	0.210	0.759 (0.149)	**-0.015** (-0.030, 0.001)	**0.045***

CI confidence interval, HSUV health state utility value
* statistically significant (P-value ≤ 0.05)
Adjusted: the regression analysis was adjusted for age, gender and bone mineral density (BMD).

Table 4. The comparison of SF-6D HSUV before and after a subsequent fracture

Estimates	Subsequent total fractures (n=50)		Subsequent femoral/vertebral/multiple fractures (n=15)		Subsequent other fractures (n=35)	
	Pre-subsequent fx	Post-subsequent fx	Pre-subsequent fx	Post-subsequent fx	Pre-subsequent fx	Post-subsequent fx
Mean (SD)	0.772 (0.111)	0.720 (0.124)	0.718 (0.114)	0.662 (0.128)	0.795 (0.103)	0.746 (0.117)
Median (IQR)	0.795 (0.131)	0.752 (0.197)	0.730 (0.217)	0.616 (0.214)	0.810 (0.099)	0.757 (0.210)
Mean difference (SD)	-0.052 (0.100)		-0.056 (0.099)		-0.050 (0.102)	
P-value	**0.001**		**0.047**		**0.007**	

fx fracture, SD standard deviation, IQR interquartile range

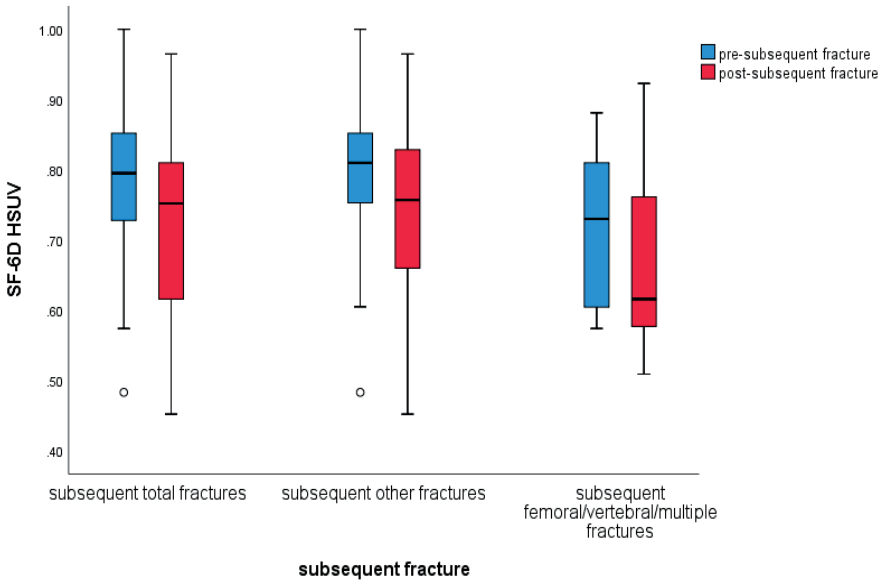

Figure 2. The comparison of SF-6D HSUV before and after a subsequent fracture by the location of subsequent fracture

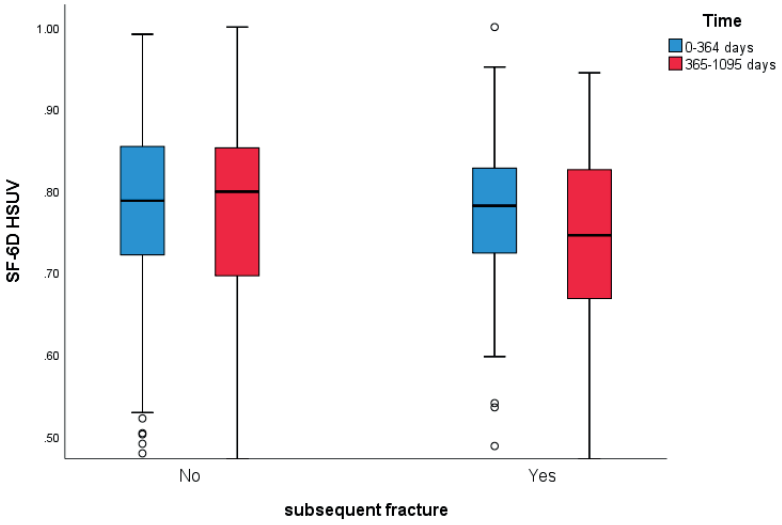

Figure 3. The The comparison of SF-6D HSUV for patients with and without subsequent fracture by different time periods

REFERENCES

1. Sozen T, Ozisik L, Calik Basaran N. An overview and management of osteoporosis. *Eur J Rheumatol*. 2017;4(1):46-56. doi:10.5152/eurjrheum.2016.048
2. Lötters FJB, van den Bergh JP, de Vries F, Rutten-van Mölken MPMH. Current and Future Incidence and Costs of Osteoporosis-Related Fractures in The Netherlands: Combining Claims Data with BMD Measurements. *Calcif Tissue Int.* 2016;98(3):235-243. doi:10.1007/s00223-015-0089-z
3. Van Geel TACM, Huntjens KMB, Van Den Bergh JPW, Dinant GJ, Geusens PP. Timing of subsequent fractures after an initial fracture. *Curr Osteoporos Rep.* 2010;8(3):118-122. doi:10.1007/s11914-010-0023-2
4. Tran T, Bliuc D, Hansen L, et al. Persistence of Excess Mortality Following Individual Nonhip Fractures: A Relative Survival Analysis. *J Clin Endocrinol Metab*. 2018;103(9):3205-3214. doi:10.1210/jc.2017-02656
5. McLellan AR, Gallacher SJ, Fraser M, McQuillian C. The fracture liaison service: Success of a program for the evaluation and management of patients with osteoporotic fracture. *Osteoporos Int.* 2003;14(12):1028-1034. doi:10.1007/s00198-003-1507-z
6. Åkesson K, Marsh D, Mitchell PJ, et al. Capture the Fracture: A Best Practice Framework and global campaign to break the fragility fracture cycle. *Osteoporos Int.* 2013;24(8):2135-2152. doi:10.1007/s00198-013-2348-z
7. Lems WF, Dreinhöfer KE, Bischoff-Ferrari H, et al. EULAR/EFORT recommendations for management of patients older than 50 years with a fragility fracture and prevention of subsequent fractures. *Ann Rheum Dis.* 2017;76(5):802-810. doi:10.1136/annrheumdis-2016-210289
8. Eisman JA, Bogoch ER, Dell R, et al. Making the first fracture the last fracture: ASBMR task force report on secondary fracture prevention. *J Bone Miner Res.* 2012;27(10):2039-2046. doi:10.1002/jbmr.1698
9. Svedbom A, Borgström F, Hernlund E, et al. Quality of life after hip, vertebral, and distal forearm fragility fractures measured using the EQ-5D-3L, EQ-VAS, and time-trade-off: results from the ICUROS. *Qual Life Res.* 2018;27(3):707-716. doi:10.1007/s11136-017-1748-5
10. Wolowacz SE, Briggs A, Belozeroff V, et al. Estimating Health-State Utility for Economic Models in Clinical Studies: An ISPOR Good Research Practices Task Force Report. *Value Heal.* 2016;19(6):704-719. doi:10.1016/j.jval.2016.06.001
11. Borgström F, Lekander I, Ivergård M, et al. The International Costs and Utilities Related to Osteoporotic Fractures Study (ICUROS) - Quality of life during the first 4 months after fracture. *Osteoporos Int.* 2013;24(3):811-823. doi:10.1007/s00198-012-2240-2
12. Lesnyak O, Svedbom A, Belova K, et al. Quality of life after fragility fracture in the Russian Federation: results from the Russian arm of the International Cost and Utility Related to Osteoporotic Fractures Study (ICUROS). *Arch Osteoporos.* 2020;15(1). doi:10.1007/s11657-020-0699-6
13. Si L, Winzenberg TM, De Graaff B, Palmer AJ. A systematic review and meta-analysis of utility-based quality of life for osteoporosis-related conditions. *Osteoporos Int.* 2014;25(8):1987-1997. doi:10.1007/s00198-014-2636-2
14. Singh S, Whitehurst DG, Funnell L, et al. Breaking the cycle of recurrent fracture: implementing the first fracture liaison service (FLS) in British Columbia, Canada. *Arch Osteoporos.* 2019;14(1). doi:10.1007/s11657-019-0662-6

15. Inderjeeth CA, Raymond WD, Briggs AM, Geelhoed E, Oldham D, Mountain D. Implementation of the Western Australian Osteoporosis Model of Care: a fracture liaison service utilising emergency department information systems to identify patients with fragility fracture to improve current practice and reduce re-fracture rates: a 12-. *Osteoporos Int.* 2018;29(8):1759-1770. doi:10.1007/s00198-018-4526-5
16. Adachi JD, Ioannidis G, Berger C, et al. The influence of osteoporotic fractures on health-related quality of life in community-dwelling men and women across Canada. *Osteoporos Int.* 2001;12(11):903-908. doi:10.1007/s001980170017
17. Jun HJ, Kim KJ, Lee JS, Yang SH. Association between osteoporotic fractures and quality of life based on the Korean Community Health Survey of 2010. *J Phys Ther Sci.* 2015;27(10):3325-3328. doi:10.1589/jpts.27.3325
18. Vranken L, Wyers CE, van Rietbergen B, et al. The association between prevalent vertebral fractures and bone quality of the distal radius and distal tibia as measured with HR-pQCT in postmenopausal women with a recent non-vertebral fracture at the Fracture Liaison Service. *Osteoporos Int.* 2019;30(9):1789-1797. doi:10.1007/s00198-019-05081-9
19. Kanis JA, Adachi JD, Cooper C, et al. Standardising the descriptive epidemiology of osteoporosis: Recommendations from the Epidemiology and Quality of Life Working Group of IOF. *Osteoporos Int.* 2013;24(11):2763-2764. doi:10.1007/s00198-013-2413-7
20. Genant HK, Wu CY, van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. *J Bone Miner Res.* 1993;8(9):1137-1148. doi:10.1002/jbmr.5650080915
21. Versteegh M, M. Vermeulen K, M. A. A. Evers S, de Wit GA, Prenger R, A. Stolk E. Dutch Tariff for the Five-Level Version of EQ-5D. *Value Heal.* 2016;19(4):343-352. doi:10.1016/j.jval.2016.01.003
22. Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. *J Health Econ.* 2002;21(2):271-292. doi:10.1016/S0167-6296(01)00130-8
23. Mangen MJJ, Bolkenbaas M, Huijts SM, van Werkhoven CH, Bonten MJM, de Wit GA. Quality of life in community-dwelling Dutch elderly measured by EQ-5D-3L. *Health Qual Life Outcomes.* 2017;15(1):1-6. doi:10.1186/s12955-016-0577-5
24. Fischer K, Trombik M, Freystätter G, Egli A, Theiler R, Bischoff-Ferrari HA. Timeline of functional recovery after hip fracture in seniors aged 65 and older: a prospective observational analysis. *Osteoporos Int.* 2019;30(7):1371-1381. doi:10.1007/s00198-019-04944-5
25. Adachi JD, Adami S, Gehlbach S, et al. Impact of prevalent fractures on quality of life: Baseline results from the global longitudinal study of osteoporosis in women. *Mayo Clin Proc.* 2010;85(9):806-813. doi:10.4065/mcp.2010.0082
26. Jinbayashi H, Aoyagi K, Ross PD, Ito M, Shindo H, Takemoto T. Prevalence of vertebral deformity and its associations with physical impairment among Japanese women: The Hizen-Oshima study. *Osteoporos Int.* 2002;13(9):723-730. doi:10.1007/s001980200099
27. Bliuc D, Alarkawi D, Nguyen T V., Eisman JA, Center JR. Risk of subsequent fractures and mortality in elderly women and men with fragility fractures with and without osteoporotic bone density: The dubbo osteoporosis epidemiology study. *J Bone Miner Res.* 2015;30(4):637-646. doi:10.1002/jbmr.2393
28. Inose H, Kato T, Ichimura S, et al. Risk factors for subsequent vertebral fracture after acute osteoporotic vertebral fractures. *Eur Spine J.* 2021;(0123456789). doi:10.1007/s00586-021-06741-3

29. Shah A, Wu F, Jones G, Cicuttini F, Toh LS, Laslett LL. The association between incident vertebral deformities , health-related quality of life and functional impairment : a 10 . 7-year cohort study. *Published online* 2021.
30. Yeam CT, Chia S, Tan HCC, Kwan YH, Fong W, Seng JJB. A systematic review of factors affecting medication adherence among patients with osteoporosis. *Osteoporos Int.* 2018;29(12):2623-2637. doi:10.1007/s00198-018-4759-3
31. Gonnelli S, Caffarelli C, Nuti R. Obesity and fracture risk. *Clin Cases Miner Bone Metab.* 2014;11(1):9-14. doi:10.11138/ccmbm/2014.11.1.009
32. Yan LL, Daviglus ML, Liu K, et al. BMI and health-related quality of life in adults 65 years and older. Obes Res. 2004;12(1):69-76. doi:10.1038/oby.2004.10
33. Sayah F Al, Qiu W, Xie F, Johnson JA. Comparative performance of the EQ-5D-5L and SF-6D index scores in adults with type 2 diabetes. *Qual Life Res.* 2017;26(8):2057-2066. doi:10.1007/s11136-017-1559-8

CHAPTER 7

A head-to-head comparison of EQ-5D-5L and SF-6D in Dutch patients with fractures visiting a Fracture Liaison Service

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ABSTRACT

Aims: This study compared the psychometric properties of EQ-5D-5L and SF-6D to assess the interchangeability of both instruments in patients with a recent fracture presenting at a Fracture Liaison Service (FLS).

Materials and methods: Data from a prospective observational study in a Dutch FLS clinic were used. Over 3 years, subjects were interviewed at several time points using EQ-5D-5L and SF-36. Floor and ceiling effects were evaluated. Agreement was evaluated by intra-class correlation coefficients and visualized in Bland–Altman plots. Spearman's rank correlation coefficients were applied to assess convergent validity. Mann–Whitney U test or Kruskal–Wallis H test as well as effect size (ES) were used to explore known-groups validity. Responsiveness was explored using standardized response mean (SRM) and ES. For each measurement property, hypotheses on direction and magnitude of effects were formulated.

Results: A total of 499 patients were included. EQ-5D-5L had a considerable ceiling effect in comparison to SF-6D (21 vs. 1.2%). Moderate agreement between the (UK and Dutch) EQ-5D-5L and SF-6D was identified with intra-class correlation coefficients of 0.625 and 0.654, respectively. Bland–Altman plots revealed proportional bias as the differences in utilities between two instruments were highly dependent on the health states. High correlation between instruments was found (UK: rho=0.758; Dutch: rho=0.763). EQ-5D-5L and SF-6D utilities showed high correlation with physical component score but low correlation with mental component score of SF-36. Both instruments showed moderate discrimination (ES > 0.5) for subgroup by baseline fracture type, and moderate responsiveness (SRM> 0.5) in patients that sustained a subsequent fracture.

Conclusion: Both EQ-5D-5L and SF-6D appeared to be valid utility instruments in patients with fractures attending the FLS. However, they cannot be used interchangeably given only moderate agreement was identified, and differences in utilities and ceiling effect were revealed. Comparable construct validity and responsiveness were indicated, and neither instrument was found to be clearly superior.

PLAIN LANGUAGE SUMMARY

The EQ-5D and SF-36 as generic multi-domain questionnaires are widely used to measure the health-related quality-of-life (HRQoL) in a sample of the persons who suffer from the diseases or the general population. Their responses could be converted to patients or societal Health State Utility Values (HSUVs) with the range of 0 ("death") to 1 ("full health"). A specific application of HSUV is to calculate quality-adjusted life years as the indicator of effectiveness to evaluate whether the cost of a new intervention is justified in terms of health gains through cost-utility analysis in health economics, the evidence can be further used to inform decision-making. However, different instruments differ in construct and valuation, potentially leading to different estimates for the person's same "health state", and healthcare decisions could be compromised when researchers or decision-makers are not aware of potential differences in HSUV. Therefore, it is important to gain insight into the specific psychometric properties of these instruments, and to understand whether instruments are interchangeable. Our study is based on data from a Dutch Fracture Liaison Service (FLS is a program for secondary fracture prevention), compared the psychometric properties and interchangeability of two instruments (EQ-5D-5L and SF-6D) in patients with a recent fracture presenting at the FLS, and suggested both instruments are valid in utility elicitation in our target population. However, they cannot be used interchangeably given only moderate agreement and differences in utilities. Neither instrument was found to be clearly superior given comparable construct and longitudinal validity, but different instruments values in different aspects of HRQoL assessment.

INTRODUCTION

Patients with prior fractures are at high risk of a subsequent fracture in their remaining lifetime, up to 86% [1]. This risk is particularly elevated in the first two years after an initial fracture [2,3]. Bone fractures can result in acute as well as chronic health physical impairments [4]. The high incidence and morbidity imposed by fractures are associated with physical, psychological and social consequences that can further affect health-related quality of life (HRQoL) [5]. Fracture Liaison Services (FLSs) as a coordinated, multi-disciplinary model of care, are advocated as the best practice for secondary fracture prevention. We recently reported significant improvements in HRQoL within 12 months following the initial fracture of patients attending FLS in the Netherlands [6].

Health state utility value (HSUV) as a specific type of HRQoL assessment which reflects the strength of preference for a given health state. A specific application of HSUV is to calculate quality-adjusted life years (QALYs) by integrating the time spent in that particular health state (quantity) and its corresponding preference-based value (HSUV) [7,8]. QALYs as the indicator of effectiveness, are used to evaluate whether the cost of a new treatment is justified in terms of health gains through cost-utility analysis (CUA). The evidence of economic evaluation can be further used to inform decision making [9]. For societal decisions (e,g., reimbursement), it is recommended to elicit the population's preferences/values of the health states (societal HSUV), as these are assumed to be less biased as the patients preferences, and as the general population has a democratic right to participate (indirectly) in such decisions [10].

HSUVs can be estimated in a variety of ways including direct and indirect methods. The most common direct utility elicitation techniques are gambling with respect to a hypothetical treatment that may result in perfect health or death (standard gamble, SG) or trading-off part of future life for a shorter time in perfect health (time trade-off, TTO) [7]. However, these choice task based techniques are complicated, and face-to-face interview or interactive online survey is necessary, which are time-consuming. A EuroQol visual analog scale (EQ-VAS), known as rating scale, is a simpler direct preference elicitation method. Patients are asked to evaluate their current health state on a graduated scale ranging from 0 to 100. Compared to SG and TTO, EQ-VAS are elicited in a choice-less context, and respondents are not required to make trade-offs within their utility function [11], however which is generally considered to be methodologically inferior to SG and TTO due to measurement biases [7]. Consequently, the indirect utility elicitation method, named multi-attribute utility instruments (MAUIs), is increasing applied

to obtain HSUVs in recent years. These instruments consists of a generic multi-domain HRQoL questionnaire and corresponding utility algorithm or set of weights (tariffs) obtaining (through a scoring function) from direct utility assessment of a sample of the persons who suffer from the diseases or general population [8] for converting responses to patients or societal HSUVs. These indirect instruments are widely used given the main benefit of allowing comparisons between various diseases, interventions and health programs [1]. The EuroQol 5-dimension (EQ-5D) is the most dominant MAUI especially given the increasing availability of societal country-specific health utilities. The Short Form 6-dimension (SF-6D) is also widely used, which produces societal health utilities based on an algorithm using a subset of 11 questions from the 36-item Short Form Survey (SF-36) [12].

The use of generic indirect utilities in CUA is supported by country-specific guidelines for economic evaluations, along with the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases and the US branch of the International Osteoporosis Foundation ((ESCEO-IOF) guideline for conduct of economic evaluations in osteoporosis [13]. In the field of bone fractures, the widespread implementation of the FLS (until 11th April, 721 FLSs were registered across 50 countries under Capture the Fracture Campaign initiated by International Osteoporosis Foundation) stimulated interest into the CUA of FLS [13]. On this line, the HSUVs of patients attending the FLS have been assessed in some of these studies using different instruments. However, instruments differ in (i) descriptive content of the construct 'health utility', and (ii) valuation method to derive the scoring algorithms (TTO for the EQ-5D, and SG for the SF-6D), potentially leading to different estimates for the person's same 'health state'. This can contribute to differences in incremental cost-utility ratio (ICUR), as indicated by a previous study [14]. Potentially, healthcare decisions could have been compromised when researchers or decision makers are not aware of potential differences in HSUV. Therefore, it is important to gain insight into the specific psychometric properties of these instruments, and to understand whether caution is needed in interpretation or whether instruments are interchangeable.

The psychometric properties of EQ-5D and SF-6D have been compared in multiple studies in patients with different diseases including low back pain [15], coronary heart disease [16] and diabetes [17]. Different conclusions were made regarding the interchangeability of the questionnaires. To our knowledge, longitudinal data on the sensitivity of HSUVs (responsiveness/longitudinal validity) are sparse in literature, especially in the field of fractures and no studies included patients presenting at an FLS. The objective of our study was therefore to compare the psychometric properties (construct validity, known-group validity, and

responsiveness/longitudinal validity) and interchangeability of EQ-5D-5L and SF-6D in a prospective Dutch patients with a recent fracture presenting at an FLS.

METHODS

Design and study population

Patients included in the analyses participated in a 3-year prospective observational study ('FX MoVies Study') conducted between October 2014 and June 2016 at the FLS of VieCuri medical center in Venlo [18]. The study protocol was approved by an independent Medical Ethics Committee and complied with the Declaration of Helsinki (registration number NL45707.072.13). All patients gave written informed consent prior to participation. Totally, 1380 FLS attenders were screened for eligibility, of whom 990 were eligible to participate and a total of 500 relatively healthy patients aged between 50 and 90 years with a recent radiologically confirmed fracture participated eventually. Patients with a high-energy traumatic fracture, bone metastasis, failure of prosthesis, or osteomyelitis; non-Caucasian patients, and patients with cognitive problems were excluded.

After inclusion, dual X-ray absorptiometry (DXA) measurement, vertebral fracture assessment (VFA) and a blood test were scheduled for each participant. Both HRQoL questionnaires (EQ-5D-5L and SF-36) were completed by patients in paper, along with a detailed questionnaire to evaluate risk factors for fractures, at the first FLS visit following inclusion. Three and 6 months after inclusion, the HRQoL questionnaires were posted to patients. Although EQ-5D-5L and SF-36 were self-reported questionnaires, quality control was performed during data collection, i.e. a research assistant conducted an additional telephone call to verify whether patients sustained a new fall or a subsequent fracture and to provide support to complete the questionnaires if needed. Twelve, 24, and 36 months after inclusion, patients had a physical visit at FLS clinic and were invited again to complete the paper versions of HRQoL questionnaires. Given patients' first visit at FLS was scheduled 3-4 months after their index fracture (which was regarded as baseline), therefore no availability of immediate HRQoL data after fracture.

Demographics and disease-related characteristics

The socio-demographics included age at time of fracture, gender, and body mass index (BMI). A detailed questionnaire was used to evaluate clinical risk factors for fractures and collect fracture-related characteristics including medical history, previous anti-osteoporosis medication (AOM) use, calcium and vitamin D intake, previous fractures, previous falls (last year), parental hip fracture, use of a walking

aid, smoking, and visual and hearing impairment. Besides, bone mineral density (BMD) was measured by DXA, and prevalent vertebral fracture (VF) by VFA. The definition and classification of BMD and prevalent VF has been described in detail in previous studies [6,18]. In addition, laboratory tests were performed to detect contributors to secondary osteoporosis and metabolic bone diseases. For all participants, time of mortality and suffering subsequent fractures were recorded during 3-year follow-up.

Indirect health state utility valuation

HSUVs are scored on a cardinal scale anchored at 0 ('death') and 1 ('full health'), with some instruments also allowing for negative values representing states worse than death [7,19]. Given the unavailability of Dutch algorithm to translate SF-36 health status measure to SF-6D societal HSUVs, the SG-based UK (version 1) algorithm developed by Brazier et al [20] was applied. The utility values range from +0.291 to +1. The SF-6D estimates a preference-based single index measure for health in terms of six dimensions (physical functioning, role limitation, social functioning, mental health, pain, and vitality), each dimensions contains four to six levels. The EQ-5D-5L comprises five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) to quantify health status, each dimension has five levels ranging from no problem to extreme problem. The elicitation of the EQ-5D-5L uses TTO alongside discrete choice experiment (DCE), with value sets available for many countries. For our analyses, we used both UK and Dutch value sets for comparison [21,22]. The EQ-5D-5L utilities theoretically range from -0.446 to +1 and -0.285 to +1 for the Netherlands and UK, respectively. Besides, the EQ-VAS was used to evaluate/mark patients' overall health status on the day of the interview on a 20 cm vertical scale with end points of 0 (the worst health you can imagine) and 100 (the best health you can imagine). The EQ-VAS was rescaled to a 0-1 value for comparison.

Statistical analysis

Multiple imputation

Multiple imputation (MI) with fully conditional specification was employed to impute missing EQ-5D and SF-6D utilities. Patients' missing utilities at six time-points were drawn using predictive mean matching. The details of MI can be found in our previous study [6].

Patient characteristics and descriptive statistics

Baseline characteristics were reported as means and standard deviations (SD) for continuous variables, and as number (%) for categorical variables. Baseline HSUV for EQ-5D-5L (UK and Dutch), EQ-VAS and SF-6D were skewed and reported as mean

(SD), observed range, median (IQR inter-quartile range). Floor and ceiling effects were evaluated by calculating the proportion of respondents scoring the highest (ceiling) or lowest (floor) possible score across any given domain, measuring the sensitivity and coverage of a questionnaire at each end of the scale [23]. For EQ-5D-5L, the proportion of patients in the worst (11111) and best (55555) possible health states are accounted as floor and ceiling effect, respectively. For SF-6D, the proportion of minimal (0.29) and maximal possible HSUV score (1.00) were calculated.

Interchangeability between EQ-5D-5L and SF-6D questionnaires
Assessment of interchangeability between two questionnaires comprised of agreement, construct validity (convergent and known-group validities) and responsiveness (longitudinal validity). Hypotheses were established for each analysis, as shown in Table 1. Agreement and construct validity were investigated using baseline HSUV, and responsiveness using 3-year HSUV data.

Agreement between EQ-5D-5L and SF-6D Agreement tests the capacity to arrive at identical results for the same subjects using different instruments/measures. Given both EQ-5D-5L and SF-6D HSUVs measure the same 'construct' (i.e., the societal preference for health on a scale anchored at 0 and 1), good agreement is expected. The agreement between (Dutch and UK) EQ-5D-5L and SF-6D HSUVs was evaluated using intra-class correlation coefficients (ICCs). The ICCs were calculated based on a two-way random effects model using single measures and absolute agreement, and was interpreted according to the following limits "poor" (ICC < 0.50), "moderate" (0.50 < ICC < 0.75), "good" (0.75 < ICC < 0.90) or "excellent" (ICC>0.90) [24].

Additionally, the Bland–Altman plot was used to visually quantify the agreement between measures as a function of the average of the two. For all subjects, mean values and differences between two scores were plotted on X and Y-axis, respectively. The mean of differences and 'limit of agreement' (calculated as the mean difference ±1.96 SD) were indicated by three lines in the plot. Good agreement was considered when the calculated mean difference is close to zero and approximately 95% of scatter points lying inside the 'limits of agreement'[25].

Construct validity Construct validity tests whether both questionnaires measure the same construct. First, convergent validity refers to the degree to which two measures of constructs are correlated with that it is theoretically predicted to correlate with, which was investigated using Spearman's rank correlation coefficients between EQ-5D-5L and SF-6D HSUVs, between both HSUVs and EQ-

VAS, between both HSUVs and the Physical Component Score (PCS) and the Mental Component Score (MCS) of the SF-36, and between both HSUVs and eight domains (physical functioning PF, role physical RP, bodily pain BP, general health GH, vitality VT, social functioning SF, role emotional RE, and mental health MH) of the SF-36. The coefficients of 0.9–1.0 is considered as very highly correlated, 0.7–0.9 as highly correlated, 0.5–0.7 as moderately correlated, and 0.3–0.5 as low correlated [26]. Hypotheses on the magnitude of effect are presented in Table 1.

"Known-groups" validity is used to assess whether a test or questionnaire can discriminate between two or more groups known to differ on the variable of interest. It was evaluated by calculating the EQ-5D-5L and the SF-6D HSUVs for subgroups of patients: age (≤ 65 years, >65 years), gender (male, female), BMD (normal, osteopenia, osteoporosis), baseline fracture location (femoral/vertebral/multiple fractures, other fractures), self-reported previous fracture (yes, no), prevalent VFs (yes, no), falls in the past year (yes, no) and the previous AOM use (yes, no). Mann-Whitney U-tests were implemented for dichotomous variables and Kruskal-Wallis H tests for polytomous variables. Cohen's d, a standardized effect size (ES) [27] was used to quantify the magnitude of differences between groups on HSUVs. ES's were then assigned ordinal change categories using the Cohen's criteria: negligible difference (|ES| <0.2), small difference (0.2 ≤|ES| <0.5), moderate difference (0.5≤|ES|<0.8), or large difference ((|ES| ≥0.8) [27]. Different hypotheses were made for different subgroups (see Table 1).

Responsiveness Responsiveness refers to the ability of a HSUV measure to capture true underlying change (recovery or worsening) in the patients' health status over time [28] and is an important measurement property for longitudinal validity. During 3-year follow-up, five patients died, the contribution of these patients to the data on responsiveness is limited. In addition, based on our previous longitudinal study [6], the change of both EQ-5D-5L and SF-6D HSUV over 3 years was not statistically significant, as was not unexpected given patients were included upon 3 months after the fracture. Therefore recovery following a fracture would not be situation eligible to assess responsiveness. However, significant change in HSUV was identified for patients before and after subsequent fracture. We therefore chosen the worsening situation and assessed the responsiveness only in this target group (i.e., patients had subsequent fracture during 3-year follow-up, n=50). To capture the maximum impact of a subsequent fracture, the HSUV just before and immediately after the subsequent fracture was treated as pre- and post-HSUV, respectively (i.e., if one patient had a subsequent fracture at 6 months, the HSUV at 3 months was treated as pre-HSUV and the HSUV at 6 months as post-HSUV) [6].

Table 1. Hypotheses regarding the interchangeability between EQ-5D and SF-SD.

Interchangeability	Hypotheses	Magnitude	Results			Met or not?		
Agreement	Good agreement between EQ-5D and SF-6D utility	ICC > 0.75	ICC = 0.625 (UK), ICC = 0.654 (Dutch)			No		
Convergent validity	High correlation between EQ-5D and SF-6D utility	rho > 0.70	rho = 0.758 (UK), rho = 0.763 (Dutch)			Yes		
	Hypotheses	Magnitude	UK EQ-5D	Dutch EQ-5D	SF-6D	UK	Dutch	SF-6D
	High correlation between utility and EQ-VAS	rho > 0.70	rho = 0.640	rho = 0.642	rho = 0.628	No	No	No
	Moderate-to-high correlation between utility and PCS	rho > 0.50	rho = 0.810	rho = 0.804	rho = 0.778	Yes	Yes	Yes
	Utility and MCS		rho = 0.235	rho = 0.254	rho = 0.452	No	No	No
	Utility and PF		rho = 0.758	rho = 0.744	rho = 0.690	Yes	Yes	Yes
	Utility and RP		rho = 0.655	rho = 0.654	rho = 0.735	Yes	Yes	Yes
	Utility and BP		rho = 0.720	rho = 0.715	rho = 0.687	Yes	Yes	Yes
	Utility and GH		rho = 0.527	rho = 0.537	rho = 0.520	Yes	Yes	Yes
	Utility and VT		rho = 0.551	rho = 0.566	rho = 0.677	Yes	Yes	Yes
	Utility and SF		rho = 0.607	rho = 0.623	rho = 0.783	Yes	Yes	Yes
	Utility and RE		rho = 0.451	rho = 0.450	rho = 0.543	No	No	Yes
	Utility and MH		rho = 0.460	rho = 0.478	rho = 0.614	No	No	Yes
Known-group validity	Negligible-to-small difference: ≤ 65 vs. > 65 years	|ES| < 0.5	|ES| = 0.096	|ES| = 0.075	|ES| = 0.008	Yes	Yes	Yes
	Negligible to small difference: women vs. men	|ES| < 0.5	|ES| = 0.143	|ES| = 0.143	|ES| = 0.385	Yes	Yes	Yes
	Negligible to small difference: normal BMD vs. osteopenia BMD	|ES| < 0.5	|ES| = 0.012	|ES| = 0.017	|ES| = 0.041	Yes	Yes	Yes
	Negligible to small difference: normal BMD vs. osteoporosis BMD	|ES| < 0.5	|ES| = 0.147	|ES| = 0.150	|ES| = 0.151	Yes	Yes	Yes
	Small difference: with vs. without AOM treatment	0.2 ≤ |ES| < 0.5	|ES| = 0.466	|ES| = 0.446	|ES| = 0.439	Yes	Yes	Yes
	Moderate difference: with vs. without previous fractures	0.5 ≤ |ES| < 0.8	|ES| = 0.066	|ES| = 0.075	|ES| = 0.083	No	No	No
	Moderate difference: with vs. without previous falls in the last year	0.5 ≤ |ES| < 0.8	|ES| = 0.277	|ES| = 0.286	|ES| = 0.307	No	No	No
	Moderate difference: with vs. without prevalent VFs	0.5 ≤ |ES| < 0.8	|ES| = 0.214	|ES| = 0.205	|ES| = 0.145	No	No	No
	Moderate to large difference: femoral/vertebral/multiple fx vs. other fx	|ES| ≥ 0.5	|ES| = 0.613	|ES| = 0.607	|ES| = 0.647	Yes	Yes	Yes
Responsiveness	Moderate-to-large responsiveness to utility was expected before and after subsequent fracture	|ES| ≥ 0.5 or |SRM| ≥ 0.5	|ES| = 0.397 |SRM| = 0.573	|ES| = 0.386 |SRM| = 0.531	ES| = 0.468 |SRM| = 0.520	Yes	Yes	Yes

Abbreviations. ICC, intraclass correlation coefficient; PCS, physical component score; MCS, mental component score; PF, physical functioning; RP, role physical; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role emotional; MH, mental health; fx, fracture; AOM, anti-osteoporosis medication; VF, vertebral fracture; ES, effect size; SRM. standardized response mean; BMD, bone mineral density; vs, versus.

RESULTS

Patient characteristics

Given one patient did not complete any questionnaire, who was therefore excluded from the analysis, therefore a total of 499 patients with one or more recent fractures were included eventually. Demographics and disease-related characteristics are presented in Table 2. The average age of included patients was 64.6±8.6 years, most patients were females (71.3%). 13.2% (n=66) patients reported baseline femoral or vertebral or multiple fractures, and most patients suffered other fractures (clavicle/scapula, humerus, radius/ulna, hand/foot, rib/sternum, pelvis, tibia/fibula/patella fracture). Approximately 11% patients received therapy with AOM prior to FLS visit, treatment was initiated or continued in 35% of patients after attending the FLS. Besides, 22% patients were diagnosed with osteoporosis and 27% with at least one VF. The average time gap between patients' baseline fracture and the first time of FLS visit was 107 days.

Table 2. Baseline characteristics of patients with a recent fracture at FLS.

Characteristics	Total
Mean age, years (SD)	64.6 (8.6)
Female (%)	356 (71.3%)
BMI, kg/m^2 (SD)	27.7 (4.4)
Baseline fracture type (%)	
Femoral/vertebral/multiple fractures	66 (13.2%)
Femur	21 (4.2%)
Vertebra	25 (5.0%)
Multiple fractures	20 (4.0%)
Other fractures	433 (86.8%)
Clavicle/scapula	13 (2.6%)
Humerus	47 (9.4%)
Radius/ulna	125 (25.1%)
Hand/foot	140 (28.1%)
Rib/sternum	17 (3.4%)
Pelvis	11 (2.2%)
Tibia/fibula/patella	80 (16.0%)
BMD (%) Normal	135 (27.1%)
Osteopenia	254 (50.9%)
Osteoporosis	110 (22.0%)
VFA VF (%) No VF	366 (73.3%)
Only Grade 1	65 (13.0%)
Grade 2 or 3	68 (13.6%)
Current smoking (%)	69 (13.8%)
Secondary osteoporosis (%)	83 (16.6%)
Vitamin D deficiency (%)	179 (35.9%)
Use of a walking aid (%)	26 (5.2%)
Visual impairment (%)	459 (92.0%)
Hearing impairment (%)	44 (8.8%)
Parental hip fracture (%)	23 (4.6%)
Previous fracture (%)	261 (52.3%)
Previous treatment with AOM (%)	54 (10.8%)
Falls in past year (%)	142 (28.5%)
Mean time length between fracture and FLS visit, days (SD)	107.3 (30.4)

Abbreviations. BMI, body mass index; SD, standard deviation; BMD, bone mineral density; VFA, vertebral fracture assessment; VF, vertebral fracture; AOM, anti-osteoporosis medication; FLS, fracture liaison service.

Descriptive EQ-5D-5L and SF-6D statistics

As shown in Table 3, the mean EQ-5D-5L HSUV using the UK value set was higher than which was estimated using the Dutch value set, both were higher than the mean SF-6D HSUV. As presented in Figure 1, compared to the distribution of SF-6D HSUV, the distribution of both UK and Dutch EQ-5D-5L HSUVs were highly left-skewed. The mean difference between the SF-6D and (UK and Dutch) EQ-5D-5L HSUV were -0.080 (SD 0.109) and -0.047 (SD 0.125), respectively. The mean EQ-VAS was lower than (Dutch and UK) EQ-5D-5L HSUV, but higher than SF-6D HSUV. Ceiling effect was low for SF-6D (1.2%), but relatively high for both EQ-5D-5L value sets (21%). The EQ-VAS measured 33 (6.6%) patients having the best imaginable health. No tool yielded a floor effect.

Table 3. Descriptive statistics of EQ-5D and SF-6D utility scores, n=499.

	Theoretical range	Observed range	Mean (SD)	Median (inter-quartile range)	Ceiling effect *N* (%)	Floor effect *N* (%)
EQ-5D-5L (Dutch value set)	(−0.446, 1.000)	(−0.344, 1.000)	0.813 (0.187)	0.852 (0.765, 0.887)	105 (21.0%)	0 (0%)
EQ-5D-5L (UK value set)	(−0.285, 1.000)	(−0.175, 1.000)	0.845 (0.166)	0.879 (0.801, 0.937)	105 (21.0%)	0 (0%)
SF-6D	(0.291, 1.000)	(0.337, 1.000)	0.766 (0.121)	0.788 (0.680, 0.852)	6 (1.2%)	0 (0%)
EQ-VAS	(0, 1.000)	(0.200, 1.000)	0.797 (0.143)	0.800 (0.700, 0.900)	33 (6.6%)	0 (0%)

Abbreviations. *N*, number; SD, standard deviation.

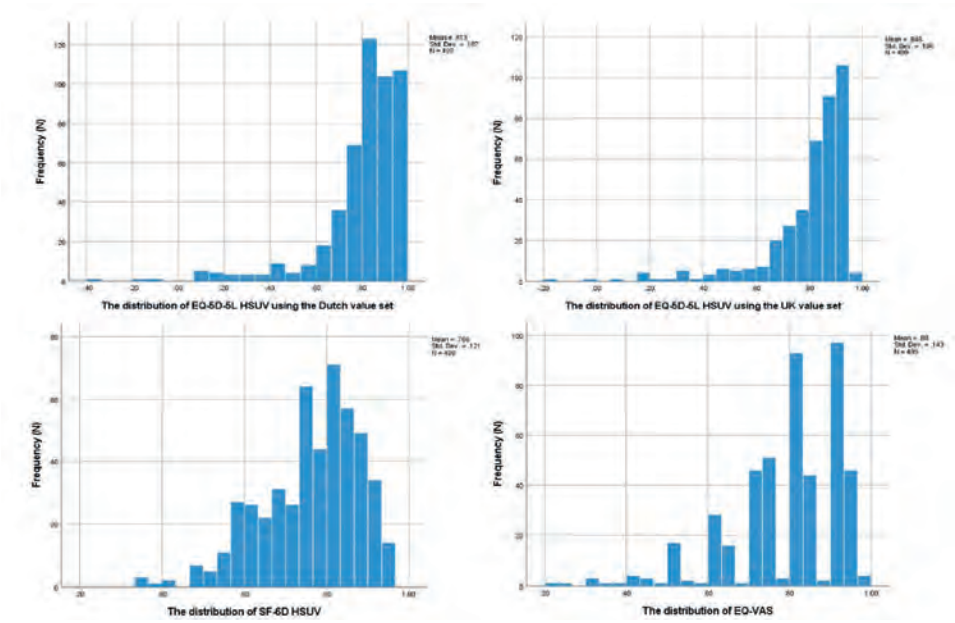

Figure 1. The distribution of EQ-5D-5L and SF-6D HSUVs and EQ-VAS.

Agreement between the EQ-5D-5L and SF-6D

As shown in Table 1, the agreements between SF-6D and (UK and Dutch) EQ-5D-5L HSUV was moderate, with ICCs of 0.625 (95% CI: 0.276-0.785) and 0.654 (95% CI: 0.546-0.733), respectively, which did not meet our hypothesis. The agreement between both EQ-5D-5L HSUV was excellent as we hypothesized, with an ICC of 0.968 (95% CI: 0.755-0.989).

The Bland–Altman plot (Figure 2A) of the UK EQ-5D-5L value set and the SF-6D presented that 94.6% of the difference scores were between the limits of agreement (-0.133 and 0.294). EQ-5D-5L index scores exceeded SF-6D index scores for the majority of observations 85.4% (426 out of 499) with a mean difference of 0.080. In addition, the Bland–Altman plot (Figure 2B) of the Dutch EQ-5D-5L value set and the SF-6D presented a mean difference of 0.047 between two instruments, but ranging over the mean average from -0.198 to 0.293, containing 94.6% of the difference scores. 75.9% (379 out of 499) of the Dutch EQ-5D-5L index scores were higher than the SF-6D index scores. Both figures indicated that the agreement between EQ-5D-5L and SF-6D appeared to be relatively weak at the lower end of the scale where utility scores were outside the limits of agreement lines, the difference of HSUVs (absolute value) between two instruments was initially declining and then rising with the increase of mean HSUV. The differences between the two

measurements really depended on the health status of the individual patient. EQ-5D-5L yielded higher score for better health state (healthy patients), whereas SF-6D tended to produce higher score for poorer health state (unhealthy patients). However, for those patients with mid-range index scores, the EQ-5D-5L and SF-6D were more aligned.

The Bland–Altman plot (Figure 2C) of the UK and Dutch EQ-5D-5L value sets showed that 94.8% of the difference scores were between the limits of agreements (ranging from -0.029 to 0.094 over the mean average of scores). 78.2 % (390 out of 499) of the UK EQ-5D-5L values were higher than the Dutch EQ-5D-5L, 21.2% were equal, and 0.60% were lower. The differences between UK and Dutch EQ-5D-5L HSUV were most striking in worse health states (with lower mean utility values).

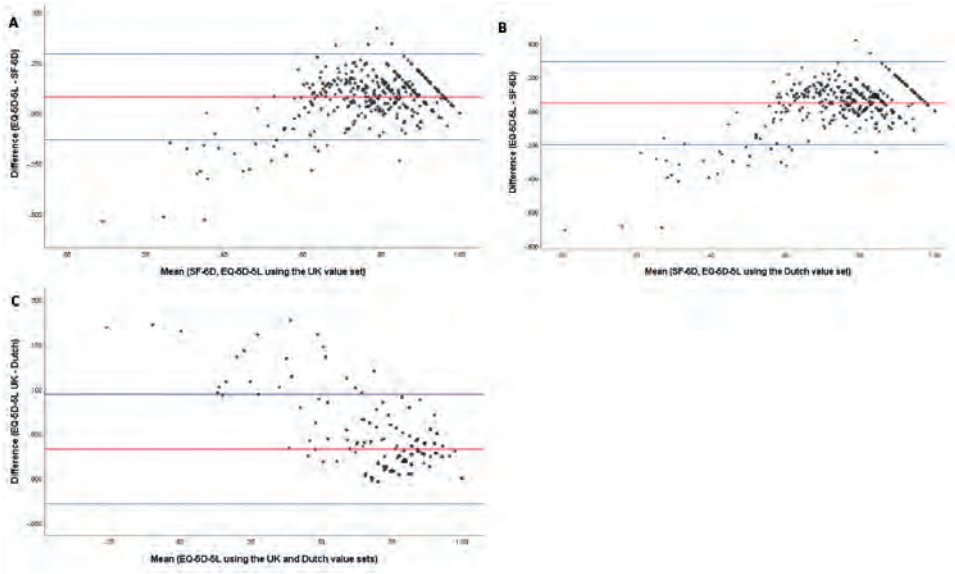

Figure 2. Bland–Altman plots of difference in utility scores between (a) the SF-6D and the EQ-5D-5L using the UK value set, (b) the SF-6D and the EQ-5D-5L using the Dutch value set, and (c) the EQ-5D-5L using the UK and Dutch value sets.

Convergent validity

The result of convergent validity (with Spearman's correlation coefficients) are presented in Table 1 and Supplement (Table 1). For HSUVs, both UK and Dutch EQ-5D-5L HSUV were highly correlated with SF-6D HSUV (rho=0.758, 0.763, respectively) as we hypothesized. For correlation between HSUVs and EQ-VAS, PCS/MCS, eight domains of the SF-36, 82%, 64%, 64% hypotheses were met for SF-6D,

Dutch EQ-5D-5L and UK EQ-5D-5L, respectively. Specifically, moderate correlation was captured between (UK and Dutch) EQ-5D-5L HSUV and EQ-VAS (rho=0.640, 0.642, respectively), and between SF-6D HSUV and EQ-VAS (rho=0.628), which was against our hypothesis as high correlation is expected. Both (UK and Dutch) EQ-5D-5L (rho=0.810, 0.804, respectively) and SF-6D (rho=0.778) HSUV were highly correlated with PCS as hypothesized, however, low correlation was identified with MCS, especially for EQ-5D-5L utility. Moderate to high correlations were identified between SF-6D HSUV and all eight domains of the SF-36 as hypothesized. For UK and Dutch EQ-5D-5L HSUV, moderate to high correlations were captured with six domains of the SF-36 (PF, RP, BP, GH, VT, SF), low correlations were seen with role emotional and mental health.

Known-groups validity

The mean EQ-5D-5L and SF-6D HSUVs and nonparametric statistical results across a range of different subgroups is displayed in Table 1 and Supplement (Table 2). Both (UK and Dutch) EQ-5D-5L and SF-6D indicated significant difference ($P<0.05$) in HSUV regarding different genders (female<male), different baseline fracture location (femoral/vertebral/multiple fractures<other fractures), falls in the last year (with<without), and previous AOM use (with<without). No statistical difference in HSUV was found in terms of different age groups, BMD, with/without previous fracture, and with/without prevalent vertebral fracture.

However, given ES is more statistically powerful and appropriate than P value to test the known-group validity, our hypotheses were made based on ES, and the overall results showed that the same hypotheses (67%) were met by SF-6D, UK and Dutch EQ-5D-5L, suggesting both instruments are valid and with comparative validity. Specifically, our hypotheses were met for five subgroup comparisons: both (UK and Dutch) EQ-5D-5L ($|ES|=0.613$, 0.607, respectively) and SF-6D ($|ES|=0.647$) discriminate moderately between patients with femoral/vertebral/multiple fractures and other fractures with $|ES|$ larger than 0.5. Besides, as we hypothesized, negligible to small difference was identified for patients stratified by age, gender, and BMD (with $|ES|<0.5$). Finally, small difference ($0.2 \leq |ES|<0.5$) was captured between patients who initiated AOM treatment or not as we hypothesized. However, moderate difference (our hypothesis) was not identified between patients with/without previous fracture, previous falls in the last year, and prevalent VFs.

Responsiveness

The responsiveness of HSUV before and after subsequent fracture was displayed in Table 1 and Supplement (Table 3). Significant decrease in both (UK and Dutch) EQ-5D-5L and SF-6D was identified with mean change of 0.071/0.078 and 0.052,

respectively. Our hypothesis was met as medium responsiveness (SRM>0.5) was captured for patients with the subsequent fracture during the 3-year follow-up.

DISCUSSION

This study compared the psychometric properties of EQ-5D-5L and SF-6D to assess the interchangeability of these two instruments in patients with a recent fracture presenting at a FLS. We found that although SF-6D and EQ-5D-5L utilities were highly correlated, only moderate agreement was identified between two instruments, and Bland–Altman plot revealed proportional bias as the differences in utilities between two instruments were highly dependent on the health states (mean values), moreover, EQ-5D-5L had considerable ceiling effect in comparison to SF-6D, indicating these two instrument are not interchangeable. However, both instruments appeared to be valid utility instruments, and comparable construct and longitudinal validity were indicated (i.e., both instruments met or deviated most of our hypotheses simultaneously). Given neither instrument was found to be clearly superior, clear recommendation cannot be made, but different instruments values in different aspects of HRQoL assessment.

One main strength of our study is the use of 3-year longitudinal data allowing to investigate how sensitive the HSUVs are to the change in health status. To our knowledge, only one previous study [30] was conducted in the field of bone fractures, and no study focused on patients presenting at an FLS. The discrepancies in HSUV were also indicated in other studies such as patients with chronic diseases [31] and patients had undergone surgery for lumbar disc herniation [30]. Interchangeability of EQ-5D and SF-6D was also questioned in these studies. The impact of these discrepancies on the acceptability of cost-utility ratios was explored by a previous study [14], indicating the incomparability of the results of CUA using different instruments reduces the credibility of the use of incremental cost–utility ratios for decision-making. Given no other studies investigated the interchangeability between EQ-5D and SF-6D in the field of bone fractures (and patients attending the FLS), we have limited evidence to confirm our findings, however, the potential reasons for identified discrepancies in the context of patients with a recent fracture presenting at a FLS were discussed below.

For utility values, both UK and Dutch EQ-5D-5L values were higher than SF-6D values in the majority of observations, which is consistent with previous studies [16,32,33]. Besides, because of the selection bias (patients with more severe fractures, older patients, or patients who were hospitalized did not attend the

FLS, and approximately half of FLS attenders did not consent to participate in this study), relatively healthy patients were enrolled in our study, in line with the literature that healthier patients have significantly higher mean scores on the EQ-5D; whereas, less healthy patients have significantly higher mean scores on the SF-6D [30]. Consequently, these might have potential implications in cost-effectiveness analysis, i.e., using EQ-5D HSUV on healthier patients would lead to higher estimated QALYs compared to using SF-6D HSUV, with potential impact on ICUR. The relative healthy patients can also explain the considerable ceiling effect of EQ-5D-5L.

Additionally, Bland–Altman plot revealed proportional bias as the discrepancies in utilities between instruments were highly dependent on the health status (mean values). Higher SF-6D scores at the lower end of the utility scale but does not explain the relationship at the upper end of the scale, where EQ-5D-5L scores are higher. This proportional bias could already be predicted by the difference in the distribution of SF-6D and EQ-5D-5L HSUV. Moreover, as we mentioned before, different techniques are used to obtain scoring function for both instruments (SG for SF-6D and TTO for EQ-5D). Therefore the discrepancies might be attributable to the differences in the descriptive content and the variation in scoring algorithms (TTO vs. SG) as explained in some studies [30,32,34,35]. Considering the ICC might be affected by scaling differences between the EQ-5D and SF-6D, ICC was recalculated after truncating the EQ-5D-5L index score at 0, results were consistent with those without truncation and conclusions remained.

Furthermore, increasingly there is attention for the discrepancies in clinimetric properties in subgroups of patients. However, the question on difference in validity of instruments by 'subgroups' is complex for several reasons. Stratified analyses have been proposed, but the value is limited because other confounders might also explain the discrepancy. In other words, even when differences across subgroups are identified, it is still difficult to explain whether the differences are attributable to the error or the truth. Therefore, this issue is methodologically unresolved, and there is no agreement upon the method to uncover the source of variability in clinimetric properties. The relevant research is definitely of future interest when moving to stratified medicines. With regard to our study, the sample size was too small to perform stratified analyses, therefore we investigated the association between several variables (demographics and disease-related characteristics) and the discrepancies in HSUV, the results indicated that the discrepancies in HSUV was independent on these variables (Supplement Table 4). As for interpretation, the results suggest the construct validity is likely similar between subgroups represented by these variables. In addition, with the availability of more data and

large sample size in the future, the discrepancies in clinimetric properties between instruments caused by demographics and disease-related characteristics might be investigated by conducting stratified analyses, however the results should be interpreted by caution.

Unsurprisingly, high agreement was identified between Dutch and UK EQ-5D-5L utilities, it can be explained that both value sets employed the EuroQoL Group's Valuation Technology (EQ-VT) protocol and both scoring function was based on TTO and DCE [31]. However, some differences were also observed, the discrepancies in utility can be explained by the cultural differences attached to aspects of health in UK and the Netherlands.

With regard to the convergent validity, high correlation between EQ-VAS and EQ-5D/SF-6D utility was not identified, it can be explained that respondents are required to make trade-offs within their EQ-5D/SF-6D utility function, however, this is not case for EQ-VAS, different techniques would lead to difference in scoring. Besides, through inspection, we found that the correlation coefficient between EQ-5D and EQ-VAS is a bit higher than that between SF-6D and EQ-VAS, an explanation could be that EQ-VAS is one section of EQ-5D, and both EQ-5D and EQ-VAS use 'today' as the recall period, which is 4 weeks for SF-6D, difference in scoring could be therefore caused [32]. In addition, compared to SF-6D, EQ-5D utility was more correlated with PCS and physical health related scales of SF-36, and less correlated with MCS and mental health related scales of SF-36. This is consistent with findings from Richardson and colleagues that show that the EQ-5D-5L was more sensitive to physical health than the SF-6D [36]. It can be explained that most domains of EQ-5D (mobility, self-care, usual activities and pain) are related to physical health whereas SF-6D has balanced domains covering both physical and psychological health.

Some potential clinical applications were revealed, first, in real-world clinical setting, if the researchers focus more on patients' functional status (recovery) attending the FLS, the EQ-5D questionnaire might be more appropriate to use. The SF-36 seems more useful to evaluate the mental and emotional component of health. The EQ-5D in clinical setting might underestimate the additional effect of intervention on mental health. And the low correlation of EQ-5D HSUV with mental health scale might be relevant when evaluating non-pharmacological trials such a shared decision making studies or lifestyle advice. Besides, researchers can select more appropriate instrument based on their targeted recall period (EQ-5D uses 'today' as the recall period, which is recent 4 weeks for SF-36).

For known-group validity, although some studies indicated that EQ-5D was more efficient than SF-6D at detecting clinically relevant differences [15,32], comparable discrimination property between these two instruments was identified in our study. Unsurprisingly, both instruments can discriminate well between patients with femoral/vertebral/multiple fractures and other fractures. One explanation is that patients with relatively severe fractures (hip, vertebrae) would largely impair their physical function, incurring substantial loss in QoL at the same time. And patients with multiple clinical fractures would experience an additive effect, resulting in disability similar to a single hip or vertebral fracture as supported by a previous study [37]. In addition, only minor difference between patients with/without previous fracture, falls, and prevalent VFs was identified, it can be explained from two aspects: first, patients in our study attended the FLS 107 days after their index fracture on average, their previous impairments might have been recovered through natural fracture recovery and/or through treatment in the emergency department before attending the FLS, leading to already improved HRQoL; second, as we mentioned, relatively healthy patients were included in our study, difference in HSUV between subjects and their counterparts would therefore be inapparent. Negligible to small difference was hypothesized for subgroups stratified by gender, age and BMD as these factors are not closely and directly related to physical function and patients' HRQoL. As expected, small difference was identified for patients with/without AOM treatment. Theoretically, largely improved QoL is expected after treatment initiation, however, the potential side effect of AOM might affect patients' QoL, and some rare side effect (overstated by the press) even scare some patients away, leading to poor persistence and treatment efficacy.

For responsiveness, as our hypothesis, medium responsiveness of HSUV was observed by both instruments in the group of patients before and after subsequent fracture. However, it should be noted that only 50 patients had subsequent fracture during three year follow-up, the sample size is not large, therefore the interpretation of longitudinal validity should be done with caution. In addition, as we mentioned given patients were included upon 3 months after the fracture, we can only investigated whether two instruments have a different 'responsiveness' to a worsening situation (i.e., following a subsequent fracture during follow-up), in the future if we could obtain patients' HRQoL data immediately after fracture, investigating the responsiveness to recovery course would also be an option.

This study has several limitations. First, this was a single-center study from the Netherlands, the generalizability and extrapolation of our findings should be performed with caution. Second, as we mentioned, we had selection bias (relatively healthy patients with fractures were included in our study) and lacked utility scores

immediately after fracture, which limits us to accurately estimate the true HSUV for patients after fracture, to capture the difference in HSUV between subgroups, and to investigate the responsiveness in overall subjects. Third, we estimated SF-6D utility and PCS/MCS using the UK value set and physical/mental factor score coefficients given the lack of Dutch-specific norm, which might limit our estimation to reflect the true preference of the Dutch population.

CONCLUSION

This study compared the psychometric properties of EQ-5D-5L and SF-6D to assess the interchangeability of these two instruments. Both EQ-5D-5L and SF-6D appears to be valid utility instruments in patients with fractures attending the FLS. However, they cannot be used interchangeably given only moderate agreement was identified, and differences in utilities and ceiling effect were revealed. Comparable construct and longitudinal validity between these two instruments were indicated, and neither instrument was found to be clearly superior.

ELECTRONIC SUPPLEMENTARY MATERIAL:

Separate tables for the analyses of validity

Table 1. Convergent validity: correlations between utilities, EQ-VAS, summary scores and scales of SF-36

	SF-6D utility	EQ-VAS	SF-36									
			PCS	MCS	PF	RP	BP	GH	VT	SF	RE	MH
EQ-5D utility (Dutch)	0.763	0.642	0.804	0.254	0.744	0.654	0.715	0.537	0.566	0.623	0.450	0.478
EQ-5D utility (UK)	0.758	0.640	0.810	0.235	0.758	0.655	0.720	0.527	0.551	0.607	0.451	0.460
SF-6D utility	/	0.628	0.778	0.452	0.690	0.735	0.687	0.520	0.677	0.783	0.543	0.614

All correlations significant at 0.01 level.
PCS physical component score, MCS mental component score, PF physical functioning, RP role physical, BP bodily pain, GH general health, VT vitality, SF social functioning, RE role emotional, MH mental health, VAS visual analog scale

Table 2. Known group validity of EQ-5D-5L and SF-6D utilities

Variables	EQ-5D (Dutch)			EQ-5D (UK)			SF-6D		
	Mean (SD)	*P*-value	|ES|	Mean (SD)	*P*-value	|ES|	Mean (SD)	*P*-value	|ES|
Age									
≤ 65	0.819 (0.189)	0.269	0.075	0.852 (0.167)	0.162	0.096	0.765 (0.118)	0.901	0.008
> 65	0.805 (0.185)			0.836 (0.165)			0.766 (0.126)		
Gender									
Male	0.832 (0.194)	0.026*	0.143	0.862 (0.173)	0.018*	0.143	0.798 (0.120)	<0.001*	0.385
Female	0.805 (0.184)			0.838 (0.163)			0.752 (0.119)		
BMD									
Normal	0.818 (0.186)	0.559	Ref.	0.850 (0.166)	0.586	Ref.	0.767 (0.118)	0.323	Ref.
Osteopenia	0.821 (0.175)		0.017	0.852 (0.156)		0.012	0.772 (0.123)		0.041
Osteoporosis	0.788 (0.213)		0.150	0.824 (0.188)		0.147	0.749 (0.120)		0.151
Baseline fracture location									
Femoral/vertebral/multiple fx	0.706 (0.227)	<0.001*	0.607	0.749 (0.200)	<0.001*	0.613	0.697 (0.127)	<0.001*	0.647
Other fractures	0.829 (0.175)			0.859 (0.156)			0.776 (0.117)		
Previous fracture									
Yes	0.806 (0.197)	0.981	0.075	0.840 (0.176)	0.981	0.066	0.761 (0.126)	0.545	0.083
No	0.820 (0.175)			0.851 (0.155)			0.771 (0.115)		
Prevalent VFs									
Yes	0.784 (0.212)	0.079	0.205	0.818 (0.187)	0.068	0.214	0.752 (0.131)	0.180	0.145
No	0.824 (0.176)			0.855 (0.158)			0.770 (0.117)		
Falls in the last year									
Yes	0.773 (0.206)	<0.001*	0.286	0.811 (0.180)	<0.001*	0.277	0.738 (0.132)	0.004*	0.307
No	0.828 (0.177)			0.858 (0.159)			0.776 (0.115)		
Previous AOM use									
Yes	0.726 (0.252)	<0.001*	0.446	0.765 (0.224)	<0.001*	0.466	0.716 (0.131)	0.002*	0.439
No	0.823 (0.176)			0.855 (0.156)			0.771 (0.119)		

SD standard deviation, BMD bone mineral density, VF vertebral fracture, AOM anti-osteoporosis medication,
ES effect size, ref reference

Table 3. Responsiveness: the change of EQ-5D-5L and SF-6D utilities before and after subsequent fracture

Follow up	Instrument	Mean utility (SD)	Mean change (SD)	|ES|	|SRM|
Pre-subsequent fracture	EQ-5D (Dutch)	0.803 (0.202)	Reference		
	EQ-5D (UK)	0.836 (0.179)			
	SF-6D	0.772 (0.111)			
Post-subsequent fracture	EQ-5D (Dutch)	0.725 (0.248)	-0.078 (0.147)*	0.386	0.531
	EQ-5D (UK)	0.765 (0.221)	-0.071 (0.124)*	0.397	0.573
	SF-6D	0.720 (0.124)	-0.052 (0.100)*	0.468	0.520

SD standard deviation, ES effect size, SRM standardized response mean
* significant at 0.05 level.

Table 4. Predictors associated with discrepancies in EQ-5D-5L and SF-6D utility

	Coefficients	Coefficients Std. Error	P-value
Constant	0.094	0.050	0.060
Female	0.025	0.013	0.043
Age (<65 vs. >65 years)	-0.001	0.001	0.108
Baseline fracture type (femoral/vertebral/multiple fractures vs. other fractures)	-0.034	0.017	0.052
Osteoporosis (yes vs. no)	-0.003	0.014	0.847
Previous fracture (yes vs. no)	-0.003	0.011	0.812
Prevalent vertebral fracture (yes vs. no)	-0.004	0.014	0.792
Falls in the last year (yes vs. no)	-0.019	0.012	0.126
Parental hip fracture (yes vs. no)	-0.038	0.027	0.157
Osteoporosis in family (yes vs. no)	0.007	0.006	0.263
Previous AOM use (yes vs. no)	-0.030	0.019	0.107
Current smoking (yes vs. no)	-0.003	0.016	0.848
Alcohol use (yes vs. no)	0.023	0.014	0.105

AOM anti-osteoporosis medication, Std standard

REFERENCE

1. Kanis JA, Johnell O, De Laet C, et al. A meta-analysis of previous fracture and subsequent fracture risk. *Bone*. 2004;35(2):375-382. doi:10.1016/j.bone.2004.03.024
2. Johansson H, Siggeirsdóttir K, Harvey NC, et al. Imminent risk of fracture after fracture. *Osteoporos Int*. 2017;28(3):775-780. doi:10.1007/s00198-016-3868-0
3. Kanis JA, Johansson H, Odén A, et al. Characteristics of recurrent fractures. *Osteoporos Int*. 2018;29(8):1747-1757. doi:10.1007/s00198-018-4502-0
4. Bikbov MM, Fayzrakhmanov RR, Kazakbaeva GM, et al. Frequency and Associated Factors of Bone Fractures in Russians: The Ural Eye and Medical Study. *Sci Rep*. 2018;8(1):1-9. doi:10.1038/s41598-018-25928-1
5. Adachi JD, Ioannidis G, Olszynski WP, et al. The impact of incident vertebral and non-vertebral fractures on healthrelated quality of life in postmenopausal women. *BMC Musculoskelet Disord*. 2002;3:1-6. doi:10.1186/1471-2474-3-11
6. Li N, van Oostwaard M, van den Bergh JP, et al. Health-related quality of life of patients with a recent fracture attending a fracture liaison service: a 3-year follow-up study. *Osteoporos Int*. 2021;(0123456789). doi:10.1007/s00198-021-06204-x
7. Meregaglia M, Cairns J. A systematic literature review of health state utility values in head and neck cancer. *Health Qual Life Outcomes*. 2017;15(1):1-13. doi:10.1186/s12955-017-0748-z
8. Boonen A, Van Der Heijde D, Landewé R, et al. How do the EQ-5D, SF-6D and the well-being rating scale compare in patients with ankylosing spondylitis? *Ann Rheum Dis*. 2007;66(6):771-777. doi:10.1136/ard.2006.060384
9. Svedbom A, Borgström F, Hernlund E, et al. Quality of life after hip, vertebral, and distal forearm fragility fractures measured using the EQ-5D-3L, EQ-VAS, and time-trade-off: results from the ICUROS. *Qual Life Res*. 2018;27(3):707-716. doi:10.1007/s11136-017-1748-5
10. Dolan P. Ideas at Issue Whose Preferences Count ? Published online 1999:482-486.
11. Dolan P, Sutton M. Mapping visual analogue scale health state valuations onto standard gamble and time trade-off values. *Soc Sci Med*. 1997;44(10):1519-1530. doi:10.1016/S0277-9536(96)00271-7
12. Ware JE. SF36 Health survey : Manual and Interpretation Guided. Massachusetts. *Nimrod Press Bost*. Published online 1993.
13. Hiligsmann M, Reginster J, Tosteson ANA, et al. Recommendations for the conduct of economic evaluations in osteoporosis : outcomes of an experts ' consensus meeting organized by the European Society for Clinical and Economic Aspects of Osteoporosis , Osteoarthritis and Musculoskeletal Diseases (ESCEO . Published online 2019:45-57.
14. Joore M, Brunenberg D, Nelemans P, et al. The impact of differences in EQ-5D and SF-6D utility scores on the acceptability of cost-utility ratios: Results across five trial-based cost-utility studies. *Value Heal*. 2010;13(2):222-229. doi:10.1111/j.1524-4733.2009.00669.x
15. Ye Z, Sun L, Wang Q. A head-to-head comparison of EQ-5D-5 L and SF-6D in Chinese patients with low back pain. *Health Qual Life Outcomes*. 2019;17(1):1-11. doi:10.1186/s12955-019-1137-6
16. van Stel HF, Buskens E. Comparison of the SF-6D and the EQ-5D in patients with coronary heart disease. *Health Qual Life Outcomes*. 2006;4:10-12. doi:10.1186/1477-7525-4-20

17. Mulhern B, Meadows K. The construct validity and responsiveness of the EQ-5D, SF-6D and Diabetes Health Profile-18 in type 2 diabetes. *Health Qual Life Outcomes*. 2014;12(1):1-10. doi:10.1186/1477-7525-12-42
18. Vranken L, Wyers CE, van Rietbergen B, et al. The association between prevalent vertebral fractures and bone quality of the distal radius and distal tibia as measured with HR-pQCT in postmenopausal women with a recent non-vertebral fracture at the Fracture Liaison Service. *Osteoporos Int*. 2019;30(9):1789-1797. doi:10.1007/s00198-019-05081-9
19. Wolowacz SE, Briggs A, Belozeroff V, et al. Estimating Health-State Utility for Economic Models in Clinical Studies: An ISPOR Good Research Practices Task Force Report. *Value Heal*. 2016;19(6):704-719. doi:10.1016/j.jval.2016.06.001
20. Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. *J Health Econ*. 2002;21(2):271-292. doi:10.1016/S0167-6296(01)00130-8
21. Versteegh M, M. Vermeulen K, M. A. A. Evers S, de Wit GA, Prenger R, A. Stolk E. Dutch Tariff for the Five-Level Version of EQ-5D. *Value Heal*. 2016;19(4):343-352. doi:10.1016/j.jval.2016.01.003
22. Devlin NJ, Shah KK, Feng Y, Mulhern B, van Hout B. Valuing health-related quality of life: An EQ-5D-5L value set for England. *Heal Econ (United Kingdom)*. 2018;27(1):7-22. doi:10.1002/hec.3564
23. Terwee CB, Bot SDM, de Boer MR, et al. Quality criteria were proposed for measurement properties of health status questionnaires. *J Clin Epidemiol*. 2007;60(1):34-42. doi:10.1016/j.jclinepi.2006.03.012
24. Koo TK, Li MY. A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. *J Chiropr Med*. 2016;15(2):155-163. doi:10.1016/j.jcm.2016.02.012
25. Lakota EA, Landersdorfer CB, Nation RL, et al. Personalizing Polymyxin B dosing using an adaptive feedback control algorithm. *Antimicrob Agents Chemother*. 2018;62(7):307-310. doi:10.1128/AAC.00483-18
26. de Vet HCW, Terwee CB, Mokkink LB. *Measurement in Medicine: A Practical Guide [M]*. London: Cambridge University press; 2011.
27. Cohen J. A Power Primer. 1992;112(1):155-159. doi:10.1037/0033-2909.112.1.155
28. Terwee CB, Dekker FW, Wiersinga WM, Prummel MF, Bossuyt PMM. On assessing responsiveness of health-related quality of life instruments: Guidelines for instrument evaluation. *Qual Life Res*. 2003;12(4):349-362. doi:10.1023/A:1023499322593
29. Norman GR, Wyrwich KW, Patrick DL. The mathematical relationship among different forms of responsiveness coefficients. *Qual Life Res*. 2007;16(5):815-822. doi:10.1007/s11136-007-9180-x
30. Selva-Sevilla C, Ferrara P, Gerónimo-Pardo M. Interchangeability of the EQ-5D and the SF-6D, and comparison of their psychometric properties in a spinal postoperative Spanish population. *Eur J Heal Econ*. 2020;21(4):649-662. doi:10.1007/s10198-020-01161-4
31. Sakthong P, Munpan W. A Head-to-Head Comparison of UK SF-6D and Thai and UK EQ-5D-5L Value Sets in Thai Patients with Chronic Diseases. *Appl Health Econ Health Policy*. 2017;15(5):669-679. doi:10.1007/s40258-017-0320-3
32. Sayah F Al, Qiu W, Xie F, Johnson JA. Comparative performance of the EQ-5D-5L and SF-6D index scores in adults with type 2 diabetes. *Qual Life Res*. 2017;26(8):2057-2066. doi:10.1007/s11136-017-1559-8
33. Wu J, Han Y, Zhao FL, Zhou J, Chen Z, Sun H. Validation and comparison of EuroQoL-5 dimension (EQ-5D) and Short Form-6 dimension (SF-6D) among stable angina patients. *Health Qual Life Outcomes*.

2014;12(1):1-11. doi:10.1186/s12955-014-0156-6

34. Brazier J, Deverill M, Green C, Harper R, Booth A. A review of the use of health status measures in economic evaluation. *Health Technol Assess (Rockv)*. 1999;3(9). doi:10.3310/hta3090
35. Brazier J, Roberts J, Tsuchiya A, Busschbach J. A comparison of the EQ-5D and SF-6D across seven patient groups. *Health Econ*. 2004;13(9):873-884. doi:10.1002/hec.866
36. Richardson J, Khan MA, Iezzi A, Maxwell A. Comparing and explaining differences in the magnitude, content, and sensitivity of utilities predicted by the EQ-5D, SF-6D, HUI 3, 15D, QWB, and AQoL-8D multiattribute utility instruments. *Med Decis Mak*. 2015;35(3):276-291. doi:10.1177/0272989X14543107
37. Adachi JD, Adami S, Gehlbach S, et al. Impact of prevalent fractures on quality of life: Baseline results from the global longitudinal study of osteoporosis in women. *Mayo Clin Proc*. 2010;85(9):806-813. doi:10.4065/mcp.2010.0082

CHAPTER 8

A model-based cost-effectiveness analysis of fracture liaison services in China

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ABSTRACT

Purpose: The study aimed to assess the potential cost-effectiveness of fracture liaison services (FLS) from the Chinese healthcare perspective with a lifetime horizon.

Methods: A previously validated Markov microsimulation model was adapted to estimate the cost-effectiveness of FLS compared to no-FLS. The evaluation was conducted in patients aged 65 years with a recent fracture. Treatment pathways were differentiated by gender, FLS attendance, osteoporosis diagnosis, treatment initiation, and adherence. Given the uncertainty in FLS cost, the cost in the base-case analysis was assumed at US$200. Analyses were also performed to determine the maximum cost for making the FLS cost-saving and cost-effective at the Chinese Willingness-to-pay (WTP) threshold. One-way sensitivity analyses were conducted.

Results: When compared with no-FLS, the FLS was dominant (lower costs, higher quality-adjusted life years) in our target population at the FLS cost of US$200 per patient. For every 100 patients who were admitted to the FLS, approximately four hip fractures, nine clinical vertebral fractures, and three wrist fractures would be avoided over their lifetimes. Our findings were robust to numerous one-way sensitivity analyses; however, the FLS was not cost-effective in patients aged 80 years and older.

Conclusion: FLS could potentially lead to lifetime cost-saving in patients who have experienced a fracture. Our study informs the potential cost-effectiveness of FLS and the knowledge gap in China; more future research incorporating Chinese-specific real-world data are needed to confirm the results of our study and to better evaluate the cost-effectiveness of FLS in China.

Keywords: Cost-effectiveness, Fracture liaison services, Fracture, osteoporosis

INTRODUCTION

Osteoporosis causes loss of bone mass and deterioration of bone microarchitecture, which is the main risk factor for fragility fractures. Osteoporosis-related fractures can lead to an increased risk of subsequent fractures and reduced quality of life. In the context of the aging population and increasing life expectancy, osteoporosis places a large medical and economic burden on healthcare systems [1]. This burden is more profound in countries like China, which is stressed by limited healthcare resources and a large population [2]. The estimated age-standardized lifetime prevalence of osteoporosis was 6.46% and 29.13% for Chinese men and women aged 50 years and older, respectively [3]. In one study performed in eight provinces of China [4], the estimated osteoporosis-related fracture incidence rate was 160.3/100,000 person-years, with 120.0 and 213.1/100,000 person-years in men and women aged 50 years or older, respectively. The annual cost of hospitalization was estimated in a recent Chinese study [5], ranging from US$3,142 for hand and wrist fractures to US$10,355 for hip fractures per patient.

Despite the availability of various effective pharmaceutical interventions for fracture prevention, osteoporotic fractures are still undertreated [6]. One study [7] explored the management of osteoporosis after a fragility fracture among postmenopausal women in six Asian countries, reporting a substantial treatment gap (67%) six months after the index fracture. The gaps were even more profound in mainland China, where the treatment initiation rate was lower than the average in these six Asian countries. Another Chinese study (in which the diagnosis rate of osteoporosis was 56.8%) reported that a bone mineral density (BMD) measurement had never been conducted in 42% of patients with fragility fractures, that nearly 30% of patients had never received basic calcium and/or vitamin D supplementation, and that following fragility fractures, only 28% of elderly patients were prescribed with pharmaceutical treatment for osteoporosis besides calcium and vitamin D [8].

In response to the care gap in the elderly after fragility fractures, the International Osteoporosis Foundation (IOF) launched the Capture the Fracture (CTF) Campaign in 2012 to facilitate implementation of the Post-Fracture Care (PFC) coordination program, such as fracture liaison services (FLS), for secondary fracture prevention. FLS is advocated as the best practice covering all aspects, including patient identification, education, risk evaluation, treatment, and long-term monitoring, to directly improve patient care and reduce spiraling fracture-related healthcare costs. A recently published meta-analysis indicated that FLS reduced the risk of subsequent fractures by 30% [9]. To date (13 June, 2022), 739 FLS (registered in the CTF Campaign) have been implemented in 50 countries worldwide. In recent

years, the number of FLS in the Asia-Pacific (AP) region has risen rapidly [10], with 41 FLS in China currently registered in the CTF Campaign (mainland China: 6; Taiwan: 31; Hong Kong: 4). However, in comparison with European countries, the number of FLS remains limited in China, and the intensity of implementing FLS is inadequate.

To help the implementation of FLS, it is important to assess the cost-effectiveness of FLS models. Given limited healthcare resources and budgets, economic evaluations are used increasingly nowadays to support the setting of priorities in healthcare. Accordingly, in recent years several cost-effectiveness analyses of FLS have been conducted, and 16 studies published up to December 2016 were summarized in a systematic review by Wu et al. [11]. This review suggested that FLS were cost-effective compared with usual care or no treatment, regardless of the program intensity or the country; 47% of studies even documented cost savings. However, economic evidence regarding the FLS implementation in China is largely lacking, and due to the limited transferability of cost-effectiveness analyses between countries, it is important to investigate the potential economic value of FLS from the Chinese healthcare perspective with a lifetime horizon. The objective of this study was therefore to assess the potential cost-effectiveness of FLS in China. Given the uncertainty in FLS costs, analyses were also performed to determine the maximum cost that for making the FLS cost-saving and cost-effective at the Chinese Willingness-to-pay (WTP) threshold.

METHODS

A previously validated Markov microsimulation model [12] was adapted to estimate the cost-effectiveness of FLS compared to no-FLS with a lifetime horizon from the Chinese healthcare perspective. The individual-level simulation allows the tracking of patient characteristics and disease histories, and avoids unnecessary transition restrictions [13]. In this way, the number and the type of subsequent fractures were recorded for each individual using 'tracker variables'. The model was developed using TreeAge Pro 2021 software (TreeAge Pro Inc., Williamston, MA, USA) and was conducted in line with recommendations for the conduct of economic evaluations in osteoporosis provided by the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) and the US branch of the International Osteoporosis Foundation (IOF) [14] and with the Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) Statement [15]. Appendices I and II include details of the two checklists. A description of the model is provided here below.

Model structure

The population of our analysis was patients who had recently suffered a fracture; both males and females were included because of large differences in the probability of osteoporosis, fracture incidence, and risk of subsequent fractures. The prevalence of osteoporosis was derived from the study of Wang et al. [16]; osteoporosis was defined as individuals with BMD T scores of −2.5 or less in any sites (lumbar spine L1 to L4, femoral neck, or total hip). The base case population had a starting age of 65 years old, which was aligned with the mean age of most FLS studies summarized in a systematic review on the effectiveness of FLS [9].

As displayed in Figure 1, the economic model consisted of a decision tree (to determine the treatment pathway), followed by a Markov model. Treatment pathways were differentiated by gender (male/female), attenders/non-attenders, diagnosis of osteoporosis or not, treatment initiation or not, leading to a total of 18 possible pathways.

After each pathway, patients entered a Markov model (see Figure 2), where all patients started in the health state of "a recent fracture" and could transit between future fracture health states (hip, vertebral and wrist), their corresponding post-fracture states, and death. Patients could experience multiple fractures at the same site or multiple sites. If a patient died, he/she would remain in the 'death' state for the rest of the simulation. In line with ESCEO-IOF guideline [14], the cycle length of this model is 6 months; each patient would be followed until they died or reached the age of 100 years.

The primary outcome was the incremental cost-effectiveness ratio (ICER) between FLS and no-FLS care, expressed as incremental cost per quality-adjusted life year (QALY) gained. The discount rate of 5% was used for both costs and QALYs as recommended by the China Guidelines for Pharmacoeconomic Evaluations (2020 edition) [17]. Data used for the model are shown in Table 1.

Treatment pathways

The FLS pathway was differentiated from the no-FLS pathway mainly in terms of the proportion of patients receiving actual FLS care (i.e., incurring FLS costs and having a higher likelihood of starting anti-osteoporosis medication), treatment adherence, and the presence of FLS costs. For both FLS and no-FLS pathways, we assumed 57.7% of patients were females. According to a recent Chinese study that summarized the prevalence of clinical fracture in the past five years [16], the proportion was comparable to a recently published study (51.29% of patients were females) which included 39,300 patients aged over 45 years with a fracture

in Jiangsu, China [5]. To make the FLS and no-FLS pathways comparable, the same (age and gender-specific) proportion of patients having osteoporosis was assumed. Afterward, in both FLS and no-FLS, patients entered different branches in terms of their treatment status (no osteoporosis, osteoporosis + no treatment, osteoporosis + treatment). In our model, we made a conservative assumption that patients without osteoporosis did not initiate treatment (although some local guidelines suggest patients with grade 2 or 3 vertebral fractures should initiate treatment irrespective of their BMD status, the relevant data was lacking in China). For patients diagnosed with osteoporosis, some patients would initiate treatment, the difference between the FLS and no-FLS pathways was that a higher proportion of patients in the FLS pathway initiated treatment compared to patients in the no-FLS pathway (i.e., 38% for FLS vs. 17.2% for no-FLS), according to a systematic review and meta-analysis [23]. In addition, the treatment adherence in the FLS pathway was also higher given the positive role of the FLS coordinator who usually provided treatment advice and long-term monitoring for patients in the FLS.

Moreover, in the FLS pathway, patients were further divided into attenders and non-attenders. The proportion of patients who attend the FLS was defined as the number of patients actually attending the FLS divided by the total number of patients eligible or invited for the FLS (and thus assuming all patients with fractures are invited). FLS attendance means that the full assessment (laboratory test), including advice on treatment, has been executed. Based on two previous literature reviews [9, 23], the average FLS attendance rate was estimated at 66% and used in our study. We further assumed that attenders and non-attenders have the same baseline fracture risk.

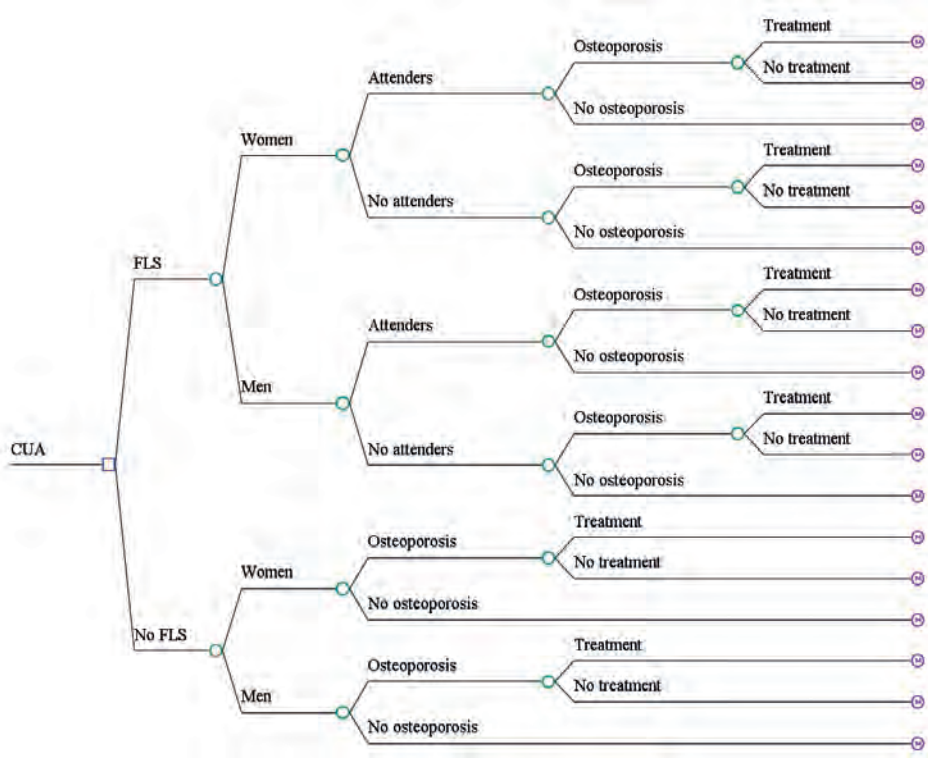

Figure 1. Patient pathways for FLS and no-FLS group
(CUA cost-utility analysis, FLS fracture liaison services)

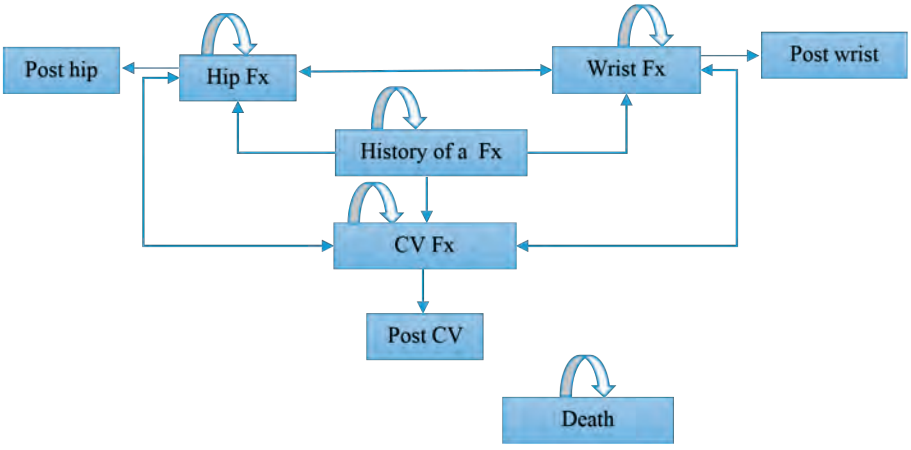

Figure 2. Structure of the Markov model
(Fx fracture, CV Fx clinical vertebral fracture)

Osteoporosis prevalence, fracture risk, and mortality

Given the lack of osteoporosis prevalence data for patients with a recent fracture in China, age- and gender- stratified osteoporosis prevalence rates for the Chinese general population were used to determine the initial probability of the simulated subjects being osteoporotic [16], for both attenders and non-attenders. The proportion of 65 year old female and male patients having osteoporosis was 37.1% and 5.4%, respectively. Considering that the prevalence of osteoporosis in the fractured population might be higher than in the general population, the baseline prevalence of osteoporosis was increased by 20% and 40% separately in one-way sensitivity analyses.

The gender-specific annual incidence rates of hip and vertebral fracture in the general population were derived from the Hefei osteoporosis project [18] and the epidemiological study of Hong Kong [19], respectively. In the absence of estimates of the annual incidence rate of wrist fracture in the Chinese population, a Norwegian study [20] was used, multiplying by 0.72 to adjust for the Asian population, as indicated in this article. Rates were converted to risk. In addition, considering our patients had a fracture at baseline, the increased risk of having a subsequent fracture was assumed (relative risk (RR) was 1.95, 3.47 for females and males, respectively), which was taken from the Dubbo Osteoporosis Epidemiology Study (DOES) [21]. However, given no relevant high-quality data in China on the increased risk following a second, third subsequent fracture, etc., we therefore conservatively did not assume, during simulation, the extra increased risk for the occurrence of new fractures.

As patients with osteoporosis have an increased risk of fracture in comparison with those without osteoporosis, the initial probabilities (we mentioned above) were then adjusted to reflect the fracture risk of patients with osteoporosis. The RR was extracted from a recently published cost-effectiveness analysis [39] which estimated the age-stratified RR based on previous studies [24,25] using previously validated methods [22]. Of note, given the lack of RR data for patients aged 60-64 years (for sensitivity analysis purposes), we assumed the same RR as patients aged 65 years. In addition, considering that not all fractures were attributable to osteoporosis, the age- and gender-specific osteoporosis attribution probability [40] was applied to make the further adjustment.

Baseline mortality rates for the age- and gender-stratified Chinese population were obtained from the China Public Health Statistical Yearbook. An increased mortality risk after hip fracture and clinical vertebral fracture was assumed for both genders [26], which is in line with previous economic studies [41]. Given that comorbidities

could also be a contributing factor for excess mortality, we further took into account that only 25% of the excess mortality following fractures was attributed to the fractures themselves [42,43].

Fracture cost

A healthcare perspective was used for cost estimation. Costs of hip and vertebral fractures referred to hospitalization costs deriving from a recently published Chinese study [5]. As this study classified wrist and hand fracture as one category, the cost of wrist fracture was obtained from another Chinese study [27]. In addition, hip fractures are also associated with long-term costs. The probability of admission to a nursing home after a hip fracture is usually very low in China and was assumed to be 5%, based on expert opinion. The annual costs for nursing home residence were retrieved from a previous study [28] which was based on prices recommended by the Chinese government. All costs were converted to the 2020 US dollar in the analysis.

Utility values

The baseline utility value (0.70) for patients with a history of fracture was estimated based on 12-month utility data after a fracture of the International Costs and Utilities Related to Osteoporotic Fractures Study (ICUROS) [29]. This study assessed the quality of life of patients with fractures from 11 countries including 2,808 patients. The health state utility values (HSUVs) for the first and subsequent years after a fracture were calculated using a multiplicative approach. The fracture-specific multipliers were also obtained from the ICUROS study [29].

Treatment effects

Oral bisphosphonates are commonly used as the first-line therapy for osteoporosis management in China [44]. In this study, we therefore assumed patients initiated treatment with weekly oral alendronate. The pooled efficacy data for bisphosphonates of the National Institute for Clinical Health and Excellence (NICE) was applied [30]. This study suggests that oral bisphosphonates resulted in a relative risk (RR) of 0.67, 0.45, and 0.81 for hip, vertebral, and wrist fracture, respectively. The treatment duration was 5 years maximum (which was consistent with Chinese guidelines for diagnosis and treatment of osteoporosis) [44]. After stopping medication, it was assumed a linear decrease of the effects for a duration similar to the duration of therapy, in line with previous economic analyses of oral bisphosphonates [45] and clinical data [46].

The real-world persistence data for weekly bisphosphonates was obtained from a Japanese study [33]; persistence refers to the duration of time from initiation

to discontinuation of the therapy, which was based on prescription data in 13 university hospitals in Japan, showing that the cumulative persistence rates with weekly bisphosphonates were 50%, 33%, 21%, 12%, and 6% at the end of first, second, third, fourth, and fifth years, respectively. The persistence rate for the first six months (56%) was estimated according to the study of Chandran et al. [34]; the same ratio between the 6 and 12 months persistence rates was assumed.

For FLS and no-FLS patients who initiated drug therapy, diagnostic and treatment costs include drug costs, bone mineral density (BMD) testing costs, general practice (GP) visit costs, and costs related to side effects. Annual drug costs, BMD testing and GP visit costs were retrieved from the National Development and Reform Commission of China (2018) [31]. It was assumed that subjects undergoing therapy had one GP visit per year, and a dual-energy X-ray absorptiometry (DXA) per two years. In addition, considering serious adverse events (i.e., osteonecrosis of the jaw and atypical femoral fractures) associated with the use of bisphosphonate therapy are an increasing concern in the public media and for patients recently, which might cause extra costs; we therefore assumed that patients treated with alendronate required 0.041 more GP consultations during the first cycle (6 months) and 0.021 GP consultations during the following cycles of treatment, in line with a previous cost-effectiveness analysis [32]. Treatment costs stopped when patients discontinued therapies.

FLS effects

Given the lack of treatment initiation and adherence data following FLS in China, we obtained relevant data from a literature review and meta-analysis [35]; these can be regarded as the average performance of any type of FLS. Therefore, according to the type of FLS-related data we obtained, we assumed the form of FLS in our study to be at the average level of intensity of intervention. Adherence refers to the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen [47]. Specifically, compared to no-FLS, the effect of FLS was included through three parameters. First, FLS are associated with costs. Estimates of the cost of FLS in mainland China were not available, and only one Taiwanese study [36] reported the FLS fee in their study; this was estimated to be US$133. In order to make the FLS cost in our study comparable to other previous studies (FLS coordinator or nurse practitioner-based care) [37,38], for base-case analysis, a one-off FLS cost of US$200 were assumed. This cost was applied only to FLS attenders. Second, we assumed that 38% and 17.2% of patients initiated treatment in the FLS (attenders) and no-FLS group, respectively. Third, higher treatment adherence was assumed for FLS (attenders) in comparison with no-FLS (57% vs. 34.1%) [35].

With regard to FLS non-attenders, first, as we mentioned before, to make FLS and no-FLS branches comparable, each patient entered the model with the same baseline fracture risk, i.e. the same baseline fracture risk was assumed for FLS attenders and non-attenders; second, FLS non-attenders did not incur one-off FLS costs; third, given the lack of relevant research data for non-attenders, it was assumed that FLS non-attenders had the same treatment initiation (17.2%) and adherence (34.1%) rates as patients in the no-FLS pathway.

Outcomes and analyses

For base-case analysis, at the FLS cost of US$200 for each patient, total healthcare costs and QALYs were estimated for both FLS and no-FLS pathways. The ICER was computed as the difference between FLS and no-FLS in terms of total costs (expressed in 2020 US dollars) divided by the difference in terms of QALYs. In addition, analyses were also conducted to determine the maximum FLS cost (per patient) that make the FLS cost-saving and cost-effective at the Chinese WTP threshold. The WTP threshold was set at US$10,500 per QALY gained, which was the one-time gross domestic product (GDP) per capita in China (year 2020) [48].

The one-way deterministic sensitivity analysis was conducted to assess the impact of a single parameter on the robustness of the model. A total of 1,000,000 trials were run for each analysis. The parameters were categorized into two types: FLS-related parameters and other parameters. For FLS-related parameters, ten one-way sensitivity analyses were conducted. First, considering that the cost of FLS in China is unclear, different costs (US$400 (doubled), US$600 (tripled)) were tested. Second, given the uncertainty of the effects of FLS on mortality, we did not include it in the base case; however, a lower mortality rate was assumed for FLS pathway in the sensitivity analysis (Odds ratio (OR): 0.73), based on a previous meta-analysis [9]. Considering that a 27% reduction of mortality risk might be high, another one-way sensitivity analysis used a decrease of 20% (with OR=0.876). Third, the FLS attendance rate was increased/decreased by 20%. Fourth, treatment adherence in the FLS pathway was also increased/decreased by 20%. Fifth, the proportion of patients initiating treatment in FLS pathway was halved and doubled separately. Of note, the increases/decreases mentioned above were in absolute percentages.

For other parameters, different values were assumed for the starting age, the proportion of women, the proportion of nursing home admissions, prevalence of osteoporosis, fracture costs, long-term costs, drug costs, treatment efficacy, baseline utility, and discount rate. A total of 23 one-way sensitivity analyses were conducted.

Table 1. Key parameters derived from literature for base-case analysis

Parameter	Female	Male	Data source
Gender (%)	57.7	42.3	[16]
Proportion of osteoporosis (%)	37.1 (60–69 years), 51.3 (70–79 years), 67.5 (80+years)	5.4 (60–69 years), 12.3 (70–79 years), 21.9 (80+years)	[16]
Fracture risk and mortality			
Fracture incidence (annual rate per 1000 person-years)			
Hip	0.96 (65–69 years), 2.34 (70–74 years), 4.08 (75–79 years), 6.44 (80–84 years), 6.59 (85–89 years), 8.67 (90+years)	0.65 (65–69 years), 1.26 (70–74 years), 2.37 (75–79 years), 5.19 (80–84 years), 5.71 (85–89 years), 8.35 (90+years)	[18]
Vertebral	5.64 (65–69 years), 8.74 (70–74 years), 12.05 (75–79 years), 21.19 (80–84 years), 26.89 (85+years)	0.95 (65–69 years), 2.26 (70–74 years), 4.50 (75–79 years), 5.94 (80–84 years), 9.54 (85+years)	[19]
Wrist	12.95 (65–69 years), 13.17 (70–74 years), 13.87 (75–79 years), 15.01 (80–84 years), 15.10 (85–89 years), 13.97 (90+years)	3.27 (65–69 years), 2.79 (70–74 years), 3.13 (75–79 years), 4.75 (80–84 years), 4.78 (85–89 years), 3.23 (90+years)	[20]
Relative risk of having a subsequent fracture	1.95	3.47	[21]
Relative risk of fracture for individuals with osteoporosis			
Hip	3.91 (65–69 years), 3.31 (70–74 years), 2.6 (75–79 years), 2.04 (80–84 years), 1.92 (85+years)		[17, 22]
Vertebral	2.59 (65–69 years), 2.15 (70–79 years), 1.82 (80+years)		[22, 23]
Wrist	1.78 (65–69 years), 1.60 (70–79 years), 1.45 (80+years)		[22, 24, 25]
All-cause mortality (per 1000) for the general population	13.06 (65–69 years), 24.36 (70–74 years), 40.89 (75–79 years), 73.98 (80–84 years), 115.29 (85–89 years), 180.24 (90–94 years), 219.46 (95–99 years), 436.34 (100+years)	21.26 (65–69 years), 37.02 (70–74 years), 59.13 (75–79 years), 98.56 (80–84 years), 146.53 (85–89 years), 211.66 (90–94 years), 212.07 (95–99 years), 507.28 (100+years)	(https://www.chinayearbooks.com/tags/china-statistical-yearbook)
Excess mortality after a subsequent fracture	1.91	2.99	[26]
Direct fracture cost (US$2020)			
Hip, first 1 year	11,166		[27]
Hip, long-term annually	4799		[28]
CV, first 1 year	6328		[27]
Wrist, first 1 year	2162		[5]
Health state utility values			
Baseline (patients with a fracture)	0.7		[29]
Hip (1st year/subs. years)	0.55/0.86		
CV (1st year/subs. years)	0.68/0.85		
Wrist (1st year/subs. years)	0.83/0.99		

Table 1 (continued)

Parameter	Female	Male	Data source
Treatment			
Treatment effects of oral alendronate (relative risk of fracture)			
Hip	0.67		[30]
Vertebral	0.45		
Wrist	0.81		
Treatment cost (USD 2020)			
Drug cost (6 months)	392.31		[31]
DXA cost	87.57		
GP cost per person	10.3		
Side effect cost	0.041 extra GP consultations during the first cycle (6 months) and 0.021 GP consultations during the following cycles		[32]
Treatment persistence (%)	56 (6 months), 50 (1 year), 33 (2 years), 21 (3 years), 12 (4 years), 6 (5 years)		[33, 34]
FLS-related data			
Treatment initiation (%)	FLS pathway: 38 no-FLS pathway: 17.2		[35]
Treatment adherence (%)	FLS pathway: 57 no-FLS pathway: 34.1		[35]
One-off FLS cost (USD 2020)	200 (base case)		Assumption based on three studies [36–38]
FLS attendance rate (%)	66		[9]

CV clinical vertebral fracture, *DXA* dual-energy X-ray absorptiometry, *FLS* fracture liaison service, *GP* general practice

RESULTS

Base-case and sensitivity analyses

Table 2 reports incremental costs and QALY, and the ICER (expressed in cost per QALY gained) of FLS compared to no-FLS. For base case analysis, in patients aged 65 years with a fracture, FLS was associated with lower lifetime total costs of US$501 in comparison with no-FLS, but leads to 0.095 additional QALY gained, indicating that FLS was dominant (more QALY for less total costs) at a cost of US$200 per patient in the Chinese context. In addition, for every 100 patients (a mix of baseline fracture types) in the FLS, about four hip fractures, nine clinical vertebral fractures and three wrist fractures would be avoided. The maximum cost of FLS that makes the FLS to be cost-saving in the Chinese setting was US$958, and the maximum cost of FLS that makes the FLS to be cost-effective at the WTP threshold of US$10,500 per QALY gained was US$2,495.

For sensitivity analyses, our results were robust to numerous one-way sensitivity analyses overall. For FLS-related parameters, the FLS was still dominant even when the cost of FLS was tripled. In addition, the incremental cost and QALY were markedly affected by incorporating a lower mortality rate in the FLS pathway, where the QALY gained increased substantially if we assumed that FLS is associated with 27% reduction in the risk of mortality. No apparent impact on incremental cost and QALY were captured by varying the FLS attendance rate, medication adherence, or proportion of treatment initiation (neither when halved nor doubled).

For other parameters, the incremental cost and/or QALY were significantly affected by varying the starting age, the proportion of females, fracture costs, baseline utility, and discount rate. Specifically, it can be seen that FLS was associated with higher total costs with an incremental cost of US$196 and an additional 0.012 QALY gained for elderly patients (80 years and older). For these patients, the ICER was estimated at US$16,451 per QALY gained, so the FLS was not cost-effective at the Chinese WTP threshold. In addition, we found increasing the proportion of women led to more costs saved and QALYs gained, but if we included only male patients, the FLS was still dominant. Moreover, the incremental cost declined markedly compared to the base case by halving the costs of fracture. The incremental QALY varied largely by increasing/decreasing baseline utility value. A 3% discount rate was associated with higher incremental costs and QALYs gained. Our results remained robust (even more economic benefits) when adjusting the prevalence of osteoporosis to more accurately reflect the prevalence of osteoporosis in our target populations.

Table 2. Incremental cost, incremental QALY, and incremental cost-effectiveness ratio (cost (USD) per QALY gained) of FLS compared with no-FLS for patients with a recent fracture

		Incremental cost (FLS-no FLS)	Incremental QALY (FLS-no FLS)	ICER
Base case		-501	0.095	Dominant
One-way sensitivity analyses (FLS-related parameters)				
FLS cost +100%		-367	0.097	Dominant
FLS cost +200%		-237	0.095	Dominant
Lower mortality rate for FLS pathway (OR=0.73)		-146	0.513	Dominant
Odds ratio of mortality +20%		-352	0.278	Dominant
FLS attendance rate -20%		-534	0.095	Dominant
FLS attendance rate +20%		-469	0.098	Dominant
Medication adherence in FLS -20%		-525	0.096	Dominant
Medication adherence in FLS +20%		-474	0.098	Dominant
One-way sensitivity analyses (other parameters)				
Age	Starting age: 60	-436	0.094	Dominant
	Starting age: 70	-161	0.041	Dominant
	Starting age: 75	-190	0.042	Dominant
	Starting age: 80	196	0.012	16,451
Gender	Proportion of women: 80%	-677	0.119	Dominant
	Proportion of women: 100%	-815	0.136	Dominant
	Proportion of women: 0%	-72	0.040	Dominant
Proportion of patients entering nursing home +100%		-531	0.098	Dominant
Proportion of patients entering nursing home -50%		-489	0.100	Dominant
Osteoporosis prevalence +20%		-638	0.095	Dominant
+40%		-771	0.106	Dominant
Nursing home cost -50%		-490	0.098	Dominant
Nursing home cost +50%		-525	0.096	Dominant
Fracture cost -50%		-175	0.098	Dominant
Fracture cost +50%		-831	0.097	Dominant
Drug cost -50%		-515	0.098	Dominant
Drug cost +50%		-477	0.096	Dominant
Baseline utility -20%		-507	0.077	Dominant
Baseline utility +20%		-500	0.116	Dominant
Treatment efficacy -20%		-507	0.096	Dominant
Treatment efficacy +20%		-507	0.099	Dominant
Discount rate: 3%		-660	0.128	Dominant
Discount rate: 0%		-1,032	0.207	Dominant

QALY quality adjusted life years, FLS fracture liaison service, ICER incremental cost-effectiveness ratio, OR odds ratio

DISCUSSION

This study suggests that FLS dominated no-FLS (more QALYs, less costs) in patients aged 65 years with a recent fracture at a one-off FLS cost of US$200 per patient in the Chinese context. Our findings were robust to numerous one-way sensitivity analyses. For the FLS to be cost-saving and cost-effective at the Chinese WTP, the maximum cost of FLS was US$958 and US$2,495, respectively. For elderly patients (80 years and older), the FLS was not cost-effective at the WTP threshold of US$10,500 per QALY gained. It can be explained that shorter life expectancy might render fewer opportunities for benefitting from the FLS.

An important implication of our study is that it seems potentially beneficial to implement FLS in China, given that it can prevent subsequent fractures, and also lead to lifetime cost savings. During the review process of our manuscript, a cost-effectiveness analysis of FLS in Taiwan was published [36]. Authors reported the benefits of FLS in patients with a hip fracture and concluded that post-fracture FLS care was cost-effective in comparison with usual care. In this study, the FLS cost was estimated to be US$133 per patient (a bit lower but still comparable to our assumption of US$200 per patient). If we apply their FLS cost, more favorable results were obtained (given the lower cost with a similar QALY). Of note, although results in the Taiwanese study were comparable to ours, there are many methodological differences. First, the Taiwanese study is a trial-based economic evaluation, which evaluated only the short-term benefit of FLS (2 years), while we performed a model-based economic evaluation to investigate the lifetime benefits of FLS. Second, the Taiwanese study used survival days as the effectiveness measurement, and reported the net monetary benefit at a specific WTP, instead of using QALY as effectiveness and presenting the incremental cost-effectiveness ratio (as in our study). Third, the Taiwanese study presented the effect of FLS only on patients with a hip fracture, and only hip refractures were counted. However, our study assumed a mix of various fractures at baseline, and subsequent hip, vertebral, and wrist fractures were all taken into account.

Additionally, another Chinese study (which is the first reporting on FLS for vertebral fractures in China: patients aged 50 years or older with a recent vertebral compression fracture were recruited) [49] also reported that the dedicated fracture service seems a solution for preventing subsequent fractures as well as decreasing healthcare costs, and concludes that the nationwide introduction of FLS in China is crucial. To ensure that patients with fractures are identified in a timely way and then invited to attend the FLS, building an FLS team with members from different fields of expertise, coordinated by a FLS coordinator, could be an alternative

approach and a starting point for China. This could be similar to the FLS team in Taiwan [36], which consists of orthopedic physicians, spine surgeons, geriatricians, endocrinologists, rheumatologists, family physicians, and coordinators. A Canadian study [50] indicated that hiring an osteoporosis coordinator to identify patients with a fragility fracture and to coordinate their education, assessment, referral, and treatment of underlying osteoporosis could reduce subsequent fractures and lead to net hospital cost-savings. Moreover, the wide gap between fragility fractures and secondary prevention is a worldwide concern, especially in the Asia-Pacific region, where the IOF combined 'Top Down' with 'Bottom Up' activities across 18 countries, including China, in 2020-2021, with the goal of increasing by 50% the number of patients reached, by fostering FLS and improving quality of its services, as shown on the CTF International Map of Best Practice. This also shows that the establishment and development of FLS would be an effective approach for China.

However, it should be noted that two systematic reviews revealed significant heterogeneity in the form of FLS and huge variation in its effects [51,52]. Wu et al [52] summarized 57 FLS-related high-quality studies published up to February 2017 and identified that FLS varied considerably in terms of the key persons coordinating the FLS (physician, nurse or other healthcare professional), setting (hospital, community), intensity (single, multiple) and duration (long or short term), which lead to further variation in clinical and economic benefits, and not all FLS could improve patient outcomes. This study also identified several components which contributed to FLS success, encompassing multidisciplinary involvement, being driven by a dedicated case manager, regular assessment and follow-up, multifaceted interventions and patient education. In addition, the Best Practice Framework [53] and eleven patient-level key performance indicators [54] developed by the IOF could serve as guidelines for China in the design of adequate FLS and improving the quality of existing services. Only FLS with relatively high-quality and sufficient services will lead to clinical and economic benefits and have the potential to be cost-effective.

The economic impact and cost-effectiveness of FLS studies (worldwide) published up to 2016 were summarized in a previous systematic review [11]. In line with several cost-effectiveness analyses [38,50,55,56], the FLS is a dominant (cost-saving) secondary fracture prevention strategy, compared to no-FLS or usual care. However, different assumptions were made in different studies, and our study has several strengths in comparison with other studies on the cost-effectiveness of FLS. First, the simulation model was adapted according to a previous Markov microsimulation model [12], which has been validated and applied in several prior studies [13,32,41,57]. Second, in our model, patients in the FLS pathway

distinguished attenders and non-attenders, which is in line with reality. This is an important differentiation, as the two groups might have different baseline fracture risk and treatment initiation rates, and the presence of FLS costs applied only to attenders. However, we found no previous studies differentiate between FLS attenders and non-attenders and made similar assumptions; this might overestimate the lifetime costs and effects in the FLS pathway and affect ICER estimation. Third, the time-dependent persistence rate for oral bisphosphates was assumed in our study, which is also revealed by real-world data [58] and applied in some cost-effectiveness analyses in osteoporosis;[13,34] however, some studies on the cost-effectiveness of FLS [55,56] just assumed a persistence rate of 100% or that the persistence rate remained the same for the whole duration of treatment. This is not realistic and might influence the result. Fourth, as we mentioned before, the effect of FLS on mortality is uncertain; therefore we did not include it in the base case. Although a lower mortality rate was assumed for FLS pathway in sensitivity analysis, we found no previous studies incorporated the effect of FLS on mortality. Fifth, the cost of side effects of oral bisphosphates treatment was incorporated in our model; these costs were not included in most studies on the cost-effectiveness of FLS.

The main limitations of our study derive primarily from a lack of precision with several important parameters, such as the FLS attendance rate, excess mortality, and persistence with treatment. The estimates from other countries (most are from developed countries) were used, as there was no relevant data for China. However, considering the heterogeneity in healthcare systems between countries, the direct transferability of clinical and economic evidence might limit the accuracy of cost-effectiveness analysis; therefore Chinese-specific real-world data is needed to confirm the results of our study and to better evaluate the cost-effectiveness of FLS in China. For future studies, we recommend collecting FLS-related real-world data, including the FLS attendance rate, FLS costs, initiation of treatment and adherence in FLS. In addition, country-specific fracture-related data such as fracture incidence, excess mortality, baseline utility (for patients with a recent fracture) and fracture disutility, fracture costs, and medication adherence are also important. Second, given that no relevant data was available for FLS no-attenders, it was assumed that the probability of treatment initiation and the treatment adherence rate were the same as for patients in the no-FLS pathway, and that FLS attenders and non-attenders had the same baseline fracture risk; these assumptions might not reflect the reality. Third, we assumed a mix of various fractures at baseline. The fracture type was not taken into account given the lack of relevant data (e.g., having osteoporosis and initiating medication according to the fracture type), therefore we did not estimate the benefits of FLS per baseline fracture type, although the ICER estimation might

depend on the baseline fracture type. Fourth, although a single utility of 0.7 was estimated based on the ICUROS study and assumed for patients with a recent fracture in our study, it might not represent the quality of life for different genders and age groups. Therefore, more detailed age- and gender-stratified baseline utilities should be applied to perform the estimation when relevant Chinese data are available. Fifth, a conservative assumption was made in our study that patients without osteoporosis did not initiate treatment. However, although according to some local guidelines (including Chinese guidelines), patients with grade 2 or 3 vertebral fractures should initiate treatment irrespective of their BMD status, we did not incorporate this in our model due to the lack of relevant data in China. We note that even if it were included, this would only lead to better economic benefit in FLS pathway. Sixth, when patients are discharged from hospital, most Chinese families prefer home care (entering a nursing home is not very common in China). The probability of entering a nursing home, and costs of nursing home and home care remain uncertain in China. Therefore, expert opinion and data from previous studies were used. Seventh, as we mentioned before, we conservatively did not assume the extra increased risk when new fractures occurred during simulation, underestimating the benefits of FLS. Eighth, one similar study [38] assigned the disutility for side effects of oral bisphosphonate like dyspepsia and osteonecrosis of jaw; this was not incorporated in our model considering the uncertainty of the data. Ninth, the probabilistic sensitivity analysis was not conducted given the distributional data for most parameters are lacking; accordingly, the uncertainty in cost-effectiveness estimates could not be explored.

CONCLUSION

FLS could potentially lead to lifetime cost-saving for patients who have experienced a fracture. Our study informs the potential cost-effectiveness of FLS and the knowledge gap in China; more future research incorporating Chinese-specific real-world data are needed to confirm the results of our study and to better evaluate the cost-effectiveness of FLS in China.

ELECTRONIC SUPPLEMENTARY MATERIAL

Appendix I: Osteoporosis-specific checklist – specific items to include when reporting economic evaluations on osteoporosis

Item	Item no.	Recommendation	Reported on page no. / line no.
Transition probabilities	1	Report the transition probabilities and how they were estimated (including increased fracture risk)	Method section + Table 1 Subtitle: Osteoporosis prevalence, fracture risk and mortality
Excess mortality after fractures	2	Describe approaches and data sources used for the excess mortality after fractures	Method section + Table 1 Subtitle: Osteoporosis prevalence, fracture risk and mortality
Fractures costs	3	Describe approaches and data sources used for fractures costs	Method section + Table 1 Subtitle: fracture cost
Fractures effects on utility	4	Describe approaches and data sources used for the effects of fractures on utility	Method section + Table 1 Subtitle: utility values
Treatment effect during treatment	5	Describe fully the methods used for the identification, selection, and synthesis of clinical effectiveness data (per fracture site)	Method section + Table 1 Subtitle: treatment effects; FLS effects
Treatment effect after discontinuation	6	Describe fully the methods used for the treatment effect after discontinuation	Method section Subtitle: treatment effects
Medication adherence	7	Describe approaches and data sources used for modeling medication adherence	Method section + Table 1 Subtitle: treatment effects; FLS effects
Treatment costs	8	Describe approaches and data sources used for therapy costs	Method section + Table 1 Subtitle: treatment effects; FLS effects
Treatment side effects	9	Describe approaches and data sources used for costs and utilities effects of adverse events	Method section + Table 1 Subtitle: treatment effects

Appendix II: CHEERS 2022 checklist—Items to include when reporting economic evaluations of health interventions

Section/item	Item No.	Guidance for reporting	Reported in section
Title			
Title	1	Identify the study as an economic evaluation and specify the interventions being compared.	Title section
Abstract			
Abstract	2	Provide a structured summary that highlights context, key methods, results, and alternative analyses.	Abstract section
Introduction			
Background and objectives	3	Give the context for the study, the study question, and its practical relevance for decision making in policy or practice.	Introduction section
Methods			
Health economic analysis plan	4	Indicate whether a health economic analysis plan was developed and where available.	Method section
Study population	5	Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).	Method section Subtitle: Model structure
Setting and location	6	Provide relevant contextual information that may influence findings.	Introduction and method section
Comparators	7	Describe the interventions or strategies being compared and why chosen.	Method section
Perspective	8	State the perspective(s) adopted by the study and why chosen.	Method section
Time horizon	9	State the time horizon for the study and why appropriate.	Method section
Discount rate	10	Report the discount rate(s) and reason chosen.	Method section Subtitle: Model structure
Selection of outcomes	11	Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	Method section Subtitle: Model structure
Measurement of outcomes	12	Describe how outcomes used to capture benefit(s) and harm(s) were measured.	Method section Subtitle: Model structure Outcomes and analyses
Valuation of outcomes	13	Describe the population and methods used to measure and value outcomes.	Method section Subtitle: Model structure Outcomes and analyses
Measurement and valuation of resources and costs	14	Describe how costs were valued.	Method section Subtitle: Fracture cost Treatment effects
Currency, price date, and conversion	15	Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	Method section Subtitle: Fracture cost
Rationale and description of model	16	If modeling is used, describe in detail and why used. Report if the model is publicly available and where it can be accessed.	Introduction and method section

(continued)

Section/item	Item No.	Guidance for reporting	Reported in section
Analytics and assumptions	17	Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.	Method section Subtitle: Treatment pathways Osteoporosis prevalence, fracture risk and mortality Utility values Treatment effects FLS effects
Characterising heterogeneity	18	Describe any methods used for estimating how the results of the study vary for subgroups.	Method section Subtitle: Outcomes and analyses
Characterising distributional effects	19	Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	NA
Characterising uncertainty	20	Describe methods to characterise any sources of uncertainty in the analysis.	Method section Subtitle: Outcomes and analyses
Approach to engagement with patients and others affected by the study	21	Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (such as clinicians or payers) in the design of the study.	NA
Results			
Study parameters	22	Report all analytic inputs (such as values, ranges, references) including uncertainty or distributional assumptions.	Method section and Table 1
Summary of main results	23	Report the mean values for the main categories of costs and outcomes of interest and summarise them in the most appropriate overall measure.	Results section and Table 2
Effect of uncertainty	24	Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.	Results section and Table 2
Effect of engagement with patients and others affected by the study	25	Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study	NA
Discussion			
Study findings, limitations, generalizability, and current knowledge	26	Report key findings, limitations, ethical or equity considerations not captured, and how these could affect patients, policy, or practice.	Discussion section
Other relevant information			
Source of funding	27	Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis	Source of funding section
Conflicts of interest	28	Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.	Conflicts of interest section

NA not applicable

REFERENCES

1. Bachour F, Rizkallah M, Sebaaly A et al (2017) Fracture liaison service: report on the first successful experience from the Middle East. *Arch Osteoporos* 12(1):4–9. doi: 10.1007/s11657-017-0372-x
2. Yu F, Xia W (2019) The epidemiology of osteoporosis, associated fragility fractures, and management gap in China. *Arch Osteoporos* 14(1). doi: 10.1007/s11657-018-0549-y
3. Zeng Q, Li N, Wang Q et al (2019) The prevalence of osteoporosis in China, a nationwide, multicenter DXA survey. *J Bone Miner Res* 34(10):1789–1797. doi: 10.1002/ jbmr.3757
4. Zhu Y, Xing X, Liu S, Chen W, Zhang X, Zhang Y (2020) Epidemiology of low-energy wrist, hip, and spine fractures in Chinese populations 50 years or older: a national population-based survey. *Medicine* (Baltimore) 99(5):e18531. doi: 10.1097/MD.0000000000018531
5. Xu L, Jan S, Chen M, Si L (2021) Sociodemographic and health system factors associated with variations in hospitalization costs for fractures in adults aged 45 years and over : a cross - sectional study of provincial health accounts in Jiangsu Province, China. *Arch Osteoporos*. Published online 1–9. doi: 10.1007/s11657-021-01009-1
6. Miller PD (2016) Underdiagnoses and undertreatment of osteoporosis: the battle to be won. *J Clin Endocrinol Metab* 101(3):852–859. doi: 10.1210/jc. 2015-3156
7. Kung AW, Fan T, Xu L et al (2013) Factors influencing diagnosis and treatment of osteoporosis after a fragility fracture among postmenopausal women in Asian countries: a retrospective study. *BMC Womens Health* 13(1):1. doi: 10.1186/1472-6874-13-7
8. Wang O, Hu Y, Gong S et al (2015) A survey of outcomes and management of patients post fragility fractures in China. *Osteoporos Int* 26(11):2631–2640. doi: 10.1007/s00198-015-3162-6
9. Li N, Hiligsmann M, Boonen A et al (2021) The impact of fracture liaison services on subsequent fractures and mortality: a systematic literature review and meta-analysis. *Osteoporos Int*. Published online. doi: 10.1007/s00198-021-05911-9
10. Chan DCD, Chang LY, Akesson KE et al (2018) Consensus on best practice standards for Fracture Liaison Service in the Asia- Pacific region. *Arch Osteoporos* 13(1). doi: 10.1007/s11657-018- 0463-3
11. Wu CH, Kao IJ, Hung WC et al (2018) Economic impact and cost-effectiveness of fracture liaison services: a systematic review of the literature. *Osteoporos Int* 29(6):1227–1242. doi: 10. 1007/s00198-018-4411-2
12. Hiligsmann M, Ethgen O, Bruyère O, Richy F, Gathon HJ, Reginster JY (2009) Development and validation of a Markov microsimulation model for the economic evaluation of treatments in osteoporosis. *Value Heal* 12(5):687–696. doi: 10.1111/j.1524-4733.2008.00497.x
13. Hiligsmann M, Reginster J (2019) Cost-effectiveness of gastroresistant risedronate tablets for the treatment of postmenopausal women with osteoporosis in France. *Osteoporos Int* 30(3):649–658. doi: 10.1007/s00198-018-04821-7
14. Hiligsmann M, Reginster J, Tosteson ANA et al (2019) Recommendations for the conduct of economic evaluations in osteoporosis: outcomes of an experts' consensus meeting organized by the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) and the US branch of the International Osteoporosis Foundation. *Osteoporos Int* 30(1):45–57. doi: 10.1007/s00198-018-4744-x

15. Husereau D, Drummond M, Augustovski F et al (2022) Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) statement: updated reporting guidance for health economic evaluations Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) statement: Updated Re. *J Med Econ* 25(S1):1–7. doi: 10.1080/13696998. 2021. 20147 21
16. Wang L, Yu W, Yin X et al (2021) Prevalence of osteoporosis and fracture in China: the China osteoporosis prevalence study. *JAMA Netw Open* 4(8):1–12. doi: 10.1001/ jamanetworkopen. 2021.21106
17. Liu Guoen. Chinese Guidelines for Pharmacoeconomic Evaluations 2020 [M]. Beijing: China Customs Press, 2020.
18. Wang J, Wang Y, Liu WD, Wang F, Yin ZS (2014) Hip fractures in Hefei, China: the Hefei osteoporosis project. *J Bone Miner Metab* 32(2):206–214. doi: 10.1007/s00774-013-0484-3
19. Bow CH, Cheung E, Cheung CL et al (2012) Ethnic difference of clinical vertebral fracture risk. *Osteoporos Int* 23(3):879–885. doi: 10.1007/s00198-011-1627-9
20. Lofthus CM, Frihagen F, Meyer HE, Nordsletten L, Melhuus K, Falch JA (2008) Epidemiology of distal forearm fractures in Oslo, Norway. *Osteoporos Int* 19(6):781–786. doi: 10. 1007/s00198-007-0499-5
21. Center JR, Bliuc D, Nguyen TV, Eisman JA (2007) Risk of subsequent fracture after low-trauma fracture in men and women. *J Am Med Assoc* 297(4):387–394. doi: 10.1001/jama.297.4.387
22. Kanis JA, Johnell O, Oden A, Jonsson B, De Laet C, Dawson A (2000) Risk of hip fracture according to the World Health Organization criteria for osteopenia and osteoporosis. *Bone* 27(5):585–590. doi: 10.1016/S8756-3282(00)00381-1
23. Vranken L, Wyers CE, van den Bergh JPW, Geusens PPMM (2017) The phenotype of patients with a recent fracture: a literature survey of the fracture liaison service. *Calcif Tissue Int* 101(3):248–258. doi: 10.1007/s00223-017-0284-1
24. Johnell O, Kanis JA, Oden A et al (2005) Predictive value of BMD for hip and other fractures. *J Bone Miner Res* 20(7):1185–1194. doi: 10.1359/JBMR.050304
25. Marshall D, Johnell O, Wedel H (1996) Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. *Br Med J* 312(7041):1254–1259. doi: 10. 1136/bmj.312.7041.1254
26. Bliuc D, Nguyen ND, Milch VE, Nguyen TV, Eisman JA, Center JR (2009) Mortality risk associated with low-trauma osteoporotic fracture and subsequent fracture in men and women. *JAMA-J Am Med Assoc* 301(5):513–521. doi: 10.1001/jama.2009.50
27. Qu B, Ma Y, Yan M et al (2014) The economic burden of fracture patients with osteoporosis in western China. *Osteoporos Int* 25(7):1853–1860. doi: 10.1007/s00198-014-2699-0
28. Si L, Winzenberg TM, Chen M, Jiang Q, Neil A, Palmer AJ (2016) Screening for osteoporosis in Chinese post-menopausal women: a health economic modelling study. *Osteoporos Int* 27(7):2259–2269. doi: 10.1007/s00198-016-3502-1
29. Svedbom A, Borgström F, Hernlund E et al (2018) Quality of life after hip, vertebral, and distal forearm fragility fractures measured using the EQ-5D-3L, EQ-VAS, and time-trade-off: results from the ICUROS. *Qual Life Res* 27(3):707–716. doi: 10.1007/s11136-017-1748-5
30. National Institute for Clinical Excellence and Health (2017)Bisphosphonates for treating osteoporosis. Technology appraisal guidance [TA464]. Available from https:// www. nice. org. uk/ guida nce/ ta464/. Access 24 Sep 2021

31. National Development and Reform Commission of China (2018). Available from http:// www. ndrc. gov. cn/. Access 24 Sep 2021
32. Hiligsmann M, Williams SA, Fitzpatrick LA, Silverman SS, Weiss R, Reginster JY (2019) Cost-effectiveness of sequential treatment with abaloparatide vs. teriparatide for United States women at increased risk of fracture. *Semin Arthritis Rheum*. 49(2):184–196. doi: 10.1016/j. semar thrit. 2019. 01. 006
33. Mori T, Crandall CJ, Ganz DA (2017) Cost-effectiveness of denosumab versus oral alendronate for elderly osteoporotic women in Japan. *Osteoporos Int* 28(5):1733–1744. doi: 10. 1007/s00198-017-3940-4
34. Chandran M, Ganesan G, Tan KB, Reginster JY, Hiligsmann M (2021) Cost-effectiveness of FRAX®-based intervention thresholds for management of osteoporosis in Singaporean women. *Osteoporos Int* 32(1):133–144. doi: 10.1007/s00198-020-05536-4
35. Wu CH, Te TuS, Chang YF et al (2018) Fracture liaison services improve outcomes of patients with osteoporosis-related fractures: a systematic literature review and meta-analysis. *Bone* 111(138):92–100. doi: 10.1016/j.bone.2018.03.018
36. Chien LN, Li YF, Yang R Sen et al (2022) Real-world cost-effectiveness analysis of the fracture liaison services model of care for hip fracture in Taiwan. *J Formos Med Assoc* 121(1):425–433. doi: 10.1016/j. jfma.2021.05.028
37. Yong JHE, Masucci L, Hoch JS, Sujic R, Beaton D (2016) Cost-effectiveness of a fracture liaison service—a real-world evaluation after 6 years of service provision. *Osteoporos Int* 27(1):231–240. doi: 10.1007/s00198-015-3280-1
38. Solomon DH, Patrick AR, Schousboe J, Losina E (2014) The potential economic benefits of improved post-fracture care: a cost-effectiveness analysis of a fracture liaison service in the US health-care system. *J Bone Miner Res* 29(7):1667–1674. doi: 10.1002/jbmr.2180
39. You R, Zhang Y, Wu DBC et al (2020) Cost-effectiveness of zoledronic acid versus oral alendronate for postmenopausal osteoporotic women in China. *Front Pharmacol* 11(April):1–10. doi: 10. 3389/fphar.2020.00456
40. Melton LJ, Thamer M, Ray NF et al (1997) Fractures attributable to osteoporosis: report from the national osteoporosis foundation. *J Bone Miner Res* 12(1):16–23. doi: 10.1359/jbmr.1997. 12.1.16
41. Hiligsmann M, Reginster JY (2011) Cost effectiveness of denosumab compared with oral bisphosphonates in the treatment of post-menopausal osteoporotic women in Belgium. *Pharmacoeconomics* 29(10):895–911. doi: 10.2165/11539980-000000000-00000
42. Kanis JA, Oden A, Johnell O, De Laet C, Jonsson B (2004) Excess mortality after hospitalisation for vertebral fracture. *Osteoporos Int* 15(2):108–112. doi: 10.1007/s00198-003-1516-y
43. Kanis JA, Oden A, Johnell O, De Laet C, Jonsson B, Oglesby AK (2003) The components of excess mortality after hip fracture. *Bone* 32(5):468–473. doi: 10.1016/S8756-3282(03)00061-9
44. YZ M, YP W, Q L (2018) Chinese guideline for diagnosis and treatment of osteoporosis (2018). *Chinese J Osteoporos* 24(December):1541
45. Hiligsmann M, Evers SM, Ben Sedrine W et al (2015) A systematic review of cost-effectiveness analyses of drugs for postmenopausal osteoporosis. *Pharmacoeconomics* 33(3):205–224. doi: 10. 1007/s40273-014-0231-1
46. Ström O, Landfeldt E, Garellick G (2015) Residual effect after oral bisphosphonate treatment and healthy adherer effects—the Swedish adherence register analysis (SARA). *Osteoporos Int* 26(1):315–325. doi:

10.1007/s00198-014-2900-5

47. Cramer JA, Roy A, Burrell A et al (2008) Medication compliance and persistence: terminology and definitions. *Value Heal* 11(1):44–47. doi: 10.1111/j.1524- 4733.2007.00213.x
48. datacommons.org. Gross domestic product per capita in People's Republic of China. Available from https:// datac ommons. org/ place/ count ry/ CHN. Access 24 Sep 2021
49. Wong RMY, Ko SY, Chau WW et al (2021) The first reported fracture liaison service (FLS) for vertebral fractures in China: is muscle the missing gap? *Arch Osteoporos* 16(1):1–6. doi: 10. 1007/s11657-021-01036-y
50. Sander B, Elliot-Gibson V, Beaton DE, Bogoch ER, Maetzel A (2008) A coordinator program in post-fracture osteoporosis management improves outcomes and saves costs. *J Bone Jt Surg – Ser A* 90(6):1197–1205. doi: 10.2106/JBJS.G.00980
51. Ganda K, Puech M, Chen JS et al (2013) Models of care for the secondary prevention of osteoporotic fractures: a systematic review and meta-analysis. *Osteoporos Int* 24(2):393–406. doi: 10.1007/s00198-012-2090-y
52. Wu C, Chen C, Chen P et al (2018) Identifying characteristics of an effective fracture liaison service: systematic literature review. *Osteoporos Int* 29(5):1023–1047. doi: 10.1007/s00198-017- 4370-z
53. International Osteoporosis Foundation. Best practice framework for fracture liaison services. Available from https:// www. Capture the fracture. org/ best- practice- frame work. Access 24 Sep 2021
54. Javaid MK, Sami A, Lems W et al (2020) A patient-level key performance indicator set to measure the effectiveness of fracture liaison services and guide quality improvement: a position paper of the IOF Capture the Fracture Working Group, National Osteoporosis Foundation and Fragility Fracture. *Osteoporos Int* 31(7):1193–1204. doi: 10.1007/s00198-020-05377-1
55. Majumdar SR, Lier DA, Rowe BH et al (2011) Cost-effectiveness of a multifaceted intervention to improve quality of osteoporosis care after wrist fracture. *Osteoporos Int* 22(6):1799–1808. doi: 10.1007/s00198-010-1412-1
56. McLellan AR, Wolowacz SE, Zimovetz EA et al (2011) Fracture liaison services for the evaluation and management of patients with osteoporotic fracture: a cost-effectiveness evaluation based on data collected over 8 years of service provision. *Osteoporos Int* 22(7):2083–2098. doi: 10. 1007/s00198-011-1534-0
57. Hiligsmann M, Maggi S, Veronese N, Sartori L, Reginster JY (2021) Cost-effectiveness of buffered soluble alendronate 70 mg effervescent tablet for the treatment of postmenopausal women with osteoporosis in Italy. *Osteoporos Int* 32(3):595–606. doi: 10.1007/s00198-020-05802-5
58. Fatoye F, Smith P, Gebrye T, Yeowell G (2019) Real-world persistence and adherence with oral bisphosphonates for osteoporosis: a systematic review. *BMJ Open* 9(4):1–18. doi: 10. 1136/bmjop en-2018-027049


8

CHAPTER 9

Cost-effectiveness analysis of fracture liaison services: a Markov model using Dutch real-world data

Submitted as:
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ABSTRACT

Purpose: The objective of this study was to investigate the lifetime cost-effectiveness of a fracture liaison service (FLS) compared to no-FLS in the Netherlands from a societal perspective and using real-world data.

Methods: Annual fracture incidence, treatment scenarios as well as treatment initiation in the years 2017-2019 were collected from a large secondary care hospital in the Netherlands. An individual-level, state transition model was designed to simulate lifetime costs and quality-adjusted life years (QALYs). Treatment pathways were differentiated by gender, presence of osteoporosis and/or prevalent vertebral fracture, and treatment status. Results were presented as incremental cost-effectiveness ratios (ICER). Both one-way and probabilistic sensitivity analyses were conducted.

Results: For patients with a recent fracture aged 50 years and older, the presence of an FLS was associated with a lifetime €45 higher cost and 0.11 additional QALY gained leading to an ICER of €409 per QALY gained, indicating FLS was cost-effective compared to no-FLS at the Dutch threshold of €20,000/QALY. The FLS remained cost-effectiveness across different age categories. Our findings were robust in all one-way sensitivity analyses, the higher the treatment initiation rate in FLS, the greater the cost-effective of FLS. Probabilistic sensitivity analyses revealed that FLS was cost-effective in 90% of the simulations at the threshold of €20,000/QALY, with women 92% versus men 84% by gender.

Conclusion: This study provides the first health-economic analysis of FLS in the Netherlands, suggesting the implementation of FLS could lead to lifetime health-economic benefits.

Keywords: Cost-effectiveness, Fracture liaison services, Osteoporosis, Fracture.

INTRODUCTION

Fractures are associated with pain, disability, loss of independence, reduced quality of life, increased subsequent fracture risk and excess mortality, resulting in a substantial and escalating healthcare and financial burden for the society. In the Netherlands, as reported by the SCOPE (Scorecard for Osteoporosis in Europe) 2021 study [1], the number of fragility fractures was estimated at 99,600 in 2019, corresponding to 273 fractures per day and 11 fractures per hour, accounting for approximately 1.8% of healthcare spending (i.e., €1.4 billion out of €75.0 billion in 2019). The projected number of fragility fractures in 2034 is 137,000, suggesting an increase of 37.4% over a 15-year interval. A prior fracture is a strong predictor of subsequent fracture as reported by a Dutch study [2] with the relative risk of subsequent fracture ranging from 5.3 within 1 year to 1.4 between 6 and 10 years after the first fracture in postmenopausal women older than 50 years compared to those without a recent fracture. Recurrent fractures are partly preventable by drug therapy and to a lesser extent by non-pharmacological interventions such as lifestyle changes. Although the high risk of subsequent fractures was acknowledged, the magnitude of drug treatment gap (defined as the percentage of persons who are eligible for treatment but not receiving a treatment) is reported to be highly variable throughout Europe, ranging between 25 and 95% [3], which was estimated to vary from 60% to 72% in the Dutch population [4]. In response to the treatment gap, post-fracture care programs such as fracture liaison services (FLS) were introduced, which is considered as the most effective organizational structure for secondary fracture prevention.

FLSs were first reported by McLellan et al. in 2003 [5] and internationally endorsed by the International Osteoporosis Foundation (IOF) [6], the European Alliance of Associations for Rheumatology (EULAR) [7], the multidisciplinary Fragility Fracture Network (FFN) [8], and the American Society of Bone and Mineral Research ASBMR) [9]. In the Netherlands, the guideline on osteoporosis and fracture prevention (2011) [10] recommends to evaluate all fracture patients of 50 years or older in preferentially a nurse-led structured program. The first FLS-related initiatives and outcomes were reported from Groningen in 2004 [11], and the FLS in VieCuri Medical Centre of Venlo was launched in 2008. To optimize FLS initiatives and facilitate the communication between healthcare professionals, a formal national network (Dutch Osteoporosis Nurses Association VF&O) [12] was launched in 2008, and a five-step approach has been proposed by van den Bergh et al. [13] in 2012 to strive for standardized FLS care. With emphasizing the importance of initiating FLS in hospitals by several Dutch scientific committees, there were 90 FLS and 95 osteoporosis nurses registered in the database of VF&O

as reported by a study published in 2015 [14].

However, the intensity and quality of implementation of FLS vary between hospitals and countries [15,16]; patient identification and selection differed markedly among FLS in terms of proportion of in- and outpatients with a fracture included, age, the inclusion of women and/or men, and fracture site (any fracture or only patients with a nonvertebral fracture) [17], potentially leading to different clinical and economic outcomes. Worldwide, with the increasing implementation of FLS, the effectiveness and efficacy of FLS was reported in many countries and summarized in several systematic reviews and meta-analyses [18-20], suggesting that FLS care is generally (cost-)effective for healthcare systems by improving patient care, reducing secondary fracture rates, and ultimately decreasing the burden on the healthcare system and society. However, we found most published economic evaluations used simulation model assessing the cost-effectiveness of FLS without use of real-world data. Considering most Dutch hospitals initiated an FLS, its cost-effectiveness remains unknown. The objective of this study was therefore to investigate the lifetime societal cost-effectiveness of an FLS compared to no-FLS in the Netherlands from a societal perspective using real-world data whenever possible.

METHODS

We adapted a previously validated Markov microsimulation model [21] to estimate the cost-effectiveness of FLS compared to no-FLS for patients with a recent fracture from the Dutch societal perspective with a lifetime horizon. Treatment pathways in our model were based on Dutch guidelines on osteoporosis and fracture prevention [10,22], recommending anti-osteoporosis drug treatment in those having osteoporosis (bone mineral density BMD) T-score ≤ -2.5 standard deviations at the lumbar spine, femoral neck or total hip, and/or a clinical or prevalent vertebral fracture (VF) (>25% reduction in vertebral body height at the anterior, mid, or posterior location) [23]) combined with a BMD T-score ≤ -1.

The model was built up using TreeAge Pro 2022 software (TreeAge Pro Inc., Williamston, MA, USA) and adhered to the osteoporosis-specific guideline of the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases and the US branch of the International Osteoporosis Foundation (IOF-ESCEO) for the design, conduct and reporting of economic evaluations [24], and also to the Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) Statement [25]. Details of these two

checklists can be found in Appendix I and II. A description of the source of real-world data, target population, model structure and input data is provided here below. Table 1 presents key model input parameters.

Real-world FLS setting

Our model structure was adapted to a real-world FLS setting (VieCuri Medical Centre, a large secondary care hospital in the Netherlands) where a nurse, specialized in osteoporosis, invites patients aged 50 years and older, who visited the emergency department because of a recent fracture, to the FLS. Details of this FLS care pathway were published previously [26]. In brief, patients attending the FLS were scheduled for an outpatient visit including dual X-ray absorptiometry (DXA) measurement to assess BMD, prevalent VF based on vertebral fracture assessment (VFA), and a blood test. Lifestyle advice and drug treatment (when applicable), based on presence of osteoporosis and/or prevalent VF according to Dutch guideline [10].

As part of the FLS care, real-world data in this study were collected in the years 2017-2019 including annual fracture incidence (by age, gender, and fracture type categories), treatment scenarios (pharmacy data) as well as treatment initiation after (2017-2019) the implementation of FLS from the VieCuri Medical Centre.

Population

Analyses were conducted in patients with an index hip, clinical vertebral (CV) or non-hip non-vertebral (NHNV) fracture aged 50 years and older. Both genders were included considering differences in various model input parameters. Based on 3-year (2017-2019) data from VieCuri Medical Centre, the population in our study entered the model with a distribution of starting age (i.e., 11%, 13%, 13%, 13%, 13%, 11%, 10%, 8% and 5% patients had a starting age between 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80-84, 85-89, and 90+ years, respectively), with women accounting for 67%.

Model structure and treatment pathways

The model structure combines a decision tree with a Markov model. The decision tree (Figure 1) distinguished groups by the presence of FLS, gender, presence of osteoporosis or VF and treatment with anti-osteoporosis drugs in this with osteoporosis and/or VF (osteoporosis and/or VF + treatment, osteoporosis and/or VF + no treatment, no osteoporosis & no VF) that is in consistent with treatment indications suggested by Dutch guideline [10]. Patients entered both FLS and no-FLS branches have identical gender distribution and prevalence of osteoporosis and/or VF. A higher proportion of treatment initiation was modelled for FLS (40%)

compared to no-FLS (5%) branch based on real-world data [27] and expert opinion, respectively.

Of note, all patients (the combination of attenders and non-attenders) were included in the FLS branch, lower mortality and subsequent fracture risk were assumed for attenders with a major/hip fracture according to a Dutch study [26], details can be found in the description of model input data section.

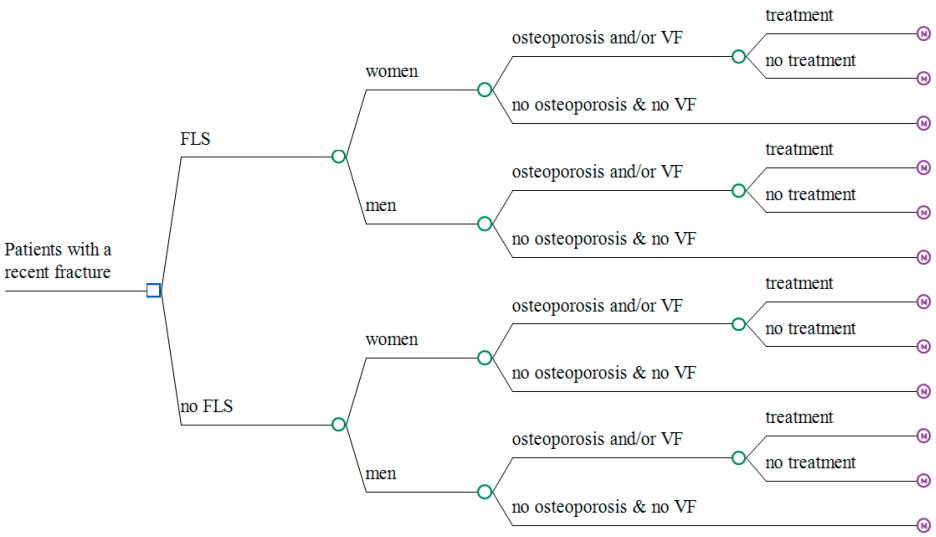


Figure 1. Patient pathways for FLS and no-FLS group
(CUA cost-utility analysis, FLS fracture liaison services, VF vertebral fracture)

After allocating persons to sub-branches of the decision tree, patients entered the Markov model (Figure 2) one-by-one to capture the long-term costs and health benefits (expressed as quality-adjusted life year, QALY). An individual-level state transition model was used to track individual trajectories (incorporating the impact of history on future events), and tracker variables were used to record the number and type of subsequent fractures. Each patient began in the 'index fracture' state (a recent fracture) and had a probability of having a new (subsequent) hip fracture, clinical CV, or NHNV fracture or of dying. Patients in a subsequent fracture state can stay in the same fracture state if they re-fracture, change to another fracture state, die or change in the next cycle to the post subsequent fracture state. Patients in a post subsequent fracture state might have another fracture at any site, move to 'recent fracture', or die. We used a lifetime horizon and a 6-month cycle as recommended by IOF-ESECO guideline [24]. Discount rate of 4% and 1.5%

was used as recommended by the Dutch guideline for economic evaluations in healthcare [28] for costs and QALYs, respectively.

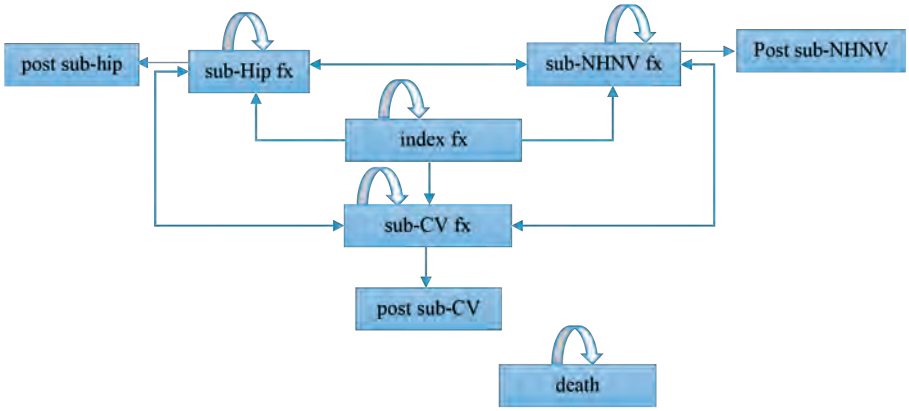


Figure 2. The structure of Markov model
(fx fracture, sub subsequent, CV fx clinical vertebral fracture, NHNV fx non-hip non-vertebral fracture)

Model input data

Osteoporosis, clinical or prevalent vertebral fracture, fracture risk

The prevalence of osteoporosis and/or clinical or prevalent VF was estimated at 49% based on a Dutch study [27] which included consecutive patients aged 50 years and older with a recent non-VF visiting the FLS of VieCuri Medical Centre.

When entering the Markov model, the annual incidence of hip, CV fracture, and NHNV fracture in the general Dutch population were obtained and estimated from fracture data in VieCuri Medical Centre in the years 2017-2019. Considering the presence of osteoporosis and/or previous fracture without treatment is associated with higher subsequent fracture risk, adjustment were made to reflect the increased fracture risk. Time-dependent relative risk (RR) of subsequent fracture was modelled as reported in Dutch studies [2,29], i.e. the pooled RR for women was 2.1 (1.7-2.6), ranging from 5.3 (4.0-6.6) within 1 year to 1.4 (1.0-1.8) within 6-10 years; 1.5 times increased risk in men relative to women was modelled; no increased risk was assumed (RR=1) after 10 years for both genders. In addition, to take into account the impact of osteoporosis, the increased risk of subsequent fracture for persons with osteoporosis relative to persons without osteoporosis was also modelled. Specifically, for patients with osteoporosis aged 50-59, 60-69, 70-79, and over 80 years, the RRs of having a hip fracture were estimated at 5.66, 3.39,

2.25, and 1.57, respectively. The RR for CV fracture ranged from 2.68 at 50 years to 1.51 at 100 years, which were slightly higher than the RRs for NHNV fracture [30]. Considering osteoporosis is not the only attributable factor for fractures, to avoid over-adjustment, age- and gender-specific osteoporosis attribution probability was modelled [31].

Mortality

Baseline mortality data for the age- and gender-stratified Dutch population was obtained from the official registry (Centraal Bureau voor de Statistiek CBS) in the years 2017-2019 [32]. We further modelled lifetime increased mortality risk after hip and CV fracture in line with a meta-analysis [33] with the RR of 2.9 and 3.76 for women and men, respectively. Considering excess mortality may also be attributable to other factors such as comorbidities, we conservatively assumed that only 25 % of the excess mortality following a hip or CV fracture could be attributable to the fractures themselves [34,35].

Fracture cost

In line with Dutch guideline for economic evaluations in healthcare [28], a societal perspective for the cost estimation was used including both direct and indirect costs. The direct gender-stratified hip, CV, and NHNV fracture costs were estimated from a Dutch study based on claims data (all costs were expressed in €2020) [36]. Hip fractures are also associated with long-term nursing home costs, the yearly cost was estimated at €25,741 (Dutch standard daily nursing home cost*365), and an average 21% of patients in the years 2017-2019 were institutionalized following the hip fracture as reported by Dutch Hip Fracture Audit [37]. To estimate productivity costs of employed persons sustained a fracture, maximum two-month work absence were assumed according to the friction cost method as suggested by the Dutch guideline for economic evaluations in healthcare [28]. Based on the work-related absence rate estimated for different fracture types (hip 0.99, CV 0.79, NHNV 0.64) in a previous study [38] and the average annual salary in the Netherlands in 2020 [39], the productivity costs for patients with a hip (CV, NHNV) fracture aged 50-54, 55-59, and 60-64 years were estimated at €7,927 (€6,325, €5,124), €7,717 (€6,166, €4,995), and €7,319 (€5,841, €4,732), respectively. Productivity costs were not included for patients aged over 65 years.

Utility values

The age- and gender-stratified baseline utilities in patients with a recent fracture were obtained from a recently published Dutch study [40] which estimated age- and gender-specific health state utility values (HSUV) by the EuroQol 5-dimension (EQ-5D) questionnaire in patients visiting the FLS in VieCuri Medical Centre. The

utility ranged from 0.813 (50 years) to 0.665 (90 years) in women, which was relatively higher in men, ranging from 0.855 to 0.743. The effects of hip and clinical vertebral fractures on utility for the first and subsequent years were derived from the large International Costs and Utilities Related to Osteoporotic Fractures Study (ICUROS) study [41]. We obtained disutility multipliers for NHNV fracture from a previous cost-effectiveness analysis [42] since NHNV fractures were not included in the ICUROS study.

Drug treatment effects and costs

As we mentioned before, in our model, 40% and 5% of patients in FLS and no-FLS branch initiated drug therapy based on real-world data [27] and expert opinion, respectively. When relating the prevalence of osteoporosis and/or clinical or prevalent VF to these treatment initiation rates, it can be estimated that 80% (40%/49% = 80%) and 10% (5%/49%=10%) of patients with osteoporosis and/or clinical or prevalent VF received drug therapies in FLS and no-FLS branches, respectively. These data were used in decision tree.

Treatment scenarios were obtained from pharmacy data in VieCuri Medical Centre, i.e. for patients initiated drug therapy, 70%, 13.0%, 14.3% and 2.7% patients received oral bisphosphonates (alendronate, risedronate, ibandronate), zoledronic acid, denosumab and teriparatide, respectively.

The pooled treatment efficacy data for oral bisphosphonates were obtained from a report by the National Institute for Clinical Health and Excellence (NICE) [43], suggesting a RR of 0.67 (95% CI: 0.48-0.96), 0.45 (95% CI: 0.31-0.65), 0.81 (95% CI: 0.46-1.44) for hip, CV, and NHNV fracture, respectively. Treatment efficacy data for zoledronic acid were extracted from HORIZON Pivotal Fracture Trial [44], reporting a RR of 0.59 (95% CI: 0.42-0.83), 0.23 (95% CI: 0.14-0.37), 0.75 (95% CI: 0.64-0.87) for hip, CV, and NHNV fracture, respectively. Aligned with a recent review of cost-effectiveness of denosumab [45], efficacy data from the FREEDOM study [46] were used, suggesting that denosumab resulted in a RR of 0.6 (95% CI: 0.37-0.97), 0.31 (95% CI: 0.26-0.41), 0.8 (95% CI: 0.67-0.95) for hip, CV, and NHNV fracture, respectively. Treatment efficacy for teriparatide were obtained from a systematic review, reporting 0.36 (95% CI: 0.15-0.81), 0.23 (95% CI: 0.17-0.32), 0.57 (95% CI: 0.54-0.74) for hip, CV, and NHNV fracture, respectively.

Treatment duration in our model was consistent with the recommendation of Dutch guidelines [10,47], namely maximum 5-year therapy with oral bisphosphonates, 3-year with zoledronic acid, 5-year with denosumab, and 2-year treatment with teriparatide followed by 3-year oral bisphosphonates. For patients initiated

treatment with oral bisphosphonates or zoledronic acid, after medication discontinuation, a linear decrease of the effects for three years (offset time) was assumed as suggested by clinicians. Considering the rebound effect, one-year offset time after discontinuing denosumab was assumed. We assumed the effect of teriparatide remained once oral bisphosphonates initiated, a linear decrease of the effects for three years was assumed after discontinuing oral bisphosphonates.

Given treatment efficacy can be largely affected by persistence, we incorporated persistence rates in the study. The persistence rate of oral bisphosphonates was obtained from a Dutch study [48], reporting 75%, 61.3%, and 45.3% after 1, 3, and 5 years, respectively. The Kaplan-Meier curve in this study indicated an approximately linear decrease in persistence over time, we therefore estimated the persistence rates after the treatment of 6 months, 2 years, and 4 years manually. Persistence rates of zoledronic acid after 1, 2, and 3 years were obtained from VieCuri Medical Centre (in the year 2018) as 100%, 69%, and 48%, respectively. The long-term persistence rates of denosumab in the Netherlands is unknown; persistence rates up to 3 years was extracted from the same systematic review [49], suggesting 100%, 81%, 67%, 55%, 35%, and 26% after 6, 12, 18, 24, 30, and 36 months, respectively. We assumed the persistence remained unchanged after 36 months given the unavailability of relevant data. Two-year persistence of 75% with teriparatide was obtained from a Dutch study [50], the persistence with sequential oral bisphosphonates was assumed the same as the first 3-year monotherapy with oral bisphosphonates.

Treatment costs in our study refer to drug costs and related side effect costs. Annual drug costs for oral bisphosphonates, zoledronic acid, denosumab, and teriparatide were retrieved from Dutch official data [51], it was estimated at €20, €258, €400 and €3,480 (in the year 2020), respectively. For side effect costs, it was assumed that patients initiated treatment requiring 0.041 extra GP consultations during the first cycle (6 months) and 0.021 GP consultations during the following cycles in line with a previous study [52]; the average standard consulting cost of the general practitioner was estimated at €34.74 (in 2020).

FLS-related model input data

Given all patients attending the FLS were registered in the diagnosis treatment combination (DBC) system (besides the fracture DBC, all FLS attenders have an osteoporosis DBC), we therefore used the mean DBC price (€450 in 2020) in the Netherlands for FLS visit [53] in our analysis. Related to FLS visit, the DBC price covers the cost of DXA, lab test, VFA, fall risk assessment etc., extra GP consultation in the follow-up was also included (once per year).

Compared to no-FLS branch, higher treatment initiation rate (40% vs. 5%) and greater treatment persistence (57% vs. 34.1%, deriving from a literature review and meta-analysis [19]) were modelled for FLS branch. In addition, we modelled a lower mortality (hazard ratio 0.43; 95% CI, 0.34-0.56) and subsequent fracture (subdistribution hazard ratio 0.80; 95% CI, 0.60-1.07) risk for FLS attenders with a hip or clinical vertebral fracture as reported by a Dutch study [26], no effect was assumed for patients with NHNV fracture.

Table 1. key model input data

Parameter	Data		Data source
	Women	Men	
Gender	67%	33%	VieCuri, 2017-2019
A distribution of starting age	11.5% (52 years), 13.4% (57 years), 13.1 (62 years), 13.4% (67 years), 13.0% (72 years), 11.4% (77 years), 10.5% (82 years), 8.6% (87 years), 5.1% (92 years)		VieCuri, 2017-2019
Osteoporosis			
Prevalence of osteoporosis and/ or C/PVF	49%		[27]
Relative risk of having fracture for individuals with osteoporosis			
Hip	5.66 (50-59 years), 3.39 (60-69 years), 2.25 (70-79 years), 1.57 (80+ years)		[30]
CV	2.68 (50-59 years), 2.18 (60-69 years), 1.77 (70-79 years), 1.51 (80+ years)		
NHNV	2.25 (50-59 years), 1.90 (60-69 years), 1.61 (70-79 years), 1.42 (80+ years)		
Osteoporosis attribution probability			
Hip	0.80 (50-64 years), 0.90 (65-84 years), 0.95 (85+ years)	0.60 (50-64 years), 0.80 (65-84 years), 0.85 (85+ years)	[31]
CV	0.80 (50-64 years), 0.90 (65-84 years), 0.95 (85+ years)	0.70 (50-64 years), 0.90 (65-84 years), 0.90 (85+ years)	
NHNV	0.575 (50-64 years), 0.60 (65-84 years), 0.70 (85+ years)	0.275 (50-64 years), 0.375 (65-84 years), 0.45 (85+ years)	
Fracture risk			
Fracture Incidence (annual rate per 1000 person-years)			
Hip	0.266 (50-54 years), 0.587 (55-59 years), 1.066 (60-64 years), 1.504 (65-69 years), 2.450 (70-74 years), 4.183 (75-79 years), 7.814 (80-84 years), 16.727 (85-89 years), 21.645 (90+ years)	0.352 (50-54 years), 0.320 (55-59 years), 0.623 (60-64 years), 0.900 (65-69 years), 1.257 (70-74 years), 3.082 (75-79 years), 4.450 (80-84 years), 8.833 (85-89 years), 17.704 (90+ years)	VieCuri, 2017-2019
CV	0.433 (50-54 years), 0.652 (55-59 years), 1.213 (60-64 years), 1.820 (65-69 years), 2.404 (70-74 years), 3.578 (75-79 years), 5.113 (80-84 years), 4.568 (85-89 years), 4.456 (90+ years)	0.480 (50-54 years), 0.735 (55-59 years), 0.762 (60-64 years), 0.825 (65-69 years), 1.437 (70-74 years), 1.706 (75-79 years), 2.383 (80-84 years), 3.296 (85-89 years), 2.379 (90+ years)	
NHNV	12.476 (50-54 years), 16.053 (55-59 years), 17.424 (60-64 years), 20.809 (65-69 years), 22.365 (70-74 years), 24.896 (75-79 years), 27.800 (80-84 years), 32.475 (85-89 years), 36.172 (90+ years)	10.864 (50-54 years), 10.405 (55-59 years), 10.198 (60-64 years), 8.811 (65-69 years), 9.348 (70-74 years), 9.218(75-79 years), 11.036 (80-84 years), 12.915 (85-89 years), 15.362 (90+ years)	

Table 1. (continued)

Parameter	Data		Data source
	Women	Men	
Relative risk of having a subsequent fracture	Pooled RR: 2.1 (1.7-2.6) 0-1 year 5.3 (4.0-6.6) 2-5 years 2.8 (2.0-3.6) 6-10 years 1.4 (1.0-1.8)	Pooled RR: 3.15 (2.55-3.9) 0-1 year 7.95 (6.0-9.9) 2-5 years 4.2 (3.0-5.4) 6-10 years 2.1 (1.5-2.7)	[2]
Mortality			
All-cause mortality (per 1000) for the general population	2.2 (50-54 years), 3.8 (55-59 years), 6.1 (60-64 years), 9.2 (65-69 years), 14.8 (70-74 years), 25.6 (75-79 years), 48.9 (80-84 years), 99.8 (85-89 years), 191.4 (90-94 years), 329.3 (95+ years)	2.9 (50-54 years), 5.0 (55-59 years), 8.3 (60-64 years), 13.5 (65-69 years), 21.9 (70-74 years), 37.9 (75-79 years), 70.1 (80-84 years), 132.5 (85-89 years), 227.3 (90-94 years), 366.4 (95+ years)	[32]
Excess mortality	2.90 (2.52-3.34)	3.76 (3.20-4.42)	[33]
Cost of a first fracture (estimated in €2020)			
Hip	18,848	16,408	[36]
Hip, yearly long-term cost	5,406		Dutch standard daily nursing home cost*365*21%
CV	12,167	9,965	[36]
NHNV	6,615	6,210	[36]
Productivity cost (estimated in €2020)			
Hip	7,927 (50-54 years), 7,727 (55-59 years), 7,319 (60-64 years)		[38,39]
CV	6,325 (50-54 years), 6,166 (55-59 years), 5,841 (60-64 years)		
NHNV	5,124 (50-54 years), 4,995 (55-59 years), 4,732 (60-64 years)		
Health state utility values			
Baseline (patients with a recent fracture)	0.813 (50-59 years), 0.813 (60-69 years), 0.809 (70-79 years), 0.665 (80+ years)	0.855 (50-59 years), 0.821 (60-69 years), 0.841 (70-79 years), 0.743 (80+ years)	[40]
Hip (1st year/subs. years)	0.55 (0.53-0.57)/0.86 (0.84-0.89)		[41]
CV (1st year/subs. years)	0.68 (0.65-0.70)/0.85 (0.82-0.87)		
NHNV (1st year/subs. years)	0.79 (0.65-0.93)/0.95 (0.81-1.09)		[42]
Treatment			
Treatment scenarios	Oral bisphosphonates: 70% Zoledronic acid: 13.0% Denosumab: 14.3% Teriparatide: 2.7%		
Effects on fracture (expressed as relative risk compared to no treatment) of medications			

Table 1. (continued)

Parameter	Data		Data source
	Women	Men	
Hip	Oral bisphosphonates: 0.67 (0.48-0.96); Denosumab: 0.60 (0.37-0.97); Zoledronic acid: 0.59 (0.42-0.83); Teriparatide: 0.36 (0.15-0.81)		[43,46]
CV	Oral bisphosphonates: 0.45 (0.31-0.65); Denosumab: 0.31 (0.26-0.41); Zoledronic acid: 0.23 (0.14-0.37); Teriparatide: 0.23 (0.17-0.32)		
NHNV	Oral bisphosphonates: 0.81 (0.46-1.44); Denosumab: 0.80 (0.67-0.95); Zoledronic acid: 0.75 (0.64-0.87); Teriparatide: 0.57 (0.54-0.74)		
Treatment cost (estimated in €2020)			
Drug cost (annually)	Oral bisphosphonates: 20 Zoledronic acid: 258 Denosumab: 400 Teriparatide: 3480		[51]
Side effect cost	1.42 (1st cycle), 0.73 (subsequent cycles)		[52]
FLS-related data			
FLS cost (€2020)	450		[53]
Treatment initiation	FLS: 40%	no-FLS: 5%	[26]; expert opinion
Treatment persistence	FLS: 57%	no-FLS: 34.1%	[19]

CV clinical vertebral fracture, NHNV non-hip non-vertebral fracture, FLS fracture liaison service, RR relative risk, C/PVF clinical or prevalent vertebral fracture

Analyses and outcomes

A total of 1,000,000 trials (1st-order Monte-Carlo simulation) were run for both base-case and one-way sensitivity analyses. With regard to the base-case analysis, total costs (including direct healthcare cost and indirect productivity cost), number of fractures prevented and QALYs were estimated for both FLS and no-FLS branches. The incremental cost-effectiveness ratios (ICER) were calculated as incremental cost (expressed in €2020) per QALY gained. Besides, multiple scenario analyses were conducted to assess the economic value of FLS in patients at different starting ages (50-80 years).

In the Netherlands, there is no single willingness-to-pay (WTP) threshold, ranging from €20,000 to €80,000 per QALY gained [54]. As suggested by Zorginstituut Nederland (ZIN), the selection of WTP threshold should base on burden of illness (BOI), the proportional shortfall (PS) method is recommended [55,56]. PS is measured on a scale from 0 (no QALY loss) to 1 (complete loss of remaining QALY). If PS falls between 0.10-0.40, the WTP threshold of €20,000/QALY is recommended; the maximum reimbursement of €50,000/QALY refers to PS=0.41-0.70; the endpoint of €80,000/QALY is in relation to the highest BOI with PS estimated at 0.71-1.00. In our study, we used a disease burden calculator released by Institute for Medical Technology Assessment (iMTA) [57], PS was estimated at 0.16, therefore the WTP threshold of €20,000/QALY is applied.

One-way sensitivity analyses were performed to test the robustness of the model results by varying a single parameter each time, including a healthcare perspective, a shorter time horizon (5 years), a different discount rate (3%, 5% for both costs and QALYs), and some other parameters including gender (100% female or male), FLS cost (±50%), treatment initiation rate in FLS and no-FLS (±50%), fracture costs (±50%), drug costs (±50%), nursing home costs (±25%), probability of nursing home (±50%), baseline utility (-20%), excess mortality attribution probability (±100%), osteoporosis attribution probability (-25%), and relative risk of subsequent fracture associated with osteoporosis/a prior fracture (-25%).

Probabilistic sensitivity analyses were also undertaken to examine the effect of the joint uncertainty surrounding the model variables. A specific distribution was attributed to each parameter around the point estimate used in the base-case analysis. Specifically, a beta distribution was used for fracture incidence (i.e., the distribution was estimated based on the number of fractures and the population in the age range of 70-74 years) and the effects of fracture on utility (based on 90% confidence interval). Besides, log-normal distributions were assumed for the relative risk of having subsequent fracture, excess mortality following a fracture,

treatment efficacy, and osteoporosis attribution probability. In addition, normal distributions with a standard deviation (SD) assumed to be 20% of the mean (given the lack of standard error) were used for fracture cost, productivity cost, nursing home cost, probability of nursing home admission, excess mortality attribution probability, and treatment initiation rate. For each probabilistic sensitivity analysis, the model was run 200 times (2nd-order Monte-Carlo simulation) based on runs of 25,000 trials per pathway. Cost-effectiveness acceptability curves (CEAC) were done to show the probability of the FLS being cost-effective compared to no-FLS as a function of WTP thresholds.

RESULTS

Base-case analysis

Table 2 presents the lifetime costs, accumulated QALYs, number of fractures, incremental cost and QALY, and the ICER (expressed in cost per QALY gained) of FLS compared to no-FLS in patients with a recent fracture at the age of 50 years and older. FLS was associated with a €45 higher cost and 0.11 additional QALY gained compared to no-FLS, the ICER was thus estimated at €409 per QALY gained, lower than the threshold of €20,000/QALY, indicating FLS was cost-effective compared to no-FLS. In 1,000,000 simulated patients with a recent fracture, FLS led to a reduction of total 53,090 lifetime subsequent fractures, namely the availability of an FLS would avoid 53 subsequent fractures over the lifetime of every 1,000 patients.

Table 3 presents the ICERs of FLS compared to no-FLS in patients at different ages. The cost per QALY gained was estimated at €1,812, €450, €627 and €421 in patients at the age of 50, 60, 70, and 80 years, respectively, suggesting the cost-effectiveness of FLS was remained in all age categories. Compared to younger groups, patients aged 80 years resulted in slightly greater QALY gained.

Table 2. Lifetime total costs, QALYs, number of subsequent fractures, and incremental cost-effectiveness ratio (cost (€) per QALY gained) of FLS compared with no-FLS at a distribution of starting age

	FLS	no-FLS	Incremental
Total cost	12,882	12,837	45
Total QALYs	10.32	10.21	0.11
Number of fractures	1.21247	1.26556	-0.05309
ICER (€ per QALY gained)			409

ICER incremental cost-effectiveness ratio, QALY quality-adjusted life years, FLS fracture liaison service

Table 3. Incremental cost, QALYs, and cost-effectiveness ratio (cost (€) per QALY gained) of FLS compared with no-FLS for patients aged 50–80 years

	Incremental cost	Incremental QALY	ICER
50 years	145	0.08	1,812
60 years	45	0.10	450
70 years	69	0.11	627
80 years	59	0.14	421

ICER incremental cost-effectiveness ratio, QALY quality-adjusted life years, FLS fracture liaison service

Sensitivity analysis

Table 4 reports the results of the one-way sensitivity analyses. Our results were robust in all one-way sensitivity analyses given the ICERs of FLS relative to no-FLS remained below €20,000 per QALY gained. When conducting the analysis from the healthcare perspective, FLS was associated with a €100 higher cost and 0.12 additional QALY gained compared to no-FLS, the ICER was thus estimated at €833 per QALY gained, suggesting FLS is still cost-effective. With a 5-year time horizon, FLS led to a reduction of 41 fractures per 1,000 patients compared to no-FLS (i.e., 8.1% fracture prevention). FLS was dominant (more QALY for less total costs) in female patients, when decreasing the FLS cost (-50%) and drug costs (-50%), and when increasing treatment initiation rate in FLS (+25%) and fracture costs (+50%). The ICERs were shown to be markedly affected by the probability of treatment initiation in the FLS, suggesting the higher the treatment initiation rate, the greater the cost-effective of FLS. In addition, women in FLS incurred with higher cumulative lifetime costs (€14,360 vs. €9,904 per patient) but also greater QALYs (10.39 vs. 10.21 per patient) compared to men in FLS; When compared to no-FLS, more favorable ICER was identified in female patients also; for every 1,000 female patients with a recent fracture, the availability of an FLS would avoid 60 subsequent fractures over their lifetime, which was 37 subsequent fractures in male patients. Other analyses suggested that the ICERs of FLS were shown to greatly increase with the impact from high to low when decreasing relative risk of subsequent fracture by a prior fracture (-25%), decreasing osteoporosis attribution probability (-25%), decreasing fracture costs (-50%), decreasing relative risk of subsequent fracture by osteoporosis (-25%), and increasing FLS cost (+50%).

Table 4. One-way sensitivity analyses on the incremental cost-effectiveness ratio of FLS compared to no-FLS in patients aged 50 years and older with a recent fracture

		Incremental cost	Incremental QALY	ICER
Base-case		45	0.11	409
Perspective	healthcare	100	0.12	833
Gender	female	-5	0.12	dominant
	male	198	0.11	1,800
FLS cost	+50%	287	0.11	2,609
	-50%	-173	0.12	dominant
FLS treatment initiation	+25%	-176	0.14	dominant
	-25%	273	0.10	2,730
No-FLS treatment initiation	+25%	82	0.11	745
	-25%	22	0.12	183
Fracture cost	+50%	-201	0.11	dominant
	-50%	304	0.11	2,764
Nursing home cost	+25%	44	0.12	367
	-25%	47	0.12	392
Drug cost	+50%	156	0.11	1,418
	-50%	-67	0.11	dominant
Probability of nursing home	+50%	48	0.12	400
	-50%	72	0.11	654
Excess mortality	0%	-136	0.09	dominant
	50%	150	0.13	1,154
Relative risk of sub. fx by osteoporosis	-25%	237	0.09	2,633
Relative risk of sub. fx by a prior fx	-25%	254	0.08	3,175
Osteoporosis attribution probability	-25%	274	0.09	3,044
Baseline utility	-20%	48	0.09	533
Discount rate	3%	60	0.09	667
	5%	56	0.07	800
Time horizon	5 years	22	0.05	440

ICER incremental cost-effectiveness ratio, QALY quality-adjusted life years, sub.fx subsequent fracture

The results of the probabilistic sensitivity analyses are reported in Figures 3 and 4. At the threshold of €20,000 per QALY gained, the cost-effectiveness acceptability curves suggest that FLS was cost-effective compared to no-FLS in 89.5% of the simulations (95.5% and 96.5% at the threshold of €50,000 and €80,000/QALY, respectively). The FLS in women was associated with a higher probability to be cost-effective compared to men (91.5% vs. 84.0%). In addition, FLS was shown to be cost-effective in 67.0%, 78.5%, 89.5% and 98.5% of the simulations at the age of 50, 60, 70, and 80 years, respectively, at a threshold of €20,000 per QALY gained; which was 78.5%, 90.5%, 96.5% and 100.0% correspondingly when the WTP threshold is €50,000 per QALY gained, and 81.0%, 93.0%, 97.5% and 100.0% when the WTP threshold is €80,000 per QALY gained. The cost-effectiveness results of FLS for different age and gender categories were also displayed using cost-effectiveness plane, details can be found in Appendix III.

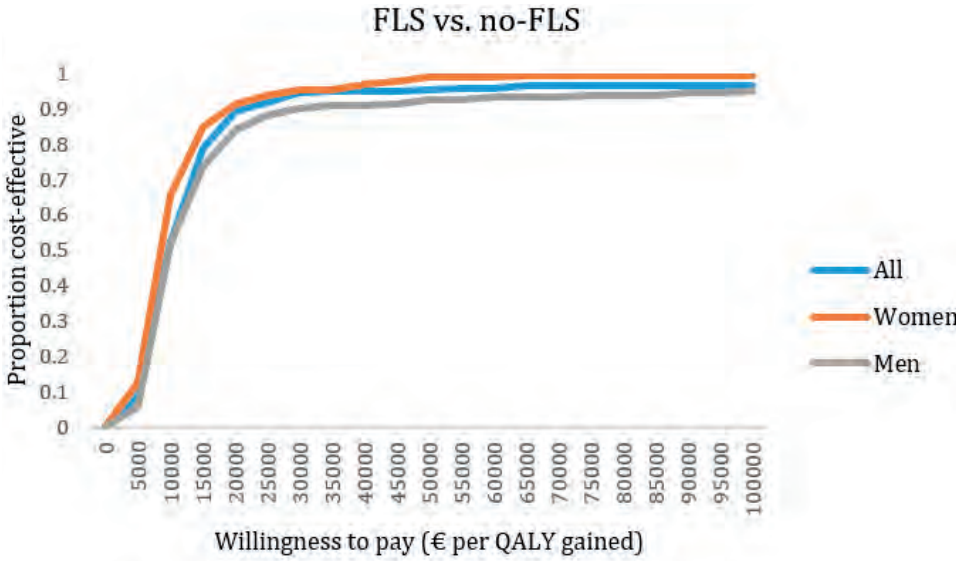


Figure 3. Cost-effectiveness acceptability curves of FLS versus no-FLS in women and men aged over 50 years with a recent fracture
(QALY quality-adjusted life years, FLS fracture liaison service)

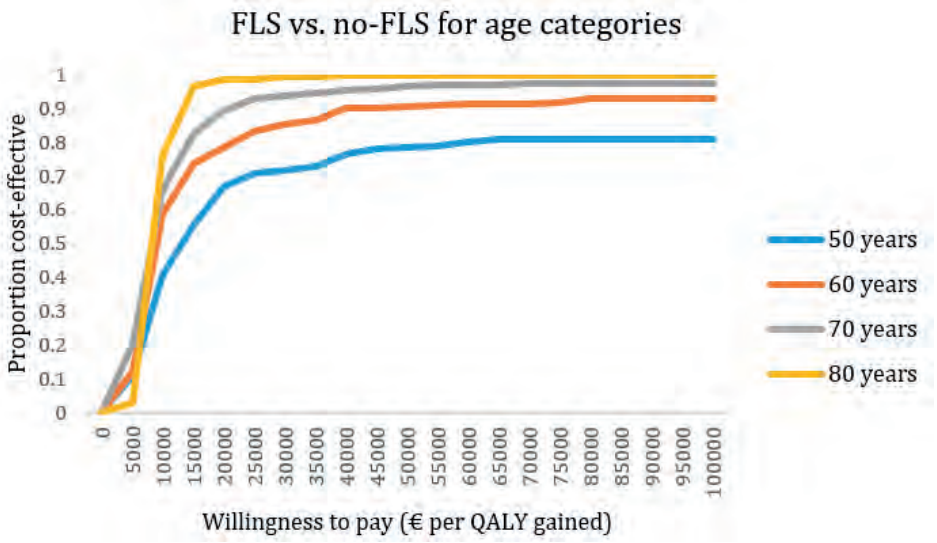


Figure 4. Cost-effectiveness acceptability curves of FLS versus no-FLS in patients at different age categories with a recent fracture
(QALY quality-adjusted life years, FLS fracture liaison service)

DISCUSSION

In this study, a Markov microsimulation model from a Dutch societal perspective and a lifetime horizon was used to estimate the cost-effectiveness of the FLS in patients aged 50 years and older with a recent fracture. In all of the simulated populations, the ICERs of FLS were below the Dutch accepted thresholds of €20,000 per QALY gained, suggesting FLS is cost-effectives compared to no-FLS. The cost-effectiveness of FLS remained favorable in all age categories. Compared to younger groups, patients aged 80 years resulted in slightly higher QALY gained. With fracture trackers in the model, FLS was estimated to lead to a reduction of 41 subsequent fractures in per 1,000 simulated individuals with the time horizon of 5 years, which was comparable to a recent UK study [58] reporting FLS was associated with a reduction of 30 subsequent fractures in per 1,000 individuals.

Our findings were robust in all one-way sensitivity analyses and probabilistic sensitivity analyses. For women, a FLS was associated with more favorable ICER and higher probability to be cost-effective compared to men. There are two potential reasons: first, men have a higher baseline mortality risk and the impact of fracture on mortality was also greater compared to women, leading to shorter life expectancy to gain benefits from the FLS, and thus less QALY gains (compared to women); second, women are associated with a higher risk of fracture recurrence than men, the presence of an FLS would thus lead to more subsequent fractures avoidance and more health benefits. Next to gender, treatment initiation in the FLS was found to be particularly influential when varied within the model; the higher treatment initiation rate was associated with greater cost-effective results. It is quite reasonable since more patients are identified and treated, more subsequent fractures are avoided, which is also the mission of post-fracture care programs.

To our knowledge, this study provides the first results about the cost-effectiveness of the FLS in the Netherlands. Our finding supports a recently issued Dutch report [59] suggesting FLS is associated with reduction in fragility fractures and offer clear cost-effectiveness compared to current practice with a time horizon of five years. Given the report related original study is not published yet, we cannot make detailed comparison regarding the modelling strategy, model input data as well as subsequent fracture risk estimation and relevant assumptions.

The main strength of our study is that real-world data from a Dutch hospital were obtained and used for several model input parameters. These data are reliable and valid since the FLS program in VieCuri Medical Centre had been implemented for 15 years, and the quality of their FLS was rated as ‘gold’ according to Best Practice

Framework (BPF) of IOF. Besides, the success of FLS implementation largely depends on the intensity of attendance and treatment; the performance of FLS in VieCuri Medical Centre has a relatively high FLS attendance rate (51%) and the initiation rate of anti-osteoporosis drugs (40% for attenders) [26], which are comparable to rates reported by several systematic reviews and meta-analysis [17-19], attributing to the cost-effective results of FLS in our study. One systematic review [15] suggested that the more intensive the FLS model, the more effective of which in subsequent fracture prevention, the greater the economic benefits. Given we only assessed the cost-effectiveness of the FLS in one Dutch FLS clinic, the impact of improving the intensity and quality of FLS on cost-effectiveness was not revealed, it would be of interest for future research. To improve the quality of FLS, the BPF and eleven patient-level key performance indicator developed by the IOF could serve as guidelines in the design of adequate FLSs and improving the quality of existing FLSs. In addition to the real-world data, most recent estimates for utility values, mortality rate, FLS cost, drug costs as well as nursing home admission were obtained from Dutch publications or official website, assuring valid estimations in our analysis.

Our results are in line with a previous international systematic review [20] of 23 cost-effectiveness analyses of FLS, suggesting the FLS was a cost-effective secondary fracture prevention strategy although it was implemented in different ways and settings. Compared to previous studies, our study has several strengths. First, drug treatment indications in the Netherlands recommended by Dutch guidelines [10,22] were reflected in our model, which is more consistent with real-life FLS setting when treating patients with a recent fracture. Second, real-world treatment scenarios including four types of medications (drug strategies as recommended by Dutch guideline) were modelled in our study, leading to real-world cost-effectiveness assessment of FLS rather than a hypothetical estimation. Third, age- and gender-stratified data were retrieved for most parameters to facilitate the investigation of differences in cost-effectiveness estimations for patients with different baseline characteristics. Fourth, most previous studies simply assumed 100% persistence to anti-osteoporosis medications; we took into account the impact of medication persistence on treatment effect by incorporating data from literature.

There are however some potential limitations in this study. First, given the lack of patients data before the implementation of FLS in VieCuri Medical Centre, we did not have an accurate treatment initiation rate for the no-FLS branch, the modelled rate of 5% was based on expert opinion. However, we explored the uncertainty of this parameter in sensitivity analysis, our results were remained. Second, for patients who suffered subsequent fractures in the simulation, the

change in treatment strategy (extension or switch) and the corresponding (new) therapy efficacy and duration were not modelled in our study given the lack of relevant data and the complexity of modelling. Third, patients entered our model with a mixture of fracture typle (hip, vertebrae, NHNV), the availability of input data was insufficient to calculate ICER separately by type of baseline, making it difficult to compared between groups (e.g., major vs. non-major fractures). Fourth, the analysis in this study was conducted based on the real-life data from a single hospital in the Netherlands, the generalizability of our results should be conducted with caution given the intensity and quality of implementation of FLS vary between hospitals and countries, potentially leading to different clinical and economic outcomes. Fifth, some assumptions such as consistent prevalence of osteoporosis and/or prevalent VF in both branches, consistence treatment efficacy, persistence, and utility multipliers in female and male patients were made given the lack of relevant data. Sixth, given the absence of productivity costs in the Netherlands, we conservatively assumed patients with a fracture had a two-month work absence at most, however, more complicated scenarios could be found in the real life given not only disease aspects but also personal characteristics and job factors have an influence on work ability and further on productivity costs.

CONCLUSION

This study provides the first economic results of FLS in the Netherlands, suggesting that FLS is cost-effective compared to no-FLS in patients aged 50 years and older with a recent fracture. The cost-effectiveness of FLS remained in all age categories. The implementation of FLS could lead to reduced subsequent fracture risk and lifetime economic benefits.

ELECTRONIC SUPPLEMENTARY MATERIAL

Appendix I: Osteoporosis-specific checklist – specific items to include when reporting economic evaluations on osteoporosis

Item	Item no.	Recommendation	Reported on page no. / line no.
Transition probabilities	1	Report the transition probabilities and how they were estimated (including increased fracture risk)	Method section + Table 1 Subtitle: Osteoporosis, clinical or prevalent vertebral fracture, fracture risk
Excess mortality after fractures	2	Describe approaches and data sources used for the excess mortality after fractures	Method section + Table 1 Subtitle: Mortality
Fractures costs	3	Describe approaches and data sources used for fractures costs	Method section + Table 1 Subtitle: Fracture cost
Fractures effects on utility	4	Describe approaches and data sources used for the effects of fractures on utility	Method section + Table 1 Subtitle: Utility values
Treatment effect during treatment	5	Describe fully the methods used for the identification, selection, and synthesis of clinical effectiveness data (per fracture site)	Method section + Table 1 Subtitle: Treatment effects and costs
Treatment effect after discontinuation	6	Describe fully the methods used for the treatment effect after discontinuation	Method section Subtitle: Treatment effects and costs
Medication adherence	7	Describe approaches and data sources used for modeling medication adherence	Method section + Table 1 Subtitle: Treatment effects and costs
Treatment costs	8	Describe approaches and data sources used for therapy costs	Method section + Table 1 Subtitle: Treatment effects and costs
Treatment side effects	9	Describe approaches and data sources used for costs and utilities effects of adverse events	Method section + Table 1 Subtitle: Treatment effects and costs

Appendix II: CHEERS 2022 checklist—Items to include when reporting economic evaluations of health interventions

Section/item	Item No.	Guidance for reporting	Reported in section
Title			
Title	1	Identify the study as an economic evaluation and specify the interventions being compared.	Title section
Abstract			
Abstract	2	Provide a structured summary that highlights context, key methods, results, and alternative analyses.	Abstract section
Introduction			
Background and objectives	3	Give the context for the study, the study question, and its practical relevance for decision making in policy or practice.	Introduction section
Methods			
Health economic analysis plan	4	Indicate whether a health economic analysis plan was developed and where available.	NA
Study population	5	Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).	Method section Subtitle: Population
Setting and location	6	Provide relevant contextual information that may influence findings.	Introduction and method section Subtitle: Model structure and treatment pathways
Comparators	7	Describe the interventions or strategies being compared and why chosen.	Method section
Perspective	8	State the perspective(s) adopted by the study and why chosen.	Introduction and method section
Time horizon	9	State the time horizon for the study and why appropriate.	Introduction and method section
Discount rate	10	Report the discount rate(s) and reason chosen.	Method section Subtitle: Model structure and treatment pathways
Selection of outcomes	11	Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	Method section Subtitle: Model structure and treatment pathways Analyses and outcomes
Measurement of outcomes	12	Describe how outcomes used to capture benefit(s) and harm(s) were measured.	Method section Subtitle: Analyses and outcomes
Valuation of outcomes	13	Describe the population and methods used to measure and value outcomes.	Method section Subtitle: Analyses and outcomes
Measurement and valuation of resources and costs	14	Describe how costs were valued.	Method section Subtitle: Fracture cost Treatment effects and costs FLS-related model input data

(continued)

Section/item	Item No.	Guidance for reporting	Reported in section
Currency, price date, and conversion	15	Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	Method section and Table 1 Subtitle: Fracture cost Treatment effects and costs
Rationale and description of model	16	If modeling is used, describe in detail and why used. Report if the model is publicly available and where it can be accessed.	Method section and Figure 1,2
Analytics and assumptions	17	Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.	Method section Subtitle: Osteoporosis, prevalent vertebral fracture, fracture risk Mortality Utility values Treatment effects and costs
Characterising heterogeneity	18	Describe any methods used for estimating how the results of the study vary for subgroups.	Method section Subtitle: Analyses and outcomes
Characterising distributional effects	19	Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	NA
Characterising uncertainty	20	Describe methods to characterise any sources of uncertainty in the analysis.	Method section Subtitle: Analyses and outcomes
Approach to engagement with patients and others affected by the study	21	Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (such as clinicians or payers) in the design of the study.	NA
Results			
Study parameters	22	Report all analytic inputs (such as values, ranges, references) including uncertainty or distributional assumptions.	Method section and Table 1
Summary of main results	23	Report the mean values for the main categories of costs and outcomes of interest and summarise them in the most appropriate overall measure.	Results section and Table 2, 3
Effect of uncertainty	24	Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.	Results section and Table 4, Figure 3, 4 Appendix III
Effect of engagement with patients and others affected by the study	25	Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study	NA
Discussion			
Study findings, limitations, generalizability, and current knowledge	26	Report key findings, limitations, ethical or equity considerations not captured, and how these could affect patients, policy, or practice.	Discussion section
Other relevant information			

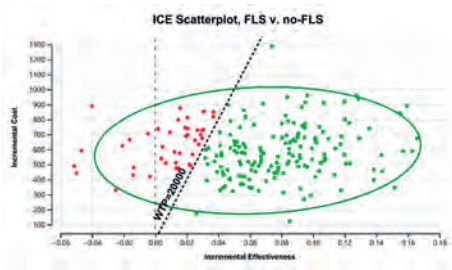
(continued)

Section/item	Item No.	Guidance for reporting	Reported in section
Source of funding	27	Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis	Source of funding section
Conflicts of interest	28	Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.	Conflicts of interest section

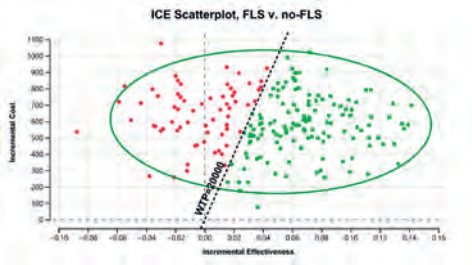
NA not applicable

Appendix III: Results displayed by the cost-effectiveness plane

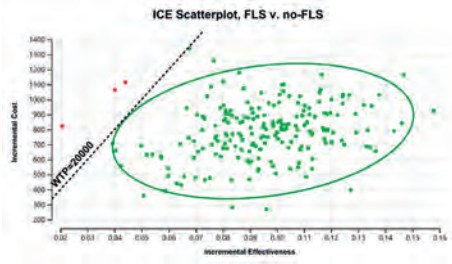
(a) patients at 50 years



(b) patients at 60 years



(c) patients at 70 years



(d) patients at 80 years

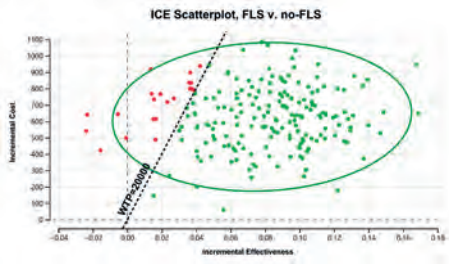
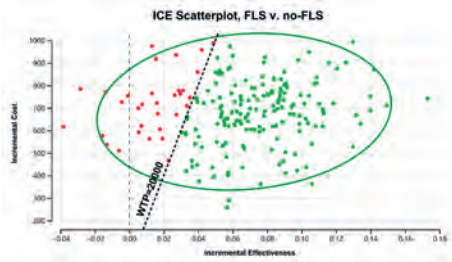


Figure 1 Cost-effectiveness plane of FLS versus no-FLS in patients at different age categories

(a) women



(b) men

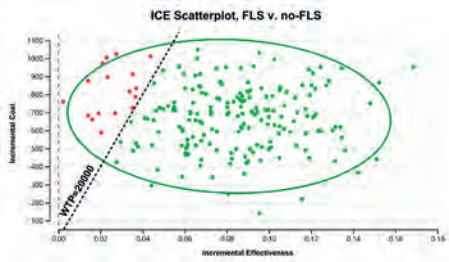


Figure 2 Cost-effectiveness plane of FLS versus no-FLS in patients at different genders

REFERENCE

1. Kanis JA, Norton N, Harvey NC, et al. SCOPE 2021: a new scorecard for osteoporosis in Europe. *Arch Osteoporos*. 2021;16(1). doi:10.1007/s11657-020-00871-9
2. Van Geel TACM, Van Helden S, Geusens PP, Winkens B, Dinant GJ. Clinical subsequent fractures cluster in time after first fractures. *Ann Rheum Dis*. 2009;68(1):99-102. doi:10.1136/ard.2008.092775
3. Solomon DH, Johnston SS, Boytsov NN, Mcmorrow D, Lane JM, Krohn KD. Osteoporosis Medication Use After Hip Fracture in U . S . Patients Between 2002 and 2011. 2014;29(9):1929-1937. doi:10.1002/jbmr.2301
4. Dunnewind T, Dvortsin EP, Smeets HM, et al. Economic Consequences and Potentially Preventable Costs Related to Osteoporosis in the Netherlands. *Value Heal*. 2017;20(6):762-768. doi:10.1016/j.jval.2017.02.006
5. McLellan AR, Gallacher SJ, Fraser M, McQuillian C. The fracture liaison service: Success of a program for the evaluation and management of patients with osteoporotic fracture. *Osteoporos Int*. 2003;14(12):1028-1034. doi:10.1007/s00198-003-1507-z
6. https://www.iofbonehealth.org/. Accessed 16 Oct 2022.
7. Lems WF, Dreinhöfer KE, Bischoff-Ferrari H, et al. EULAR/EFORT recommendations for management of patients older than 50 years with a fragility fracture and prevention of subsequent fractures. *Ann Rheum Dis*. 2017;76(5):802-810. doi:10.1136/annrheumdis-2016-210289
8. Dreinhöfer KE, Mitchell PJ, Bégué T, et al. A global call to action to improve the care of people with fragility fractures. *Injury*. 2018;49(8):1393-1397. doi:10.1016/j.injury.2018.06.032
9. Eisman JA, Bogoch ER, Dell R, et al. Making the first fracture the last fracture: ASBMR task force report on secondary fracture prevention. *J Bone Miner Res*. 2012;27(10):2039-2046. doi:10.1002/jbmr.1698
10. Dutch Institute for Healthcare Improvement CBO (2011) Richtlijn Osteoporose en Fractuurpreventie. www.diliguide.nl/document/1015/file/pdf/. Accessed 16 Oct 2022.
11. Hegeman JH, Oskam J, van der Palen J, ten Duis HJ, Vierhout PAM. The distal radial fracture in elderly women and the bone mineral density of the lumbar spine and hip. *J Hand Surg Am*. 2004;29(5):473-476. doi:10.1016/j.jhsb.2004.05.002
12. https://osteoporoseverpleegkundige.nl/. Accessed 16 Oct 2022.
13. Van Den Bergh JP, Van Geel TA, Geusens PP. Osteoporosis, frailty and fracture: Implications for case finding and therapy. *Nat Rev Rheumatol*. 2012;8(3):163-172. doi:10.1038/nrrheum.2011.217
14. van den Berg P, Schweitzer DH, van Haard PMM, van den Bergh JP, Geusens PP. Meeting international standards of secondary fracture prevention: a survey on Fracture Liaison Services in the Netherlands. *Osteoporos Int*. 2015;26(9):2257-2263. doi:10.1007/s00198-015-3117-y
15. Ganda K, Puech M, Chen JS, et al. Models of care for the secondary prevention of osteoporotic fractures: A systematic review and meta-analysis. *Osteoporos Int*. 2013;24(2):393-406. doi:10.1007/s00198-012-2090-y
16. Wu C, Chen C, Chen P, et al. Identifying characteristics of an effective fracture liaison service : systematic literature review. Published online 2018:1023-1047.
17. Vranken L, Wyers CE, van den Bergh JPW, Geusens PPMM. The Phenotype of Patients with a Recent

Fracture: A Literature Survey of the Fracture Liaison Service. *Calcif Tissue Int*. 2017;101(3):248-258. doi:10.1007/s00223-017-0284-1

18. Li N, Hiligsmann M, Boonen A, et al. The impact of fracture liaison services on subsequent fractures and mortality: a systematic literature review and meta-analysis. *Osteoporos Int*. Published online 2021. doi:10.1007/s00198-021-05911-9
19. Wu CH, Tu S Te, Chang YF, et al. Fracture liaison services improve outcomes of patients with osteoporosis-related fractures: A systematic literature review and meta-analysis. *Bone*. 2018;111(138):92-100. doi:10.1016/j.bone.2018.03.018
20. Wu CH, Kao IJ, Hung WC, et al. Economic impact and cost-effectiveness of fracture liaison services: a systematic review of the literature. *Osteoporos Int*. 2018;29(6):1227-1242. doi:10.1007/s00198-018-4411-2
21. Hiligsmann M, Ethgen O, Bruyère O, Richy F, Gathon HJ, Reginster JY. Development and validation of a markov microsimulation model for the economic evaluation of treatments in osteoporosis. *Value Heal*. 2009;12(5):687-696. doi:10.1111/j.1524-4733.2008.00497.x
22. Vereniging NI, Specialisten M. Osteoporose en fractuurpreventie Inhoudsopgave. Published online 2023.
23. Genant HK, Wu CY, van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. *J Bone Miner Res*. 1993;8(9):1137-1148. doi:10.1002/jbmr.5650080915
24. Hiligsmann M, Reginster J, Tosteson ANA, et al. Recommendations for the conduct of economic evaluations in osteoporosis : outcomes of an experts ' consensus meeting organized by the European Society for Clinical and Economic Aspects of Osteoporosis , Osteoarthritis and Musculoskeletal Diseases (ESCEO . Published online 2019:45-57.
25. Husereau D, Drummond M, Augustovski F, et al. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) Statement : Updated Reporting Guidance for Health Economic Evaluations Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) Statement : Updated Re. *J Med Econ*. 2022;25(S1):1-7. doi:10.1080/13696998.2021.2014721
26. Vranken L, de Bruin IJA, Driessen AHM, et al. Decreased Mortality and Subsequent Fracture Risk in Patients With a Major and Hip Fracture After the Introduction of a Fracture Liaison Service: A 3-Year Follow-Up Survey. *J Bone Miner Res*. 2022;37(10):2025-2032. doi:10.1002/jbmr.4674
27. van der Velde RY, Bours SPG, Wyers CE, Lems WF, Geusens PPMM, van den Bergh JPW. Effect of implementation of guidelines on assessment and diagnosis of vertebral fractures in patients older than 50 years with a recent non-vertebral fracture. *Osteoporos Int*. 2017;28(10):3017-3022. doi:10.1007/s00198-017-4147-4
28. Versteegh M, Knies S, Brouwer W. From Good to Better: New Dutch Guidelines for Economic Evaluations in Healthcare. *Pharmacoeconomics*. 2016;34(11):1071-1074. doi:10.1007/s40273-016-0431-y
29. Van Geel TACM, Huntjens KMB, Van Den Bergh JPW, Dinant GJ, Geusens PP. Timing of subsequent fractures after an initial fracture. *Curr Osteoporos Rep*. 2010;8(3):118-122. doi:10.1007/s11914-010-0023-2
30. Hiligsmann M, Reginster JY. Cost effectiveness of denosumab compared with oral bisphosphonates in the treatment of post-menopausal osteoporotic women in Belgium. *Pharmacoeconomics*. 2011;29(10):895-911. doi:10.2165/11539980-000000000-00000
31. Melton LJ, Thamer M, Ray NF, et al. Fractures attributable to osteoporosis: Report from the national

osteoporosis foundation. *J Bone Miner Res*. 1997;12(1):16-23. doi:10.1359/jbmr.1997.12.1.16

32. mortality rate. https://opendata.cbs.nl/. Accessed 16 Oct 2022.
33. Haentjens P, Magaziner J, Colón-Emeric CS, et al. Meta-analysis: Excess mortality after hip fracture among older women and men. *Ann Intern Med*. 2010;152(6):380-390. doi:10.7326/0003-4819-152-6-201003160-00008
34. Kanis JA, Oden A, Johnell O, De Laet C, Jonsson B. Excess mortality after hospitalisation for vertebral fracture. *Osteoporos Int*. 2004;15(2):108-112. doi:10.1007/s00198-003-1516-y
35. Kanis JA, Oden A, Johnell O, De Laet C, Jonsson B, Oglesby AK. The components of excess mortality after hip fracture. *Bone*. 2003;32(5):468-473. doi:10.1016/S8756-3282(03)00061-9
36. Lötters FJB, van den Bergh JP, de Vries F, Rutten-van Mölken MPMH. Current and Future Incidence and Costs of Osteoporosis-Related Fractures in The Netherlands: Combining Claims Data with BMD Measurements. *Calcif Tissue Int*. 2016;98(3):235-243. doi:10.1007/s00223-015-0089-z
37. Dutch hip fracture audit. https://dica.nl/jaarrapportage-2019/dhfa. Accessed 16 Oct 2022.
38. Meerding WJ, Looman CWN, Essink-Bot ML, Toet H, Mulder S, Van Beeck EF. Distribution and Determinants of Health and Work Status in a Comprehensive Population of Injury Patients. *J Trauma - Inj Infect Crit Care*. 2004;56(1):150-161. doi:10.1097/01.TA.0000062969.65847.8B
39. Average annual salary in the Netherlands in 2020. https://www.statista.com/statistics/538406/average-annual-salary-in-the-netherlands-by-age/. Accessed 16 Oct 2022.
40. Li N, van Oostwaard M, van den Bergh JP, et al. Health-related quality of life of patients with a recent fracture attending a fracture liaison service: a 3-year follow-up study. *Osteoporos Int*. 2021;(0123456789). doi:10.1007/s00198-021-06204-x
41. Svedbom A, Borgström F, Hernlund E, et al. Quality of life after hip, vertebral, and distal forearm fragility fractures measured using the EQ-5D-3L, EQ-VAS, and time-trade-off: results from the ICUROS. *Qual Life Res*. 2018;27(3):707-716. doi:10.1007/s11136-017-1748-5
42. Söreskog E, Lindberg I, Kanis JA, et al. Cost-effectiveness of romosozumab for the treatment of postmenopausal women with severe osteoporosis at high risk of fracture in Sweden. *Osteoporos Int*. 2021;32(3):585-594. doi:10.1007/s00198-020-05780-8
43. National Institute for Health and Clinical Excellence (NICE). Systematic reviews of clinical effectiveness prepared for the guideline "Osteoporosis assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk.
44. Dennis M. Black, Ph.D., Pierre D. Delmas, M.D., Ph.D., Richard Eastell, M.D., Ian R. Reid, M.D., Steven Boonen, M.D., Ph.D., Jane A. Cauley, Dr.P.H., Felicia Cosman, M.D., Péter Lakatos, M.D. PD, Ping Chung Leung, M.D., Zulema Man, M.D., Carlos Mautalen, M.D., Peter Mesenbrink, Ph.D., Huilin Hu, Ph.D., John Caminis, M.D., Karen Tong, B.S., Theresa Rosario-Jansen, Ph.D., Joel Krasnow, M.D., Trisha F. Hue, M.P.H., Deborah Sellmeyer, M.D., Erik Fink MD. Once-Yearly Zoledronic Acid for Treatment of Postmenopausal Osteoporosis. *N Engl J Med*. 2007;356(18):1809-1822.
45. Wan Y, Zeng F, Tan H, et al. *Cost-Effectiveness Analyses of Denosumab for Osteoporosis: A Systematic Review*. Vol 33.; 2022. doi:10.1007/s00198-021-06268-9
46. Cummings SR, Martin JS, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *Obstet Gynecol Surv*. 2009;64(12):805-807. doi:10.1097/01.

ogx.0000363236.41902.96

47. Lems WF, Geusens P. Osteoporose en fractuurpreventie. *Leerb Reumatol en Klin Immunol*. Published online 2013:215-226. doi:10.1007/978-90-313-9894-2_20
48. Klop C, Welsing PMJ, Elders PJM, et al. Long-term persistence with anti-osteoporosis drugs after fracture. *Osteoporos Int*. 2015;26(6):1831-1840. doi:10.1007/s00198-015-3084-3
49. Koller G, Goetz V, Vandermeer B, et al. Persistence and adherence to parenteral osteoporosis therapies: a systematic review. *Osteoporos Int*. 2020;31(11):2093-2102. doi:10.1007/s00198-020-05507-9
50. van Maren MA, Wyers CE, Driessen JHM, et al. Two-year persistence with teriparatide improved significantly after introduction of an educational and motivational support program. *Osteoporos Int*. 2019;30(9):1837-1844. doi:10.1007/s00198-019-05052-0
51. https://www.medicijnkosten.nl/. Accessed 16 Oct 2022.
52. Hiligsmann M, Williams SA, Fitzpatrick LA, Silverman SS, Weiss R, Reginster JY. Cost-effectiveness of sequential treatment with abaloparatide vs. teriparatide for United States women at increased risk of fracture. *Semin Arthritis Rheum*. 2019;49(2):184-196. doi:10.1016/j.semarthrit.2019.01.006
53. DBC-zorgproduct. https://www.opendisdata.nl/msz/zorgproduct/131999067. Accessed 16 Oct 2022.
54. Institute DNHC. Cost-effectiveness in practice. https://www.zorginstituutnederland.nl/. Accessed 16 Oct 2022.
55. Vijgen S, Heesch F van, Obradovic M. Ziektelast in de praktijk. *Dutch Natl Heal Care Inst*. Published online 2018:1-34. https://www.zorginstituutnederland.nl/publicaties/rapport/2018/05/07/ziektelast-in-de-praktijk
56. Reckers-Droog VT, van Exel NJA, Brouwer WBF. Looking back and moving forward: On the application of proportional shortfall in healthcare priority setting in the Netherlands. *Health Policy (New York)*. 2018;122(6):621-629. doi:10.1016/j.healthpol.2018.04.001
57. https://imtamodels.shinyapps.io/iDBCv2_1/. Accessed 16 Oct 2022.
58. Pinedo-Villanueva R, Burn E, Maronga C, Cooper C, Kassim Javaid M. Expected benefits and budget impact from a microsimulation model support the prioritisation and implementation of Fracture Liaison Services. *J Bone Miner Res*. 2023;00(00):1-13. doi:10.1002/jbmr.4775
59. https://www.osteoporosis.foundation/sites/iofbonehealth/files/2023 01/2022_country_profile_ned_25.01.pdf. Accessed 19 Feb 2023.

CHAPTER 10

Summary

Osteoporosis, (bone) fractures and metabolic bone diseases are associated with significant morbidity, reduction in health-related quality of life, excess mortality as well as considerable healthcare expenditures, representing therefore an important public heath challenge. A prior fracture is a well-documented major risk factor for subsequent fractures. Pharmacological treatments including anabolic and anti-resorptives agents as well as sequential therapy have proven efficacy in reducing increased fracture risk. Despite the wide availability of these pharmacologic interventions, a substantial proportion of patients with osteoporosis or at high risk of (recurrent) fractures remain underdiagnosed and/or undertreated, leading to substantial treatment gap. Poor adherence and persistence to osteoporotic medication remains a major problem increasing the treatment gap. In further response to this treatment gap, post-fracture care program such as fracture liaison service (FLS), is nowadays widely advocated as the most appropriate and effective approach for secondary fracture prevention in persons aged 50 years and older with a recent bone fracture. Recently, with the international endorsement by scientific societies, an increasing number of FLSs have been implemented throughout the world. Several questions remain concerning the effect of the FLS on various outcomes. Correspondingly, studies were conducted to investigate the effectiveness and cost-effectiveness of anti-osteoporosis medications as well as the implementation of an FLS in country-specific hospital settings.

Part I of this dissertation focused on economic evaluations in both women and men with osteoporosis, on factors involved in adherence or persistence to medication and behaviours; and on understanding the complexities of the communication of fracture risk to an individual.

Part I contains three chapters. In **Chapter 2**, we conducted a systematic review to update information on cost-effectiveness of drugs in women with osteoporosis and critically appraised the quality of included economic evaluations using an osteoporosis-specific guideline. In this chapter, 27 studies published between 1 July, 2013 and 31 December, 2019 were included, representing the perspective of 15 countries and evaluating 12 different active drugs. Compared to traditional oral bisphosphonates, newer interventions (denosumab, zoledronic acid, gastro-resistant risedronate, and teriparatide) were generally cost-effective or even dominant (better health outcome for lower costs) in women aged 50 years and older with osteoporosis. Sequential therapy (anabolic first followed by an antiresorptive) opposed to monotherapy (such as oral alendronate) as initial treatment in postmenopausal women indicated extra health benefits (larger gains in quality-adjusted life years), and potential cost-effectiveness in very high risk population although the cost-effectiveness of sequential therapy depends on acquisition costs

of anabolic agents even when accounting for low costs of bisphosponates that were out of patent. In terms of study quality, the average score for quality assessment was 17 out of 25 (range 2–15). Items such as 'an additional effect on costs and/or utility after multiple fractures', 'adverse events' as well as 'proportion of excess mortality attributed to the fracture' were frequently unreported and room for improvement was observed for most studies which could potentially be explained by the fact that most studies were published prior to the osteoporosis-specific guideline. We concluded that newer interventions were generally cost-effective or even dominant when compared to oral bisphosphonates. Greater adherence to guideline recommendations (in particular the ESCEO-IOF guideline) was expected for future studies.

In **Chapter 3**, a systematic review was conducted to summarize information on the cost-effectiveness of treating men with osteoporosis, to compare the cost-effectiveness results between men and women, and to critically appraise study quality including inspection the source of model input data. In this chapter, a total of 25 studies published between 1 January, 2000 and 30 June, 2022 were included. These studies were classified into economic evaluations of active anti-osteoporosis drugs (n=8) or nutrition supplements (n=4), medication intervention thresholds (n=5), screening strategies (n=6), and post-fracture care programs (n=2). Most studies were conducted in European countries, followed by North America. Bisphosphonates and nutrition supplements were shown to be generally cost-effective compared to no treatment in men aged over 60 years with osteoporosis or prior fractures. Two studies suggested that denosumab was cost-effective in men aged 75 years and older with osteoporosis compared to bisphosphates and teriparatide. Intervention thresholds at which bisphosphonates were found to be cost-effective varied among studies focusing on men with a 10-year probability of a major osteoporotic fracture ranging from 8.9% to 34.2% for different age categories. A few studies suggested cost-effectiveness of screening strategies and post-fracture care programs in men aged 65 years and older with osteoporosis or a recent fracture. Similar findings regarding the cost-effectiveness of drugs and intervention thresholds in women and men were captured, with slightly greater ICERs in men. The quality of the studies included had an average score of 18.8 out of 25 (range 13-23.5). Hip fracture incidence and mortality risk were mainly derived from studies in men, while fracture cost, treatment efficacy, and disutility were commonly derived from studies in women or studies combining both sexes. We concluded that medicines and nutrition supplements are generally cost-effective in men over 60 years of age with osteoporosis or prior fractures, reimbursement for these active drugs should be considered as part of the standard of care. Similar findings regarding the cost-effectiveness of interventions in women and men

with osteoporosis were captured, fracture risk reduction should therefore be the primary consideration in the treatment for osteoporosis irrespective of sex.

In **Chapter 4**, we conducted a scoping review to study the current status of patient adherence to osteoporosis medications, the determinants and consequences of non-adherence as well as the complexities of fracture risk communication. Low adherence to osteoporotic medications is well recognized by published studies, leading to increased risk of fractures and representing a substantial clinical and economic burden. Studies reported that multiple factors were identified for non-adherence, including patient-related factors such as older age and misconceptions about osteoporosis, therapy-related factors such as higher dosing frequency and medication side effects. Besides, patient perceptions and preferences for osteoporosis medications were also shown to impact adherence behavior including persistence. Interventions including patient education, drug regimen implementation, monitoring and supervision, interdisciplinary collaboration, and shared decision-making were common initiatives to facilitate interaction/communication between patients and doctors, to help patients improve health literacy related to osteoporosis or fracture, and to further improve the medication adherence. To quantify individuals' fracture risk, several risk algorithms have been developed, the majority of guidelines internationally use FRAX® as the measure of fracture risk over 10 years. Developing online tools to convert output of those fracture risk algorithms into friendly and visual presentation could facilitate professionals communicating with patients about fracture risk. Using available and effective educational materials in daily practice to communicate in a highly efficient manner about risk could be an important step in enhancing patient education, self-management of the disease, acceptance of treatment and, ultimately, adherence to treatment. We concluded that patient understanding of risk of fracture should be confirmed by making sure that patients feel free to ask questions and express their concerns. This will contribute to an optimal patient-centered approach. Visual aids could help patients understand their fracture risk and further improve their adherence to medication.

Part II of this dissertation focuses on clinical and economic outcomes of FLS. Five chapters were contained in Part II. In **Chapter 5**, we summarized the current evidence by conducting a systematic review and meta-analysis to investigate the impact of FLS on subsequent fractures and mortality. A total of 16 studies published between January 1, 2010, and April 30, 2020 and comparing FLS to no-FLS were included. Twelve studies compared outcomes before (pre-FLS) and after (post-FLS) FLS implementation, two studies compared outcomes between hospitals with and without FLS, and two other studies performed both comparisons. The

meta-analysis suggested that the FLS care was associated with a significantly lower probability of subsequent fractures (odds ratio: 0.70, 95% CI: 0.52–0.93, P=0.01). The reduction was even larger (odds ratio: 0.57, 95% CI: 0.34–0.94, P=0.03) in studies with relatively longer follow-up (>2 years). Overall, no significant difference in mortality was observed (odds ratio: 0.73, 95% CI: 0.49–1.09, P=0.12), however, a significantly lower probability of mortality was identified in the six pre-post FLS comparisons (odds ratio: 0.65, 95% CI: 0.44–0.95, P=0.03). No difference was further observed in mortality stratified by follow-up time. The average score for quality assessment using self-designed tool (by combining and modifying criteria of existing quality assessment tools, i.e. ROBINS-I, Newcastle–Ottawa scale, and NIH tool) was 5.4 out of 10 (range 3-8.5). Only 50% of studies fulfilled more than half of the criteria. We concluded that FLS is associated with a significantly lower probability of subsequent fractures and mortality although the latter was only found in studies comparing outcomes before and after the introduction of an FLS. Some important methodological issues were unmet in the currently available studies, the most important one was all eligible patients (not only attenders) should be included in the FLS group and all analyses, otherwise the results would be biased (these studies were regarded as very high selection bias and were excluded from the main meta-analysis in our study, i.e. only tested in sensitivity analysis).

In **Chapter 6**, we assessed the 3-year health state utility value (HSUV) (as measured by EQ-5D-5L and SF-6D) in patients with a recent fracture presenting at an FLS after a mean of 3.5 months (SD: 1.0) post-fracture, and explored factors associated with HSUV. We found that the EQ-5D HSUV in patients aged 50 years and older presenting the FLS because of a recent fracture did not change significantly over 3 years following their first visit (P=0.52), although slightly but significantly higher HSUV was captured at 6 months (mean difference: 0.015, P=0.02) and 12 months (mean difference: 0.018, P=0.01). There was no significant difference in the course of EQ-5D HSUV across fracture locations (P=0.86). A significant increase in HSUV was only captured for patients had shorter time period (<107 days) between FLS visit and their index fracture, indicating the recovery from the fracture in this group. Sustaining a subsequent fracture was associated with significant loss of health utility (mean difference: −0.078, P<0.001). Subsequent fracture, previous treatment with anti-osteoporosis medication, a prevalent vertebral fracture (grade 2 or 3), use of a walking aid, previous falls, and higher BMI were negatively associated with mean EQ-5D HSUV over 3 years. We concluded that the 3-year change in HSUV was not statistically significant, although significant improvements were observed at 6 and 12 months post-fracture in comparison with baseline.

In **Chapter 7**, we compared the psychometric properties (construct validity, known-group validity, and responsiveness/longitudinal validity) of EQ-5D-5L and SF-6D to assess the interchangeability of both instruments in patients with a recent fracture presenting at an FLS. Moderate agreement between the (UK and Dutch) EQ-5D-5L and SF-6D was identified with intra-class correlation coefficients of 0.625 and 0.654, respectively. Bland-Altman plots revealed proportional bias, as the differences in utilities between two instruments were highly dependent on the health states. Notwithstanding, high correlation between instruments was found (UK: rho=0.758; Dutch: rho=0.763). EQ-5D-5L and SF-6D utilities showed high correlation with physical component but low correlation with mental component score of SF-36. Both instruments showed moderate discrimination (effect size (ES)>0.5) for subgroup by baseline fracture type, and moderate responsiveness (0.5<standardized response mean (SRM)<0.8) in patients that sustained a subsequent fracture. We concluded that both EQ-5D-5L and SF-6D appeared to be valid utility instruments in patients with fractures attending the FLS. Construct validity and responsiveness (change after recurrent fracture) were comparable. However, these two instruments cannot be used interchangeably given only moderate agreement and differences in utilities and ceiling effect were revealed. Of note, trial discrimination could not be tested.

In **Chapter 8**, we assessed the potential economic benefits of the FLS from the Chinese healthcare perspective with a lifetime horizon using a Markov microsimulation model. We found when compared with no-FLS, that FLS was dominant (lower costs, higher QALYs) in China at the FLS cost of $200 per patient. The FLS was however not cost-effective in patients aged 80 years and older. We concluded that FLS care could potentially lead to lifetime cost-saving in patients who have experienced a fracture in China. More future research incorporating Chinese-specific real-world data are needed to confirm the results of our study and to better evaluate the cost-effectiveness of FLS in China.

In **Chapter 9**, we assessed the cost-effectiveness of FLS in patients with a recent fracture from the Dutch societal perspective using real-life data. We found that for patients with a recent fracture aged 50 years and older, the availability of an FLS was associated with a €45 higher cost and 0.11 additional QALY gained leading to an ICER of €409 per QALY gained, indicating FLS was cost-effective compared to no-FLS at the Dutch threshold of €20,000/QALY. For every 1,000 patients attending the FLS, 53 subsequent fractures were avoided during their lifetime. For patients at the ages of 50, 60, 70 and 80 years, FLS was consistently cost-effective; patients aged 80 years resulted in slightly greater QALY gained compared to younger groups. Our results were robust in all one-way sensitivity analyses. At a

threshold of €20,000 per QALY gained, FLS was cost-effective compared to no-FLS in 90% of the simulations. This study provides the first economic results of FLS in the Netherlands. We concluded that the availability of an FLS is cost-effective compared to no-FLS in patients with a recent fracture aged 50 years and older in the Netherlands. The implementation of FLS could lead to lifetime health-economic benefits.

CHAPTER 11

General Discussion

Given the increasing burden of osteoporosis and fractures, the wide implementation of fracture liaison services (FLSs) for secondary fracture prevention and the importance of economic evaluations when prioritizing health interventions and informing decision-making, the aim of this dissertation was to study the cost-effectiveness of osteoporosis management as well as to explore the clinical and economic effectiveness of FLS.

This dissertation consists of two parts. In the first part (Chapters 2-4) we performed a systematic review of cost-effectiveness analyses of drugs for osteoporosis (Chapter 2), provided an overview of cost-effectiveness of treating men with osteoporosis (Chapter 3), and summarized evidence on effective tools for communicating risk of fracture (Chapter 4). The second part (Chapters 5-9) addressed the clinical and economic outcomes of FLS care in the Netherlands and China. We evaluated the impact of FLS on subsequent fractures and mortality (Chapter 5), explored the health-related quality of life (HRQoL) using longitudinal data and compared the psychometric properties of EQ-5D-5L and SF-6D to assess the interchangeability of these two instruments in patients with a recent fracture presenting at an FLS in Chapters 6 and 7, and assessed the cost-effectiveness of FLS in mainland China and the Netherlands in Chapters 8 and 9.

In this chapter, we first discuss methodological aspects of this dissertation; we then summarize key points/messages and implications for clinical practice and research, and finally provide future perspectives regarding osteoporosis and fracture prevention.

METHODOLOGICAL CONSIDERATIONS

Reviewing the literature

Four chapters (Chapters 2, 3, 4, 5) of this dissertation concern a review of literature published in peer-reviewed journals. Two systematic narrative reviews (Chapters 2, 3) were performed to summarize information on the cost-effectiveness of treating women or men with osteoporosis respectively. A scoping review (Chapter 4) was conducted to investigate medication adherence for osteoporosis and communication strategies regarding risk of fracture. Finally, a systematic review with meta-analysis was performed to capture the effectiveness of FLS on subsequent fracture and mortality (Chapter 5).

Different reviews focus on different aspects in evidence collection and interpretation. A systematic narrative review is usually conducted to provide

a descriptive and qualitative summary of available evidence mainly from peer-reviewed publications and to evaluate the quality of studies; a scoping review with the purpose of scoping a body of literature to identify knowledge gaps. By contrast, a quantitative systematic literature review or meta-analysis aims to synthesize data across included studies quantitatively and thus provides estimates of the magnitude of effects. In this dissertation, a meta-analysis (Chapter 5) was performed to evaluate the magnitude of effects of the FLS on subsequent fracture and mortality, however, we found it difficult to conduct a meaningful meta-analysis for economic evaluations given the main limitation of heterogeneity in populations, intervention details as well as outcomes, therefore only qualitative systematic reviews were conducted in Chapter 2 and 3. We also found several published studies [1,2] have explored the possibilities and methods of performing meta-analyses of economic evaluation studies [3], it remains challenging as reported for two main reasons. First, economic evaluations are heterogeneous, which can be caused by model type, model structure, population, willingness to pay, perspective, time horizon, and discount rate [2]. Second, the health economic evaluations are context-specific, usually conducted in individual country settings, causing model input data differ greatly between countries (i.e. transferability between regions/countries). Besides, the Cochrane handbook for Systematic Reviews of Interventions as well as a recent working group of ISPOR also indicated that there are no agreed methods for pooling estimates of cost-effectiveness (synthesizing ICERs) [4]. Improving the quality, transparency and transferability of economic evaluations across jurisdictions could be helpful to synthesize health economic data.

For economic evaluations, several reporting guidelines have been developed to assess the quality underlying studies of systematic reviews. Currently, checklists such as CHEERS/CHEERS 2022 statement, defining the minimum amount of information required, are commonly used to conduct the quality assessment. However, CHEERS has been used inappropriately as indicated by CHEERS 2022 [5], i.e. CHEERS is not a quality appraisal tool, but a tool to help reporting and potentially to assess the quality reporting (but poor reporting does not mean poor quality). In addition, guidelines for economic evaluation often lack disease specificities, therefore disease-specific checklists are important to be developed and applied to assess whether methodological standards were fully met in economic evaluation studies.

In the field of osteoporosis, an ESCEO-IOF guideline was developed and published in 2019 which provides guidance for the design, conduct, and reporting of economic evaluations in osteoporosis to improve their transparency, comparability, and methodologic standards [6]. This osteoporosis-specific guideline was used in our

two systematic reviews (Chapters 2, 3) to appraise the quality of included economic evaluation studies. We found several issues should receive more attention. First, not all economic analyses have included an increased risk after fracture events within the model though it has been reported by extensive studies, and the increased risk was often constrained to a specific fracture site rather than multiple sites, and the additional effect on costs and/or utility after multiple fractures was also scarcely included (Chapters 2, 3). The main reason is the lack of relevant data, therefore future studies would be needed to know the effects of fractures at the same and different sites on fracture risk as well as costs and utility. Second, excess mortality caused by vertebral fracture (most papers only included the effect caused by hip fracture) and to what extent the mortality is attributable to fracture event were not taken into account by some economic evaluations (Chapters 2, 3). Neglecting these issues would overestimate patients' life years as well as the effect of fracture on mortality. Third, the misuse of model input data in economic evaluations of men with osteoporosis raised a major issue. As we indicated in our study (Chapter 3) that in the case of lacking male-specific data such as utility and treatment efficacy, it might not weaken the analysis to use female data given similarities in women and men were revealed by research, however, it is important that male-specific data should be used for several parameters, in particular for fracture incidence, increased risk after subsequent fractures, excess mortality, and fracture costs owing to the differences between men and women.

Chapter 4 is the first scoping review summarizing evidence on effective tools for communicating risk of fracture. All studies identified in this review agreed that communication of risk is an essential component in the care of patients, however the implementation in clinical practice remains inadequate even though most clinicians may feel that shared decision making is already standard in their practice. We found the common method for communicating risk of fracture in clinical practice is sending patients an individualized letter, after a DXA test, with information about the risk of fracture and educational material about osteoporosis. However, these information with medical and statistical jargons cannot be well understood by most patients without extra verbal explanations and are largely neglected. We identified the ways in which information is presented by clinicians, the ability of the clinician to modify their language according to the needs of the patient, and the relationship between clinicians and patients are important issues that should be taken into account in clinical practice. A growing body of research supports the use of visual presentation of diagnostic and health risk information as an efficient way to communicate risk, detailed information about our recommendations for clinical practice can be found in latter section (key points and implications for clinical practice).

A systematic review and meta-analysis was conducted in Chapter 5 to assess the effect of FLS on subsequent fracture and mortality. Some methodological considerations were highlighted in our study. First, selection bias during patients' enrollment was identified in some studies, i.e., only FLS attenders were included in FLS cohort leading to a comparison between all patients before the implementation of FLS (or in a hospital without FLS) versus FLS attenders, results could be biased as we know FLS non-attenders are generally older patients with more severe fractures, or patients who were hospitalized, ignoring these patients would overestimate the effect of FLS. Second, very few studies have taken into account the competing risk of mortality, potentially leading to an overestimation of the fracture incidence. Third, the immortal time between fracture and FLS visit was ignored by most studies, resulting in bias in estimation. Fourth, studies included in the meta-analysis had a relatively short follow-up time, limiting the possibility to capture the effect of FLS in particular on mortality. Recommendations for these frequently ignored issues can also be found in latter section (key points and implications for research).

Health utilities in patients attending the FLS

Two chapters (Chapters 6, 7) of this dissertation explored the health-related quality of life (HRQoL), one addressing the course of utility over time and the other the comparative validity of two different measurement instruments, the EQ-5D and SF-6D. The main methodological issues specifically relevant for findings from Chapter 6 concern selection bias (relatively healthy patients were included) and the lack of utility values before and immediately after fracture, as utilities were only collected following the first visit to the FLS, which was on average 3.5 months after the fracture. This limits accurate estimation of the evolution/responsiveness of HSUV related to fractures within and between (groups of) patients. In addition, the data that were used in both chapters were obtained from a single center from the Netherlands. Therefore, these findings cannot be generalized and extrapolated without caution. For the study exploring the interchangeability of different instruments (Chapter 7), country-specific value set for utilities instruments is not available in each country, in this case, the UK or the US valuation set is commonly used, however, populations norms differ greatly between countries, ignoring the patient perspective might lead to biased estimations. Therefore, applying a value set of which the population norm is comparable to the target country would be important.

Economic evaluations of the FLS in different countries

We applied two cost-effectiveness analyses on the health-economic benefits of FLS, one for China and another for the Netherlands (Chapters 8, 9). Both studies were

model-based economic evaluation (adapted from a previously validated Markov microsimulation model) and used a lifetime horizon with cycle length of 6 months. However, the cost-effectiveness estimation in China was more uncertain given the lack of country-specific FLS-related data, whereas real-world FLS and fracture-related data were collected and used in the Dutch model, leading to more precise and valid estimations. Besides, a healthcare perspective was taken in the Chinese model while the Dutch model also included a societal perspective was presented in line with the guideline of conducting economic evaluations in both countries. In addition, the real-world treatment scenarios and all fracture types (hip, vertebrae, non-hip non-vertebrae) were included in the Dutch model (Chapter 9), however, assumptions were made for treatment scenarios in China and only three types of fracture (hip, vertebrae, wrist) were modeled due to the lack of data (Chapter 8). Moreover, outdated and non-country-specific data were the main issue in the Chinese model (data from other countries were used for some model parameters). By contrast, most Dutch data were available and obtained from Dutch official website or Dutch publications. Both studies posed challenges that often relate to the absence of relevant data to parameterize the models. More future research incorporating Chinese-specific real-world data is needed to confirm the results of our study and to better evaluate the cost-effectiveness of FLS in China. In the Netherlands, it also remains difficult to assess the cost-effective of FLS because current data on the natural course of health and costs after a fracture are difficult to capture and not available; besides, long-term data on fractures, medication adherence and mortality are not available, and specification was not separately made for FLS attenders and non-attenders. In addition, it should be noted that although the FLS was widely implemented in the Netherlands, the comparison between FLSs is still challenging given that FLSs varied in terms of the key persons coordinating the FLS (physician, nurse, or other healthcare professional), setting (hospital, community), intensity (single, multiple), and duration (long or short term), which lead to further variation in clinical and economic benefits.

KEY POINTS AND IMPLICATIONS FOR CLINICAL PRACTICE AND RESEARCH

Based on the findings in these chapters, we have summarized key points and implications for clinical practice and research (Table 1).

Systematic reviews of cost-effectiveness of interventions for osteoporosis

The two systematic reviews of cost-effectiveness of interventions for osteoporosis in men and women (Chapters 2, 3) suggest that anti-osteoporotic drugs and

nutrition supplements are generally cost-effective in men and women aged 60 years and older with prior fractures or with osteoporosis (with slightly higher ICERs in men). This has important implications when prioritizing health interventions for patients with osteoporosis, and it seems not necessary to differentiate men and women in the process of decision-making. The additional health benefits indicated by sequential therapy (compared to monotherapy) and potential cost-effectiveness in very high risk population would be useful and insightful for clinical practice. Future studies adhering to ESCEO-IOF guideline in the design and conduct cost-effectiveness analysis (CEA) in the field of osteoporosis is recommended. More attention should be paid on frequently unreported items such as "increased risk of fractures after fracture", "excess mortality" and "additional effect on costs/utility caused by multiple fracture sites". In addition, male-specific data should be used especially for fracture incidence, increased risk after subsequent fractures, excess mortality, and fracture costs in future economic evaluations in men with osteoporosis.

Medication adherence and fracture risk communication

With regard to medication adherence and fracture risk communication (Chapter 4), it is obvious that low adherence to osteoporosis medication could lead to increased risk of fractures, representing a substantial clinical and economic burden. Interventions are needed in clinical practice to make patients understand their fracture risk and improve the medication adherence. In current clinical practice, after a DXA test, an individualized letter containing information about the risk of fracture are usually sent to patients. However, the written content of the letter is poorly expressed and/or not well understood by the patient given their limited health literacy. We therefore recommend to use simplified language (e.g., avoidance of clinical or statistical jargon, use of simple and well-structured sentences). Numeric data (e.g., frequencies, percentage, probabilities data) should be adapted to the literacy levels of patients. Besides, pictorial representations of fracture risk (visual aid) would also be a good way to communicate fracture risk. A previous study [7] provided preferences of patients for four different visual depictions of fracture risk (faces array, arrow, bar and stoplight) and indicated bar graphs and stoplight color systems seem to be the most preferred and understandable visual methods for communicating information about risk of fracture. faces array is rated as the most difficult one. In addition, FRAX® as a tool for assessing individuals'risk of fractures is also found helpful in improving participants' perception of the risk of fracture, their desire to change bone health habits and acceptance of treatment. One study [8] suggested that FRAX® should be integrated into bone densitometry reporting or incorporated into comprehensive, user-friendly, decision aids.

With regard to future research, we did not identify any study that looked at whether there could be any differences between risk communication with patients having osteoporosis and patients with a prior fracture, as different populations could potentially differ in their preferences and needs. Therefore it would be interesting for future studies to explore whether similar or different communication strategies are required for different populations. Besides, the effect of emerging methods and tools on fracture risk communication should be investigated. In addition, it would be of interest to understand cultural differences on the understanding of health information and fractures risks by investigating patients from different countries/ backgrounds.

Clinical outcomes of FLS

Based on the findings in Chapter 5, FLS care is associated with a significantly lower subsequent fracture and mortality risk. Therefore, the wide implementation of FLSs should be supported to increase deployment of FLS for patients. Here below are some key points for studies when exploring the clinical outcomes of FLS. First, avoiding selection bias during patients' enrollment is crucial to guarantee the comparability of two cohorts, i.e. patients who were unable or not willing to visit the FLS should be included in the FLS group and in all analyses, according to the intention-to-treat principle when a FLS population is compared to a non-FLS population. Second, when analyzing subsequent fracture risk, the competing risk of mortality should be considered. A competing risk survival regression analysis should be a standard procedure when analyzing subsequent fracture risk in FLS research. The method of Fine and Gray [9] is commonly used which deals with the competing risk of mortality by retaining participants in the risk set with a diminishing weight when they die, rather than simply censoring them at the time of death [10]. Third, when comparing FLS versus no FLS care, it is also important to take into account the immortal time bias. Compared with a situation without FLS, patients have to be alive to attend the FLS, therefore these patients are essentially 'immortal' in the time between fracture and FLS visit. Therefore, the immortal time between the time of fracture and FLS attendance should be corrected for [11]. In most cases the study cannot be designed to avoid immortal time bias, however which can be avoided by acknowledging a change in exposure status using a time-dependent covariate [12]. Fourth, future studies should consider a follow-up duration of at least 2 years to adequately capture the effect of FLS on clinical outcomes. Fifth, to ensure the sufficient statistical power, researchers should estimate the minimum sample size required when studying the clinical outcomes of FLS, at least 80% patients should present during follow-up period, and at least 50% invited/eligible patients with a recent fracture are expected to attend the FLS.

Health utilities in patients attending the FLS

In Chapter 6 we performed a longitudinal study exploring the change of health-related quality of life (HRQoL) in patients with a recent fracture presenting at an FLS for the first time. No significant change in health state utility value (HSUV) was captured over 3 years. The primary potential reason is the lack of patients' utility values immediately after fracture and the inclusion of relatively healthy patients. Therefore for studies investigating the long-term effect of FLS on patients' quality of life, it is important to gain their HSUV immediately after fracture, otherwise it is difficult to conclude the improvement in HRQoL is attributable to the natural healing process of fracture or the effect of FLS. However, it might be challenging for FLS clinic to timely identified and invited patients with a recent fracture, this raises another consideration, i.e. implementing a clear and efficient fracture pathway in digital hospital systems is essential for case-finding and FLS invitation, further minimizing the time gap between fracture and FLS visit. In addition, selection bias should be avoided during patients' enrollment, reaching patients with more severe fractures, older patients, or patients who were hospitalized to collect their QoL data is challenging but still doable.

In Chapter 7, although our study indicated both EQ-5D and SF-6D appeared to be valid utility instruments in patients with fractures attending the FLS, the differences in HSUV should be interpreted with caution. For clinical practice/ research, the selection of instrument should be based on the research question and the time dimension. We found EQ-5D HSUV is more sensitive to physical health however SF-6D to mental health, therefore if the researchers focus more on patients' functional status (recovery) attending the FLS, the EQ-5D questionnaire might be more appropriate to use. The SF-36 seems more useful to evaluate the mental and emotional component of health. In addition, EQ-5D uses "today" as the recall period while the SF-36 used the recent 4 weeks, researchers should choose the appropriate instrument which is aligned to their targeted time dimension.

Economic evaluations of the FLS

Two model-based economic evaluations (Chapters 8, 9) suggested the cost-effective of FLS care in both China and the Netherlands. It could be a positive signal for Chinese to introduce and implement FLSs in China. For clinical practice, building an FLS team with members from different fields of expertise (rheumatologists, endocrinologists, geriatricians) coordinated by a FLS nurse, could be a starting point. Besides, IOF has developed a Mentorship program to enable the implementation of the Post-Fracture Care (PFC) coordination programs (such as FLSs) by connecting experienced PFC program champions with any institutions willing to establish a new PFC program. The mentorship program is also beneficial for China to learn

some experience of setting up FLSs from countries with similar healthcare system. Knowledge gap (whether FLS is cost-effective in China) should be closed by future studies based on real-life data. We recommend future studies collect FLS-related real-life data, including FLS attendance rate, FLS costs, treatment scenarios, initiation of treatment, and adherence in FLS. In addition, country-specific detailed epidemiology related to osteoporosis/bone fracture such as gender- and age-specific osteoporosis prevalence, incidence of fracture and healthcare costs of osteoporotic fractures are also important to perform a high-quality economic evaluation, which is also necessary to formulation projections and assist policy development.

In the Netherlands, although patients attending FLS were evaluated, treated and followed in high compliance with the IOF standards and associated with clinical and economic benefits, these positive initiatives need to be reinforced. First, given attendance and treatment initiation are two important factors for the success of FLS, ensuring there is a clear and open pathway for FLS invitation is important. Besides, a better coordination between secondary care health professionals and primary care physicians could attribute to a better long-term adherence to anti-osteoporosis medication. Adequate reimbursement might improve FLS attendance rates including the use of Dual-energy X-ray absorptiometry (DXA) with vertebral fracture assessment (VFA) in patients with a recent fracture. Second, the Best Practice Framework (BPF) and eleven patient-level key performance indicator (KPIs) developed by the International Osteoporosis Foundation (IOF) could serve as guidelines in the design of adequate FLS and improving the quality of existing services. Our study also provides information for the development of future economic evaluations of FLSs given the wide implementation in the Netherlands. In addition, studies reporting on long-term follow-up of FLS outcomes such as medication adherence, subsequent fractures and mortality are anticipated.

FUTURE PERSPECTIVES

Osteoporosis/fracture prevention management

Osteoporosis remains largely underdiagnosed and undertreated, poor medication intake and adherence is especially marked in high-risk patients [13]. Considering the escalating health and financial burden caused by fractures in the context of the ageing population, it is important to reinforce osteoporosis and fracture prevention strategies despite several initiatives that are already in place. Investigation of reasons behind underdiagnosis and undertreatment as well as poor medication adherence is the first step to come up with targeted solutions. For example, in some

countries, DXA assessment is not covered by health care insurance, resulting in substantial out-of-pocket costs, financial incentives might be helpful to get more patients diagnosed (e.g. incorporating osteoporosis screening into standard annual elderly health check). Besides, osteoporosis as a silent disease is often overlooked, increasing awareness of osteoporosis and fractures in both lay and healthcare spheres via education/training program and effectively communicating patients' risk of fracture via simplified language (adapted to the literacy levels of patients) and/or decision aids (e.g. bar graphs and stoplight color systems) could get more patients treated. In addition, better coordination between primary care physicians, secondary care health professionals and pharmacists is helpful in monitoring adherence to therapy. Moreover, although the clinical and economic benefits of anti-osteoporosis were revealed by extensive studies, the proper management of patients with osteoporosis is still ongoing, clinicians must know not only how to select the best available therapy in each clinical situation, but also how to discontinue or change treatment at a certain point in the evolution of the disease. Furthermore, discrepancies between national (updated) guidelines for osteoporosis and fracture prevention and how they were enforced by healthcare professionals were well recognized, proper implementation of guidelines should be improved in clinical practice.

Optimization of FLS implementation

Despite the recognized benefits of FLS in reducing the risk of fractures, FLS implementation could be optimized. First, in most FLS settings, patients were identified and invited from the emergency department (ED) because of a recent fracture. However, not all patients were properly registered in ED, which led to suboptimal case finding (hence lower screening and treatment rates). Therefore implementing a clear and efficient fracture pathway in digital hospital systems could get more patients identified and invited. Second, poor attendance rates have been recognized as a huge problem in most FLS clinics. It is therefore important to explore the reasons and develop tailored solutions. For example, some patients are relatively elderly with major fractures and cannot physically visit the FLS, home visit might be an option to provide proper therapy. Third, although specialist nurses and nurse practitioners are central to the activities of FLS in most hospitals, reinforcing the collaboration between healthcare professionals is important to optimize long-term adherence. Fourth, the lack of human resources was highlighted in FLS clinic [13] (leading to the low detection rates of osteoporosis), financial incentives could be supportive to improve the efficiency of the FLS care.

Research exploring clinical and economic outcomes of the medication/FLS

For research exploring the clinical outcomes of the FLS, several frequently

neglected methodological issues such as a design with comparison of total pre- and post FLS (not attenders versus non-attenders), competing risk of mortality, immortal time bias as well as longer follow-up period should be taken into account. With regard to economic evaluations of anti-osteoporosis medication/ FLS, future studies adhering to ESCEO-IOF guideline is recommended. Frequently unreported items such as "increased risk of fractures after fracture", "excess mortality" and "additional effect on costs/utility caused by multiple fracture sites" should be included in the economic model; in the case of lacking relevant national data, estimations from systematic review, meta-analysis, or other jurisdictions with similar population characteristics could be used. Besides, more studies are anticipated to be conducted in male population given the lacking evidence, and male-specific data in particular fracture incidence, increased risk after subsequent fractures, excess mortality, and fracture costs should be used in future economic evaluations in men with osteoporosis. In addition, real-world FLS-related data such as treatment initiation and scenarios, FLS attendance and costs are important to assess real-life cost-effectiveness of FLS.

Table 1. Key points and implications for clinical practice and research(er)

Studies	key points	Clinical practice	Research(er)
Systematic reviews of CEA of interventions for osteoporosis in men and women (Chapter 2 & 3)	- Active osteoporotic drugs are generally cost-effective in men and women ≥ 60 years with prior fractures or with osteoporosis, reimbursement for these active drugs should be considered as part of the standard of care - Men and women showed similar results regarding the cost-effectiveness of drugs and intervention thresholds. Fracture risk reduction is the primary consideration in the treatment for osteoporosis irrespective of sex	- Sequential therapy has the potential to generate extra health benefits in comparison with monotherapy - Osteoporosis medications are a good way of allocating resources	- Compared to studies in women, CEA in men with osteoporosis are largely insufficient - Quality was largely insufficient in most studies, adhering to ESCEO-IOF guideline in the design and conduct CEA in the field of osteoporosis is recommended - Male-specific data should be used in future economic evaluations in men with osteoporosis
Medication adherence and risk communication (Chapter 4)	- Interventions including patient education, drug regimen implementation, monitoring and supervision, interdisciplinary collaboration, and shared decision-making can facilitate communications between patients and doctor and further improve medication adherence	- Communication of numeric data on risk should be adapted to the literacy and numeracy levels of the individual patient - Appropriate use of visual aids (bar graphs and stoplight color systems) would be helpful	- Explore differences between risk communication with patients having osteoporosis/osteopenia and patients with a prior fracture - Investigate the impact of cultural differences on the understanding of health information and fractures risks
FLS clinical outcomes (Chapter 5)	- FLS care is associated with a significantly lower probability of subsequent fractures, indicating the necessity of wide implementation of FLS	- FLS should be developed and widely implemented given the revealed clinical benefit	- Avoiding selection bias during patients' enrollment is crucial to guarantee the comparability of two cohorts - Take into account competing risk of mortality and immortal time bias
Health-related quality of life in patients presenting at an FLS (Chapter 6 & 7)	- Both EQ-5D-5L and SF-6D are valid utility instruments in patients with fractures attending the FLS. However, they cannot be used interchangeably, interpreting HSUVs should be cautious	- The EQ-5D questionnaire might be more appropriate to use if the researchers focus more on patients' functional status attending the FLS - The SF-36 seems more useful to evaluate the mental and emotional component of health	- Obtaining patients' QoL immediately after fractures - Select more appropriate instruments based on their research question and time dimension

Table 1 (continued)

Studies	key points	Clinical practice	Research(er)
Cost-effectiveness of FLS in the Netherlands and in China (Chapter 8 & 9)	- China: the economic benefits of FLS is a positive signal to introduce and implement FLSs - The Netherlands: setting up a multidisciplinary team to improve the quality of current FLSs would benefit more patients and the whole society	- China: (1) building an FLS team with members from different fields of expertise, coordinated by a FLS nurse, could be a starting point for introducing FLS; (2) the BPF of IOF could serve as the guideline; (3) increasing the number of FLS is necessary - The Netherlands: (1) ensuring there is a clear and open pathway for FLS invitation; (2) a better coordination between secondary care health professionals and primary care physicians could attribute to a better long-term adherence; (3) adequate reimbursement might improve FLS attendance rates including the use of DXA with VFA	- China: knowledge gap in real-world FLS-related data - The Netherlands: more CEA research in other Dutch hospitals would be of interest - Studies reporting data in pre-FLS phase, and data regarding FLS non-attenders are needed

FLS fracture liaison service, HSUV health state utility value, AOM anti-osteoporosis medication, BPF best practice framework, IOF international osteoporosis foundation, KPI key performance indicator, CEA cost-effectiveness analysis, QoL quality of life, DXA dual-energy X-ray absorptiometry, VFA vertebral fracture assessment

REFERENCE

1. Crespo C, Monleon A, Díaz W, Ríos M. Comparative efficiency research (COMER): Meta-analysis of cost-effectiveness studies. *BMC Med Res Methodol*. 2014;14(1):1-9. doi:10.1186/1471-2288-14-139
2. Bagepally BS, Chaikledkaew U, Chaiyakunapruk N, Attia J, Thakkinstian A. Meta-analysis of economic evaluation studies: data harmonisation and methodological issues. *BMC Health Serv Res*. 2022;22(1):1-10. doi:10.1186/s12913-022-07595-1
3. Mandrik O (Lena), Severens JL (Hans., Bardach A, et al. Critical Appraisal of Systematic Reviews With Costs and Cost-Effectiveness Outcomes: An ISPOR Good Practices Task Force Report. *Value Heal*. 2021;24(4):463-472. doi:10.1016/j.jval.2021.01.002
4. Veettil SK, Syeed MS, Noviyan R, Thakkinstian A, Chaiyakunapruk N. Does meta-analysis of economic evaluations have the potential to play a role in healthcare decision-making in the United States? *J Med Econ*. 2022;25(1):750-754. doi:10.1080/13696998.2022.2083347
5. Husereau D, Drummond M, Augustovski F, et al. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) Statement: Updated Reporting Guidance for Health Economic Evaluations. *Appl Health Econ Health Policy*. 2022;20(2):213-221. doi:10.1007/s40258-021-00704-x
6. Hiligsmann M, Reginster JY, Tosteson ANA, et al. Recommendations for the conduct of economic evaluations in osteoporosis: outcomes of an experts' consensus meeting organized by the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) and. *Osteoporos Int*. 2019;30(1):45-57. doi:10.1007/s00198-018-4744-x
7. Edmonds SW, Cram P, Lu X et al (2014) Improving bone mineral density reporting to patients with an illustration of personal fracture risk. BMC Med Inform Decis Mak 14:1–12. doi: 10.1186/s12911-014-0101-y
8. Ettinger B (2008) A personal perspective on fracture risk assessment tools. Menopause 15:1023–1026. doi: 10.1097/gme.0b013e31817f3e4d
9. Fine JP, Gray RJ (1999) A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 94(446):496–509. doi:10.1080/01621459.1999.10474144
10. Nakayama A, Major G, Holliday E, Attia J, Bogduk N (2016)Evidence of effectiveness of a fracture liaison service to reduce the re-fracture rate. Osteoporos Int 27(3):873–879. doi: 10.1007/s00198-015-3443-0
11. de Bruin IJ, Wyers CE, van den Bergh JP, Geusens PP. Fracture liaison services: do they reduce fracture rates?. Therapeutic advances in musculoskeletal disease. 2017 Jul;9(7):157-64. doi: 10.1177/1759720X17706464
12. Shariff SZ, Cuerden MS, Jain AK, Garg AX. The secret of immortal time bias in epidemiologic studies. Journal of the American Society of Nephrology. 2008 May 1;19(5):841-3. doi: 10.1681/ASN.2007121354
13. https://www.osteoporosis.foundation/educational-hub/files/capture-fracturer-solutions-fracture-prevention-netherlands

Impact of the dissertation
Acknowledgements
List of Publications
Curriculum Vitae

IMPACT OF THE DISSERTATION

This dissertation contributes to optimize osteoporosis (bone fracture) management and in particular the knowledge on clinical effectiveness and economic value of the fracture liaison service (FLS). An important strategy to optimize fracture prevention is to ensure that patients at highest risk of (subsequent) fractures are timely diagnosed and treated. That is the main focus of FLS care, which is nowadays widely advocated as the most appropriate and effective approach for secondary fracture prevention, including patient identification, education, risk evaluation, treatment, and long-term monitoring. This chapter reflects on the impact of the research described in this dissertation on clinical practice, science, and society.

Clinical practice

The findings of this dissertation provide useful information for clinical practice. With regard to osteoporosis (bone fracture) management, our studies reveal that anti-osteoporosis drugs are generally cost-effective in men and women aged 60 years and older with prior fractures or with osteoporosis, patients can gain not only clinical benefits (prevent fractures) but also economic benefits. Besides, the additional health benefits indicated by sequential therapy (compared to monotherapy) and potential cost-effectiveness in very high risk population provides more options for clinical practice since it is important for clinician to know how to discontinue or change treatment at a certain point in the evolution of the disease to maintain the efficacy of prior therapy. In addition, exploring the reasons behind poor medication adherence and making patients understand their fracture risk is crucial for osteoporosis management. We found the awareness of osteoporosis in both patients and healthcare professionals is low, contributing to missed opportunities to prevent future fractures. To communicate patients' fracture risk, the written content of the letter (e.g. using clinical or statistical jargon) from the healthcare professionals is poorly expressed and/or not well understood by the patient given their limited health literacy. Using simplified plain language in the combination of online tools to convert the probability of fracture into patient-friendly visual presentations (e.g. bar graphs or stoplight color systems) could facilitate communication between healthcare professionals and patients. An optimal patient-centered approach by making sure that patients feel free to ask questions and express their concerns could also be helpful.

Regarding post fracture care program such as the fracture liaison service (FLS), on the one hand, we indicated wide implementation in clinical practice should be encouraged as FLS is associated with reduced subsequent fracture rate as well as economic benefits in patients with a recent fracture. On the other hand, the

intensity and quality of the FLS seem important to determine the success of the FLS implementation, therefore positive initiatives should be reinforced in clinical practice. For example, implementing a clear and efficient fracture pathway in digital hospital systems is important for case finding; understanding the reasons behind non-attendance and tailored care could be helpful to increase the attendance rate and get more patients treated; setting up the collaboration between primary care physicians, secondary care health professionals and pharmacists could monitor adherence to therapy; using online tools and resources provided by the International Osteoporosis Foundation could also optimize the national clinical management of FLS.

Science (research)

With regard to scientific impact, several studies in this dissertation fill the knowledge gap and contribute to science in the field of osteoporosis (bone fracture). First, two systematic reviews (Chapters 2,3) were conducted and provided an overview of cost-effectiveness of interventions for osteoporosis in men and women separately and issues regarding the study quality were reported. Given the increasing role of economic evaluation in informing decision-making about resource allocation, the research results would be relevant/interesting for reimbursement process, suggesting anti-osteoporosis medications are a good way of allocating resources. Besides, we marked the knowledge gap in economic evaluation in men with osteoporosis, the most frequently unreported criteria as well as the inappropriate use of model input data (especially in male studies) would be helpful for future researchers to close the knowledge gap and to improve the transparency and quality of the economic evaluation in the field of osteoporosis. Second, a scoping review (Chapter 4) was conducted to explore the current status of medication adherence, the reasons of non-adherence as well as strategies for fracture risk communication. The information would contribute to optimize osteoporosis management in clinical practice and address the importance of awareness of osteoporosis in both lay and healthcare spheres. Effective communication and shared decision making could increasingly put into practice. Third, a systematic review and meta-analysis (Chapter 5) was performed to investigate the impact of FLS on subsequent fracture and mortality rate. Although this is not the first study exploring the clinical effectiveness of FLS, our study was conducted with strict inclusion criteria and highlighted the frequently neglected methodological issues (such as comparability of two cohorts, competing risk of mortality, immortal time bias, and longer follow-up period). Our recommendations would be useful for future research to improve study quality and obtain valid estimation of clinical effectiveness of FLS. Fourth, another two studies (Chapters 6,7) placed the first study exploring health-related quality of life and the interchangeability instruments in patients with a recent

fracture presenting at an FLS. We highlighted the importance of avoiding selection bias in the stage of study design and noticing the differences in utilities by different instruments given healthcare decisions could be compromised when researchers or decision-makers are not aware of potential differences in utilities. Fifth, two model-based economic evaluations (Chapters 8,9) suggested the cost-effectiveness of FLS, provided positive signal to widely implement FLS and highlighted the necessity of reinforcing positive initiatives to improve the quality of FLS. These information would be useful for informing policy/regulatory/financial incentives and optimizing the implementation of FLS in real-life settings.

Society

Osteoporosis and bone fractures are a major concern for public health and are associated with substantial and escalating health and financial burden given the aging population. However, osteoporosis as a silent disease remains largely underdiagnosed and undertreated, poor treatment initiation and adherence is especially marked in high-risk patients. In the face of these challenges, this dissertation has important societal impact as it is directed to the management of patients with osteoporosis and bone fractures as well as the optimization of post-fracture care program. More specifically, it has impact on practical and policy implications to reduce healthcare and economic burden in the society.

This dissertation suggests anti-osteoporosis medications are a good way of allocating resources and the FLS is associated with clinical and economic benefits. It also highlights the necessity of increasing awareness of osteoporosis in both lay and healthcare spheres, the importance of effective communication (using patient-centered approach) to make patients understand their fracture risk and better adhere to therapy, and the benefits of widely implementing FLSs and optimizing the quality of the FLSs. These information provided by this dissertation would be useful for decision makers (can be payers, politicians, clinicians or other member of decision-making boards) in the healthcare setting to introduce some positive initiatives in clinical practice to identify more patients at risk of fracture and get more patients treated and adhered to therapy, to stimulate policy or financial incentives to support and optimize the osteoporosis management and FLS implementation, and finally in turn to lower the fracture risk and reduce the burden clinically and financially.

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给家人的一段话：

人言落日是天涯，望极天涯不见家，小时候想逃离的地方，是长大后再也回不去的地方，而最深刻的记忆却还是那一砖一瓦，一草一木。正如杨绛笔下的，我们这个家，很朴素。我们与世无求，与人无争，只求相聚在一起，相守在一起，各自做力所能及的事。碰到困难共同承担，困难就不复困难。然而，我们原本以为的岁月静好却是瞬息万变；总以为的来日方长却是世事无常。人生一梦，起起伏伏，能成为一家人即是缘分，不强求不执念，知其不可奈何而安之若命。如麦家所言，生活不是你活过的样子，而是你记住的样子。人生海海，山山而川，不过尔尔。让那些在阴雨天隐隐作痛的疤痕随风飘散，山海自有归期，风雨自有相逢。

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LIST OF PUBLICATIONS

Research papers:

1. **Li N**, Cornelissen D, Silverman S, Pinto D, Si L, Kremer I, Bours S, de Bot R, Boonen A, Evers S, van den Bergh J. An updated systematic review of cost-effectiveness analyses of drugs for osteoporosis. Pharmacoeconomics. 2021 Feb;39(2):181-209. doi: 10.1007/s40273-020-00965-9.
2. **Li N**, Beaudart C, Cauley JA, Ing SW, Lane NE, Reginster JY, Silverman S, Singer AJ, Hiligsmann M. Cost Effectiveness Analyses of Interventions for Osteoporosis in Men: A Systematic Literature Review. PharmacoEconomics. 2023 Feb 4. doi: 10.1007/s40273-022-01239-2.
3. **Li N**, Hiligsmann M, Boonen A, M. M. van Oostwaard, R. T. A. L. de Bot, C. E. Wyers, S. P. G. Bours, J. P. van den Bergh. The impact of fracture liaison services on subsequent fractures and mortality: a systematic literature review and meta-analysis. Osteoporos Int. 2021 Aug;32(8):1517-1530. doi:10.1007/s00198-021-05911-9.
4. **Li N**, van Oostwaard M, van den Bergh JP, Hiligsmann M, Boonen A, van Kuijk SM, Vranken L, Bours SP, Wyers CE. Health-related quality of life of patients with a recent fracture attending a fracture liaison service: a 3-year follow-up study. Osteoporos Int. 2022 Mar;33(3):577-588. doi: 10.1007/s00198-021-06204-x.
5. **Li N**, Boonen A, van den Bergh JP, van Kuijk SM, Wyers CE, van Oostwaard M, Vranken L, Bours SP, Hiligsmann M. A head-to-head comparison of EQ-5D-5L and SF-6D in Dutch patients with fractures visiting a Fracture Liaison Service. Journal of Medical Economics. 2022 Jan-Dec;25(1):829-839. doi: 10.1080/13696998.2022.2087409.
6. **Li N**, Si L, Boonen A, van den Bergh JP, Hiligsmann M. A model-based cost-effectiveness analysis of fracture liaison services in China. Archives of Osteoporosis. 2022 Oct 5;17(1):132. doi: 10.1007/s11657-022-01170-1.
7. Beaudart C, Hiligsmann M, **Li N**, Lewiecki EM, Silverman S. Effective communication regarding risk of fracture for individuals at risk of fragility fracture: A scoping review. Osteoporosis International. 2022 Jan;33(1):13-26. doi: 10.1007/s00198-021-06151-7.
8. Beaudart C, Boonen A, **Li N**, Bours S, Goemaere S, Reginster JY, Roux C, McGowan B, Diez-Perez A, Rizzoli R, Cooper C. Patient preferences for lifestyle behaviours in osteoporotic fracture prevention: a cross-European discrete choice experiment. Osteoporosis international. 2022 Jun;33(6):1335-46. doi: 10.1007/s00198-022-06310-4.

Book chapter:

9. Beaudart, C., **Li, N**., Hiligsmann, M., & Silverman, S. (2021). Effective Risk Communication and Improving Adherence. In Osteoporosis Treatment (pp. 115-143). Springer, Cham.

Editorial:

10. Hiligsmann M, **Li N**, Cooper C, Reginster JY, Silverman S, Carswell C, Husereau D. Improving the reporting of economic evaluation in osteoporosis: the value of CHEERS 2022 statement. Osteoporosis International. 2022 Apr 12:1-2. doi: 10.1007/s00198-022-06400-3.

CURRICULUM VITAE

Nannan Li (李囡囡) was born on January 1, 1992 in Ningxia, China. She completed secondary education in 2010, at Yinchuan No.1 Middle School. Afterwards, Nannan spent seven years in China Pharmaceutical University, she obtained a Bachelor's degree in Management (Marketing) in 2014 and a Master's degree in Public Health in 2017 with a thesis entitled "Regulation and Evaluation Strategies of Drugs in China and Abroad". During her Master (in 2016), she was an intern at Chinese Pharmaceutical Association, where she obtained research experience in the field of Pharmaceutical Affairs Law and Regulation. Qualified internship made her to be recruited as a research assistant at Chinese Pharmaceutical Association from 2017 to 2019.

In September 2019, Nannan started her Ph.D. research at the department of Health Services Research at Maastricht University with a scholarship from China Scholarship Council. During her Ph.D., she has been working on the project entitled "Optimizing fracture prevention and osteoporosis care: an economic evaluation of Fracture Liaison Services (FLS) in the Netherlands and China". The implementation of FLS is for secondary fracture prevention. In the cooperation with researchers in VieCuri Medical Center (in Venlo), Nannan collected relevant data in their FLS setting. As a dedicated and motivated Ph.D. candidate, she has followed several excellent courses such as decision modelling for economic evaluation from University of York, choice modelling and survey design from University of Leeds, and multilevel analysis of longitudinal data from Maastricht University. She gained rich experience of conducting economic evaluations, systematic review, meta-anaysis as well as discrete choice experiment. During her Ph.D. trajectory, she published several scientific research papers, a book chapter and a editorial with her colleagues. Moreover, several journals invited her to be a reviewer including Osteoporosis International, Calcified tissue international, and Expert Review of Pharmacoeconomics & Outcomes Research. She had the opportunity to attend annual World Congress on Osteoporosis, Osteoarthritis & Musculoskeletal Diseases in 2020 (virtual), 2021 (vitual), 2022 (vitual), 2023 (on-site), her posters were presented. She also attended LolaHESG as a discussant for one of her research papers.

Thanks to the swift progress of her Ph.D., she found her great interest in scientific research. It is glaring that doing research are endeavors she would like to engage in even more as a postdoctoral researcher after obtaining her doctorate degree.

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