

Review article

Systematic evidence of health economic evaluation of drugs for postmenopausal osteoporosis: A quality appraisal

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ABSTRACT

This paper systematically and critically reviewed all published economic evaluations of drugs for the treatment of postmenopausal osteoporosis. A systematic search was conducted using relevant databases for economic evaluations to include all relevant English articles published between January 2008 to January 2020. After extracting the key study characteristics, methods and outcomes, we evaluated each article using the Quality of Health Economic Studies (QHES) and the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) instruments. A total of 49 studies met the inclusion criteria. Majority of studies were funded by the industry and reported favorable cost-effectiveness. Based on the QHES total scores, studies ($n = 35$) were found to be industry-funded with higher QHES mean 82.44 ± 8.69 as compared with nonindustry funding studies ($n = 11$) with mean 72.22 ± 17.67 . The overall mean QHES scores were found to be higher 79.06 ± 11.84 , representing high quality (75–100) compared to CHEERS scores (%) 75.03 ± 11.21 . The statistical pairwise comparison between CHEERS mean (75.03 ± 11.21) and QHES mean (79.06 ± 11.84) were not statistically significant ($P = 0.10$) whereas, QHES score showed higher means as compared to CHEERS. This study suggests the overall quality of the published literatures was relatively few high-quality health economic evaluation demonstrating the cost-effectiveness of drugs for postmenopausal osteoporosis, and the majority of the literature highlights that methodological shortcoming.

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1. Introduction

Postmenopausal osteoporosis is a major public health concern and substantially associated with humanistic and economic burden [1]. It is estimated that about 200 million females suffer from osteoporosis around the world, and its 30% of all postmenopausal women have contributed in the United State (US) and in Europe [2,3]. US projected more than 2 million fractures every year due to osteoporosis and the cost increasing to \$25.3 billion by 2025 [4].

The total increased cost of the drugs for the prevention and management of osteoporosis is an enormous burden on patients

and put health care budget under strain. However, the limited number of studies on economic evaluations for the management of osteoporosis not stated clear health resources allocation. Health Technology Assessment (HTA) will play important role in decision-making to allocate effective healthcare resources to manage the disease [5].

An array of novel therapeutic approaches such as bazedoxifene, denosumab, ibandronate strontium ranelate, and zoledronic acid are available to manage osteoporosis in postmenopausal women [6]. However, the scarcity of available economical evidence decision makers facing difficulty in the selection of appropriate cost-effective treatments. Economic assessment such as cost-utility analysis (CUA), cost-effectiveness analysis (CEA) and cost-benefit analysis are required to evaluate the costs with respect to outcomes for the effective treatment [7,8].

Evaluating the quality of health economic studies (HES) is quite challenging, considering treatment with varying cost and

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effectiveness measures that must be achieved as well. Likewise, a CEA considering a variation in costs to differ in health outcomes, expressed in life years gained, whereas a CUA express the health outcomes as quality adjusted life years (QALYs) gained.

HES have been widely implemented in health policy and decision-making which is an important element of programmes for HTA internationally [2]. Therefore, transparency of reporting is an essential factor to evaluate methods, study perspective, assumption, model and possible bias of HES results. To address this question, there is several instruments has been developed to appraise the methodological quality of HES. The 'British Medical Journal,' the 'Drummond' and the Consensus on Health Economic Criteria (CHEC) checklists are well-known instruments for qualitative evaluation [9–11].

Additionally, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) issued the Consolidated Health Economic Evaluation Reporting Standards statement (CHEERS) statement for the qualitative evaluation, with the objective to guide and further standardize the reporting of HES [12]. It consists of 24 item checklists is an attempt to optimize the reporting of HES and lead to better health decisions [12].

Whereas, the international panels of health economists developed and validated the Quality of Health Economic Studies (QHES) instrument to measure and appraising the quality of HES [13]. It is intended and validated for quantitative scoring, consisting of 16 items designed to support fast, and accurate assessment of HES quality. It emphasizes on appropriate methods, valid and transparent results, and comprehensive reporting of results in the individual study, that lead to greater weight in the health care decision-making [14].

Recently, a systematic review of cost-effectiveness studies of drugs for postmenopausal osteoporosis used CHEERS to assess the quality of the studies and suggested active osteoporotic drugs as cost effective as compared to naive treated women aged over 60–65 years with low bone mass, especially those with prior vertebral fracture [15].

Monten et al. [16] concluded that CHEERS evaluation is feasible and reliable for cost-effectiveness results and yields comparable results to validated instrument.

Previous studies recommended the QHES instrument may be useful for the evaluation of future HES [17,18]. In addition, recently Azar et al. [19] conducted a systematic literature review on the cost-effectiveness of lung cancer screening and treatment methods. The author reported QHES along with Drummond checklist were mostly used in assessing the quality of published HES among various assessment tools. Transparency and reporting of methods and findings must be well established in order to evaluate quality, reliability, relevance, and generalizability of HES results.

However, to date, no studies used QHES instrument to appraise the quality of health economics studies of drugs used for the treatment of postmenopausal osteoporosis. Therefore, the aim of this study was to find out a systematic evidence landscape of HES of drugs used for postmenopausal osteoporosis and to performed a qualitative and quantitative scoring assessment. The methodological approach of included studies was critically appraised using the CHEERS checklist, and the results were applied as a scoring system compared with the QHES scores.

2. Methods

2.1. Literature search

We performed a comprehensive literature search by using electronic databases PubMed/MEDLINE, Web of Science, CEA Registry from January 2008 to January 2020 as per Preferred Reporting

Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline [20]. The eligible full-text studies identify relevant HES evaluating the cost-effectiveness of drugs used for postmenopausal osteoporosis. The PubMed search strategy used the following text words or Medical Subject Headings (MeSH): "Osteoporosis, Post-Menopausal" OR "Osteoporoses, Post-Menopausal" OR "osteoporosis" OR fracture" AND "cost effectiveness" OR "cost-effectiveness" OR "cost-utility" OR "cost utility" OR "cost benefit" OR "cost-benefit" OR "cost-minimization" OR "cost-minimization" OR "budget impact" OR "budget-impact" OR "cost consequence" OR "cost-consequence." In particular, the search keywords 'osteoporosis' and 'fractures' were used in the CEA Registry.

Manual searches were also performed on Google Scholar and bibliographies of included studies and cross references of previous reviews were also examined to identify additional relevant publications. Language other than English was not included in the analysis.

2.2. Study selection

Study selection was based on an initial screening of identified titles and abstracts and the second screening of full-text articles by 3 independent reviewers (MA, MA, and RAK). Any disagreement was resolved by third senior reviewers (PG, PK, and MS). Studies were considered eligible if they met the following inclusion criteria: (1) patients with postmenopausal osteoporosis; (2) the exposure of interest was postmenopausal osteoporotic drugs; (3) reporting treatment for the prevention of osteoporosis that compared at least 2 alternatives treatment in terms of costs and outcomes; (4) the outcome of interest was cost or effectiveness; (5) the study design was economic analysis; such as cost-effectiveness, cost-utility, cost-benefit, and cost-minimization analyses.

2.3. Data extraction

Three independent reviewers (MA, MA, and RAK) extracted the abstract judiciously according to inclusion criteria. Any discrepancies were arbitrated by the third independent reviewer (PG, PK, and MS) until consent is achieved on every issue.

Data were extracted from the included articles using standard data extracting grid and compiled in Microsoft Excel. The main study characteristics included the first author's name, year of study, country, population, interventions, comparators, types of economic evaluation, outcome measures, perspective, type of model, time horizon, discount rates, the source of funding, and authors' conclusion.

2.4. Quality assessment

Two reviewers (MA and MA) independently assessed the quality of each HES study by using QHES and CHEERS.

There are a number of published criteria for evaluating health economic research. We considered following quality assessment tools:

2.4.1. CHEERS

CHEERS checklist is used to appraise the quality of HES, through the use of the 24-item including 6 categories (title and abstract, introduction, methods, results, discussion, and other).

Scoring was marked using 'yes' (reported in full), 'partially reported,' 'no' (not reported), or 'not applicable.' In addition, scores of reporting studies we assigned as '1' if fulfilled the requirement of reporting for that item completely, '0.5' for the partial report and otherwise '0' for not mentioned. The maximum score for a study reported all information completely was 24. Furthermore, the

overall quality rating of studies was scored as excellent (100%), good (>75%, <100%), moderate (>50%, ≤75%), and low (≤50%) respectively. These criteria were reported in previous systematic reviews of HES [21,22]. Recently a systematic review of economic evaluation demonstrated studies scoring above 85% were considered as high quality [23].

2.4.2. QHES

The QHES [14] is a practical quantitative instrument including 16 dichotomous items with varying weighed point, with maximum score 100. It emphasizes appropriate methods, valid and transparent results, and comprehensive reporting of results in each individual study, and reported to be a reliable and valid instrument [13,24,25]. When appraising QHES questions, all points were only given if the authors believed that the most important criteria for the questions were met.

Based on QHES instrument, the overall scores are categorized into category 1 (0–25.0 points), category 2 (25.1–50.0 points), category 3 (50.1–75.0 points) and category 4 (75.1–100 points) as per previous literature [26]. Studies with score of at least 75 of 100 possible points are considered high-quality economic analyses [13,14].

Furthermore, in order to compare QHES and CHEERS evaluation, CHEERS was translated into a quantitative score [27]. Resulting scores of these instruments were then transformed into percentages to allow the comparison.

3. Results

3.1. Literature search and study inclusion

The PRISMA flow diagram summarizing the process of study selection is shown in Fig. 1. The electronic databases search retrieved 3027 potentially relevant records after deduplication.

After the title and abstract screening on the basis of inclusion/exclusion criteria, 2596 studies were excluded. The remaining 431 full-text articles were assessed for eligibility. Further, 382 articles were excluded with primary reason: inappropriate reporting of drugs cost (n = 95), burden of the improvement of medication adherence (n = 39), male populations (n = 33), abstract only (n = 65), review articles (n = 63), language other than English (n = 38), inappropriate methodology for reporting (n = 49). Finally, a total of 49 studies were included after meeting the inclusion criteria.

3.2. Study characteristics

An overview of the included studies is presented in Table 1. Of 49 studies, majority of studies 46 (93%) examined CEA, only 2 studies evaluated CUA and 1 study presented both CEA/CUA/budget impact analysis.

Most of the studies are conducted in Europe; Belgium (n = 7), UK (n = 5), Sweden (n = 5), France (n = 3), Switzerland (n = 2), Spain (n = 2), and one each in Germany and Italy. Other remaining studies were conducted in US (n = 9), Japan (n = 5), Canada (n = 2), one each in Australia and Iran. There were 5 studies considered multicountry.

A healthcare payer perspective was used in most of the studies (n = 26), societal perspective (n = 13), and others studies were addressed respective countries specific payer perspective.

Most of the studies 47 (96%) used QALY as a health outcome measure except the article of [28] that used avoided and fewer fractures as an outcome. Seven studies disclosed no funding. Majority of studies established Markov model (n = 29), simulation-based model (n = 14), state-transition model (n = 4), and one used a discrete event simulation model [29]. The applied annual discount rate was 1.5%–5% among these, 33 studies (67.3%) studies applied 3.0% discount rate, and 13 (26.5%) were more than 3.0%.

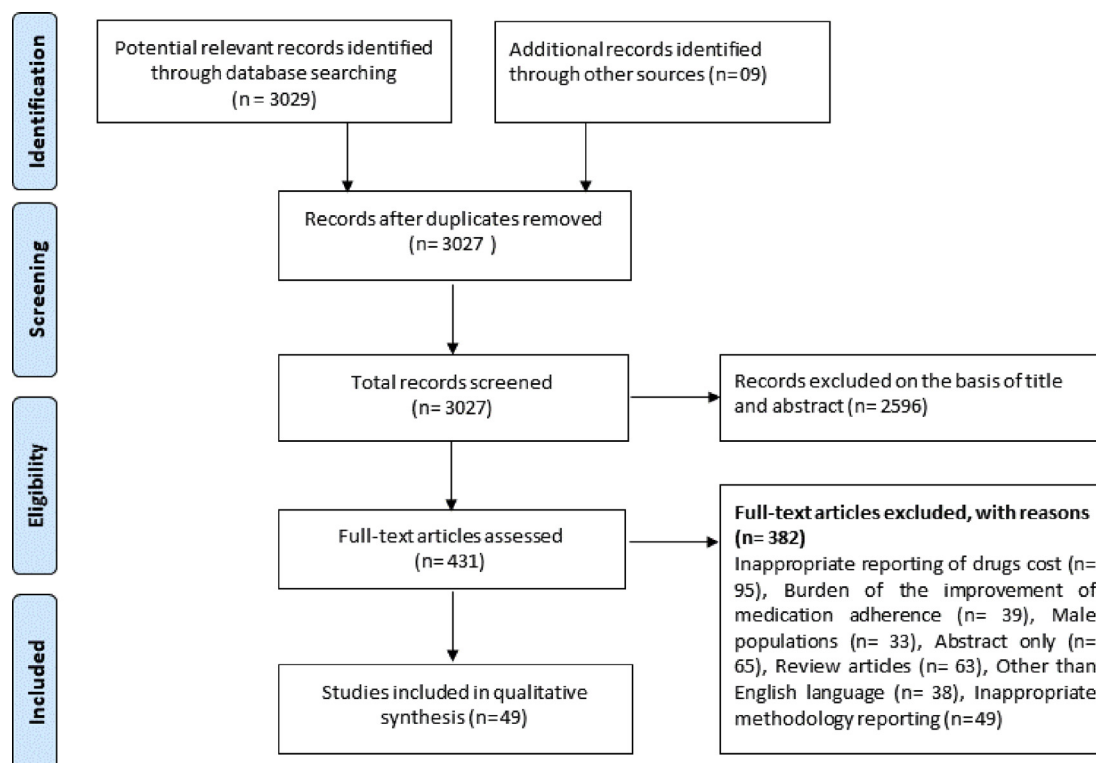


Fig. 1. Flow diagram showing study selection process.

Table 1
Characteristics of included studies.

No. Study	Country	Title	Type of study	Perspective	Outcome measure	Model type	Time horizon	Discount rates (costs, QALY)	Sponsor/funding source	
1	Jansen [49], 2008	UK, Netherland	Cost-effectiveness of a fixed dose combination of alendronate and cholecalciferol in the treatment and prevention of osteoporosis in the UK and The Netherland	CEA	Healthcare payer	QALY	Markov model	10 Years	4%, 4% (The Netherland). (3.5%, 3.5% UK)	Merck & Co
2	Lekander [68], 2008	Sweden, US, UK	Cost effectiveness of hormone therapy in women at high risks of fracture in Sweden, the US and the UK- Results based on the Women's Health Initiative randomized controlled trial	CEA	Societal	QALY	State-transition model	Lifetime	3%, 3%	Wyeth
3	Ding [69], 2008	Japan	The cost-effectiveness of risedronate treatment in Japanese women with osteoporosis	CEA	Healthcare payer	QALY	State-transition model	3 Years	5%, 5%	Scientific Research from the Ministry of Education, Science, Sports and Culture of Japan
4	Tosteson [50], 2008	US	Therapies for treatment of osteoporosis in US women: cost-effectiveness and budget impact considerations	CEA, BIA	Healthcare payer	QALY	Markov cohort model	10 Years	3%, 3%	The Alliance for Better Bone Health (Procter & Gamble Pharmaceuticals, Cincinnati, OH, and Sanofi-Aventis, Bridgewater, NJ, USA). Funding from many pharmaceutical companies
5	Kanis [53], 2008	UK	The cost-effectiveness of alendronate in the management of osteoporosis	CEA	Healthcare payer	QALY	Markov cohort model	Lifetime	3.5%, 3.5%	NR
6	Kanis [31], 2008	UK	Case finding for the management of osteoporosis with FRAX®—assessment and intervention thresholds for the UK	CEA	Healthcare payer	QALY	Markov cohort model	Lifetime	3.5%, 3.5%	NR
7	Wasserfallen [51], 2008	Switzerland	Cost-effectiveness and cost utility of risedronate for osteoporosis treatment and fracture prevention in women: a Swiss perspective	CEA, CU	Healthcare payer	QALY	Markov cohort model	Lifetime	3%, 3%	Sanofi-Aventis
8	Grima [70], 2008	Canada	Greater first year effectiveness drives favorable cost-effectiveness of brand risedronate versus generic or brand alendronate: modeled Canadian analysis	CEA	Canadian public payer perspective	QALY	Markov cohort model	Lifetime	5%, 5%	Alliance for Better Bone Health
9	Hiligsmann [71], 2009	Belgium	Development and validation of a Markov microsimulation model for the economic evaluation of treatments in osteoporosis	CEA	Healthcare payer	QALY	Markov microsimulation model	Lifetime	3%, 1.5%	ESCEO Amgen
10	Salpeter [72], 2009	US	The cost-effectiveness of hormone therapy in younger and older postmenopausal women	CEA	Societal	QALY	Markov cohort model	Lifetime	3%, 3%	Santa Clara Valley Medical Center and a Cornell Podell Emeriti Award
11	Lekander [73], 2009	US	Cost-effectiveness of hormone therapy in the US	CEA	Societal	QALY	Markov cohort model	Lifetime	3%, 3%	Wyeth
12	Berto [42], 2010	Italy	Risedronate versus alendronate in older patients with osteoporosis at high risk of fracture: an Italian CEA	CEA	Healthcare system	QALY	Markov cohort model	6 Years	3%, 3%	Sanofi-Aventis
13	Borgström [74], 2010	UK	The cost-effectiveness of strontium ranelate in the UK for the management of osteoporosis	CEA	Healthcare payer	QALY	Markov cohort model	Lifetime	3.5%, 3.5%	Servier
14	Borgström [75], 2010	UK	The cost-effectiveness of risedronate in the UK for the management of osteoporosis using the FRAX	CEA	Healthcare payer	QALY	Markov cohort model	Lifetime	3.5%, 3.5%	Alliance for Better Bone Health
15	Borgström [76], 2010	Sweden	Cost effectiveness of teriparatide and PTH (1-84)	CEA	Societal	QALY	Markov cohort model	Lifetime	3%, 3%	Lilly Europe

Table 1 (continued)

No. Study	Country	Title	Type of study	Perspective	Outcome measure	Model type	Time horizon	Discount rates (costs, QALY)	Sponsor/funding source	
16	Fardellone [1], 2010	France	in the treatment of postmenopausal osteoporosis Cost-effectiveness model of using zoledronic acid once a year versus current treatment strategies in postmenopausal osteoporosis	CEA	Societal	Fractures avoided	Simulation-based models	3 Years	NR	Novartis
17	Hiligsmann [32], 2010	Belgium	Cost-effectiveness of strontium ranelate versus risedronate in the treatment of postmenopausal osteoporotic women aged over 75 years	CEA	Healthcare payer	QALY	Markov microsimulation model	Lifetime	3%, 1.5%	Servier
18	Hiligsmann [77], 2010	Belgium	Cost-utility of long-term strontium ranelate treatment for postmenopausal osteoporotic women	CU	Healthcare payer	QALY	Markov microsimulation model	Lifetime	3%, 1.5%	Servier
19	Hiligsmann [59], 2010	Belgium	Potential clinical and economic impact of nonadherence with osteoporosis medications	CEA	Healthcare payer	QALY	Markov microsimulation model	Lifetime	3%, 1.5%	Novartis
20	Hiligsmann and Reginster [78], 2010	Belgium	Potential cost-effectiveness of denosumab for the treatment of postmenopausal osteoporotic women	CEA	Healthcare payer	QALY	Markov microsimulation model	Lifetime	3%, 1.5%	Amgen
21	Ivergård [55], 2010	US	Identifying cost-effective treatment with raloxifene in postmenopausal women using risk algorithms for fractures and invasive breast cancer	CEA	Societal	QALY	Markov microsimulation model	Lifetime	3%, 3%	Eli Lilly
22	Seeman [79], 2010	Sweden	Five years treatment with strontium ranelate reduces vertebral and nonvertebral fractures and increases the number and quality of remaining life-years in women over 80 years of age	CEA	Societal	QALY	Markov cohort model	Lifetime	3.5%, 3.5%	Servier
23	Ström [80], 2010	Sweden	FRAX and its applications in health economics-Cost-effectiveness and intervention thresholds using bazedoxifene in a Swedish setting as an example	CEA	Societal	QALY	Markov cohort model	Lifetime	3%, 3%	Pfizer
24	Thompson [43], 2010	Germany	The impact of fewer hip fractures with risedronate versus alendronate in the first year of treatment: modeled German CEA	CEA	Healthcare payer	QALY	Markov cohort model	5 Years	3%, 3%	Alliance for Better Bone Health
25	Akehrst [29], 2011	Finland, Norway, Netherlands	The cost-effectiveness of zoledronic acid 5 mg for the management of postmenopausal osteoporosis in women with prior fractures: evidence from Finland, Norway and the Netherlands	CEA	Healthcare payer	QALY	Discrete event individual-patient simulation model	Lifetime	Cost- 5.0% for Finland, 4.0% for Norway, 4.0% for the Netherlands. QALY- 5.0% for Finland, 4.0% for Norway, 1.5% for The Netherland	Novartis
26	Borgström [61], 2011	France, Germany, Italy, Spain, Sweden, UK	Cost-effectiveness of bazedoxifene incorporating the FRAX algorithm in a European perspective	CEA	Healthcare payer	QALY	Markov cohort model	Lifetime	3%, 3% for all countries except UK 3.5%, 3.5%	Wyeth
27	Hiligsmann and Reginster [36], 2011	Belgium	Cost-effectiveness of denosumab compared with oral bisphosphonates in the treatment of postmenopausal	CEA	Healthcare payer	QALY	Markov microsimulation model	Lifetime	3%, 1.5%	Amgen

(continued on next page)

Table 1 (continued)

No. Study	Country	Title	Type of study	Perspective	Outcome measure	Model type	Time horizon	Discount rates (costs, QALY)	Sponsor/funding source	
28	Jonsson [37], 2011	Sweden	osteoporotic women in Belgium Cost-effectiveness of denosumab for the treatment of postmenopausal osteoporosis	CEA	Societal	QALY	Markov cohort model	Lifetime	3%, 3%	Amgen
29	Pham [81], 2011	US	Cost-effectiveness of oral bisphosphonates for osteoporosis at different ages and levels of life expectancy	CEA	Societal	QALY	Markov cohort model	Lifetime	3%, 3%	Amgen
30	Chau [34], 2012	Canada	Cost-effectiveness of denosumab in the treatment of postmenopausal osteoporosis in Canada	CEA	Public payer	QALY	Markov cohort model	Lifetime	5%, 5%	Amgen
31	Lippuner [82], 2012	Switzerland	Cost-effective intervention thresholds against osteoporotic fractures based on FRAX in Switzerland	CEA	Healthcare payer	QALY	Markov cohort model	Lifetime	3%, 3%	MSD
32	Murphy [45], 2012	Sweden	The cost effectiveness of teriparatide as a firstline treatment for glucocorticoid-induced and postmenopausal osteoporosis patients in Sweden	CEA	Healthcare payer	QALY	Markov microsimulation model	Lifetime	3%, 4%	Lilly
33	Alzahouri [60], 2012	France	Cost-effectiveness of osteoporosis treatments in postmenopausal women using FRAX™ thresholds for decision	CEA	Healthcare system	QALY	Markov cohort model	Lifetime	4%, 3%	NR
34	Darbà [39], 2013	Spain	Cost-effectiveness of bazedoxifene versus raloxifene in the treatment of postmenopausal women in Spain	CEA	Healthcare payer	QALY	Markov cohort model	27 Years, Until patients were aged 82 years	3%, 3%	Pfizer
35	Hiligsmann [40], 2013	Belgium	Cost-effectiveness of bazedoxifene compared with raloxifene in the treatment of postmenopausal osteoporotic women	CEA	Healthcare payer	QALY	Markov microsimulation model	Lifetime	3%, 1.5%	Pfizer
36	Moriwaki [83], 2013	Japan	Cost-effectiveness of alendronate for the treatment of osteopenic postmenopausal women in Japan	CEA	Healthcare payer	QALY	Markov cohort model	Lifetime	3%, 3%	Pfizer
37	Parthan [38], 2013	US	Cost-effectiveness of denosumab versus oral bisphosphonates for postmenopausal osteoporosis in the US	CEA	US third-party payer	QALY	Markov cohort model	Lifetime	3%, 3%	Amgen
38	Ström [84], 2013	UK	Intervention thresholds for denosumab in the UK using a FRAX®-based CEA	CEA	Healthcare payer	QALY	Markov cohort model	Lifetime	3.5%, 3.5%	Amgen
39	Kim [41], 2014	Belgium, France, Germany, Ireland, Italy, Spain, Sweden, UK	Comparative cost-effectiveness of bazedoxifene and raloxifene in the treatment of postmenopausal osteoporosis in Europe, using the FRAX algorithm	CEA	Healthcare payer	QALY	Markov cohort model	Lifetime	3.0%, 3.0% for all countries, except for the UK (3.5%, 3.5%) and Ireland (4.0%, 4.0%)	Pfizer
40	Darbà [35], 2015	Spain	Cost-utility of denosumab for the treatment of postmenopausal osteoporosis in Spain	CU	Spanish National Health System	QALY	Markov model	7 Years	3%, 3%	Amgen SA, GSK
41	Mori [33], 2016	USA	Cost-effectiveness of combined oral bisphosphonate therapy and falls prevention exercise for	CEA	Societal	QALY	Markov microsimulation model	Lifetime	3%, 3%	Veterans Affairs Special Fellowship in Advanced Geriatrics.

Table 1 (continued)

No. Study	Country	Title	Type of study	Perspective	Outcome measure	Model type	Time horizon	Discount rates (costs, QALY)	Sponsor/funding source	
42	Golmohamdi [28], 2016	Iran	fracture prevention in the USA Cost-effectiveness of zoledronic acid to prevent and treat postmenopausal osteoporosis in comparison with routine medical treatment	CEA	Ministry of Health and insurance organizations perspective	Fewer fracture, QALY	NR	NR	NR	
43	Karnon [85], 2016	Australia	What are we paying for? A CEA of patented denosumab and generic alendronate for postmenopausal osteoporotic women in Australia	CEA	Australian health system perspective	QALY	State-transition model	10 Years	5%, 5%	NR
44	Mori [86], 2017	Japan	Cost-effectiveness of denosumab versus oral alendronate for elderly osteoporotic women in Japan	CEA	Societal, healthcare sector, government	QALY	Markov microsimulation model	Lifetime	3%, 3%	NR
45	O'Hanlon [46], 2017	USA	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	CEA	NR	QALY	Markov cohort model	Lifetime	3%, 3%	NR
46	Moriwaki [44], 2017	Japan	CEA of once-yearly injection of zoledronic acid for the treatment of osteoporosis in Japan	CEA	Japanese healthcare system	QALY	State-transition model	Lifetime	2%, 2%	Asahi Kasei Pharma Corporation
47	Ito [47], 2018	USA	Cost-effectiveness of single-dose zoledronic acid for nursing home residents with osteoporosis in the USA	CEA	Healthcare sector perspective	QALY	Markov cohort simulation model	Lifetime	3%, 3%	NR
48	Yoshizawa [87], 2018	Japan	CEA of drugs for osteoporosis treatment in elderly Japanese women at high risk of fragility fractures: comparison of denosumab and weekly alendronate	CEA	Societal perspective	QALY	Markov model	Lifetime	3%, 3%	NR
49	Hiligsman [48], 2019	France	Cost-effectiveness of gastro-resistant risedronate tablets for the treatment of postmenopausal women with osteoporosis in France	CEA	French payer perspective	QALY	Markov microsimulation model	Lifetime	3%, 3%	Teva and Theramex

CEA, cost-effectiveness analysis; QALY, quality adjusted life-year; BIA, budget impact analysis; FRAX, fracture risk assessment tool; NR, not reported; CU, cost-utility; PTH, parathyroid hormone.

while the remaining studies were reported 2.0% or no discount rate.

Lifetime, time horizon applied across 39 studies (79.5%), one study with the time horizon was 27 years until patients were aged 82 years, one study did not report time horizon [28], and the remaining studies were between 3 and 10 years.

The characteristics of the studies population, active treatment and comparator, and the quality scores of included studies are depicted in Table 2. The population of the included studies were women aged ranges from 50 to 90 years with a low bone mass density based on the definition of the World Health Organization (WHO) (bone mineral density [BMD] T score of -2.5) [30]. Women with a previous and high risk of fracture reported in 18 studies among, 11 studies with a previous vertebral fracture. Fracture risk algorithms such as fracture risk assessment (FRAX) tool was used across 8 studies which represent the 10-year probability of a major fracture and of hip fracture. A hormonal therapy as an intervention for postmenopausal osteoporotic drugs was used in 9 studies with different comparators.

The majority of studies ($n = 28$) compared differently branded bisphosphonate versus generic bisphosphonates and no treatment. Specially, generic alendronate was included in 11 studies whereas, no treatment was used as a comparator in 23 studies (52.3%). Studies ($n = 18$) were reported raloxifene, bazedoxifene versus no treatment and bisphosphonates. Three studies were reported bazedoxifene was cost-effective compared to raloxifene. Hormonal therapy was found to be cost-effective in the majority of studies among hysterectomized women. Active treatment was found cost-effective among women aged after 50 years with additional strong clinical risk factors such as prior fracture and parental history of hip fracture [31].

Various drugs were found cost saving to prevent fractures in women aged more than 80 years [31–33]. Denosumab was cost effective when compared with active osteoporotic drugs including generic alendronate, especially in the high-risk subgroups [33–38]. A subgroup analysis has shown, bazedoxifene was dominant over another selective estrogen receptor modulator (raloxifene) among

Table 2
Characteristics, comparators and scores of included studies.

No. Study	Population	Intervention and comparator	Authors' conclusion	QHEs score (%)	CHEERS score (%)
1 Jansen [49], 2008	Postmenopausal women aged over 50 years with a history of vertebral fracture and osteoporosis	Alendronate/vitamin D3 vs. no treatment, alendronate with dietary vitamin D supplements and ibandronate	Alendronate/vitamin D3 is cost-effective and dominant over ibandronate	84.00	70.83
2 Lekander [68], 2008	Postmenopausal women at a T score of -2.5	Hormone therapy vs. no treatment	Hormone therapy is a cost-effective	84.00	79.16
3 Ding [69], 2008	Women aged 55 years and over and treated with risedronate, those that are shown to be osteoporotic.	Risedronate vs. no treatment	Risedronate is a cost-effective	64.50	72.92
4 Tosteson [50], 2008	4 Risk groups among women with a T score ≤ -2.5	Risedronate, alendronate, ibandronate, and teriparatide	Risedronate have the most favorable cost-effectiveness profile	81.00	79.17
5 Kanis [53], 2008	Postmenopausal women aged over 50 years with different fracture risks	Generic alendronate vs. no treatment	Alendronate is a cost-effective	78.00	75.00
6 Kanis [31], 2008	Postmenopausal women aged over 50 years using FRAX	Generic alendronate vs. no treatment	Alendronate is a cost-effective	36.50	54.17
7 Wasserfallen [51], 2008	Women aged 70 years with established osteoporosis and previous vertebral fracture	Risedronate vs. no treatment	Risedronate was dominant	78.00	70.83
8 Grima [70], 2008	Postmenopausal women aged over 65 years	Branded risedronate vs. generic or branded alendronate	Risedronate is a cost-effective compared to generic or brand alendronate	85.00	85.42
9 Hiligsmann [71], 2009	Women aged 70 years with a 2-fold increase in the fracture risk of the average population	Alendronate vs. no treatment	Alendronate is a cost-effective	78.00	75.00
10 Salpeter [72], 2009	50- and 65-year-old women given hormone therapy or no therapy	Hormone therapy vs. no treatment	Hormone therapy is cost-effective	75.00	70.83
11 Lekander [73], 2009	Women with menopausal symptoms aged over 50 years	Hormone therapy vs. no treatment	Hormone therapy is cost-effective	65.50	75.00
12 Berto [42], 2010	Postmenopausal women aged ≥ 65 years with a previous vertebral fracture	Risedronate vs. generic alendronate	Risedronate is a cost-effective	94.50	75.00
13 Borgström [74], 2010	Postmenopausal women aged over 50 years using FRAX	Strontium ranelate vs. no treatment	Strontium ranelate is a cost-effective	84.00	75.00
14 Borgström [75], 2010	Postmenopausal women aged over 50 years using FRAX	Risedronate vs. no treatment	Risedronate is a cost-effective	84.00	77.08
15 Borgström [76], 2010	postmenopausal women; mean age: 70 years, total hip T score: 2.7 and 3.3 previous fractures	Teriparatide and PTH (1–84) vs. no treatment	Teriparatide seems to be a more cost-effective option PTH (1–84) compared to no treatment	93.50	72.92
16 Fardellone [1], 2010	Women with postmenopausal osteoporosis	Zoledronic acid vs. current treatment strategies	Zoledronic acid is a cost-effective	80.00	64.58
17 Hiligsmann [32], 2010	Postmenopausal osteoporotic women aged over 75 years	Strontium ranelate vs. risedronate	Strontium ranelate is a cost-effective	90.00	89.58
18 Hiligsmann [77], 2010	Women aged 70, 75, and 80 years either with a bone mineral density T score ≤ -2.5 SD or with prevalent vertebral fractures.	Strontium ranelate vs. no treatment	Strontium ranelate is a cost-effective	94.00	85.42
19 Hiligsmann [59], 2010	Women aged 65 years with a T score of -2.5	Branded bisphosphonates (and generic alendronate) vs. no treatment	Poor compliance and failure to persist with osteoporosis medications results not only in deteriorating health outcomes, but also in a decreased cost-effectiveness of drug therapy	68.00	79.17
20 Hiligsmann and Reginster [78], 2010	Women (over 60 years) postmenopausal osteoporosis	Denosumab vs. no treatment	Denosumab is cost-effective	84.00	87.50
21 Ivergård [55], 2010	Postmenopausal women aged 55, 60, and 65 years using FRAX	Raloxifene vs. no treatment	Raloxifene is cost-effective	78.00	70.83
22 Seeman [79], 2010	Subgroup of patients over 80 years of age with osteoporosis from the SOTI and TROPOS trials	Strontium ranelate vs. no treatment	Strontium ranelate is a cost-effective	54.50	29.17
23 Ström [80], 2010	Women aged 70 years with prior fracture and various T scores using FRAX	Bazedoxifene vs. no treatment	Estimation of cost-effectiveness for various types of patients with different combinations of CRFs, which more closely matches patients in clinical practice	77.00	58.33
24 Thompson [43], 2010	Postmenopausal women 65 years of age or older with a T score ≤ 2.5	Branded risedronate vs. generic alendronate	Risedronate is a cost-saving	97.00	79.17
25 Akehurst [29], 2011	Postmenopausal women aged 50–80 years who have experienced one previous fracture and have a T score of -2.5	Zoledronic vs. calcium/vitamin D, bisphosphonates	Zoledronic acid is a cost effective compared with other branded bisphosphonates	78.00	81.25
26 Borgström [61], 2011	Postmenopausal women aged over 60 years using FRAX	Bazedoxifene vs. no treatment	Bazedoxifene is a cost-effective	78.00	89.58
27 Hiligsmann and Reginster [36], 2011	Postmenopausal women aged over 60 years with T score ≤ -2.5 or with previous vertebral fracture	Denosumab vs. oral bisphosphonates, branded risedronate, and generic alendronate	Denosumab is a cost-effective compared with branded alendronate and risedronate	76.50	89.58
28 Jonsson [37], 2011	Typical Swedish patient population (women aged 71 years, T score ≤ -2.5 and a prevalence of morphometric vertebral fractures of 34%)	Denosumab vs. generic alendronate, branded risedronate, strontium ranelate and no treatment	Denosumab is a cost-effective	69.00	72.92
29 Pham [81], 2011	Cohort of women with various life expectancies beginning osteoporosis	Bisphosphonate vs. no treatment	Biphosphonate is a cost effective	84.00	72.92

Table 2 (continued)

No. Study	Population	Intervention and comparator	Authors' conclusion	QHEs score (%)	CHEERS score (%)
	treatment between the ages of 50 and 90 years				
30 Chau [34], 2012	Women aged 72 years with T score of -2.16 and 24% PVF (FREEDOM trial)	Denosumab vs. usual care (no therapy, alendronate, risedronate, raloxifene)	Denosumab is a cost-effective	85.00	85.42
31 Lippuner [82], 2012	Women aged over 50 years with different fracture probabilities	Branded alendronate vs. no treatment	Branded alendronate is a cost-effective	69.00	62.50
32 Murphy [45], 2012	Patients with a BMD T score of -3.0 , a historical vertebral fracture and an incidence vertebral fracture and patients with a BMD T score of -3.0 and an incidence vertebral fracture	Teriparatide vs. bisphosphonate and no treatment	Teriparatide is a cost-effective	84.00	75.00
33 Alzahouri [60], 2012	Postmenopausal 70-year-old woman with a T score of -2.5	Branded alendronate vs. no treatment	Branded alendronate is a cost effective	66.00	79.17
34 Darbà [39], 2013	Postmenopausal Spanish women aged 55–82 years with established osteoporosis and a high fracture risk	Bazedoxifene vs. raloxifene	Bazedoxifene is cos-effective compared with raloxifene	85.00	62.50
35 Hiligsmann [40], 2013	Women aged 70 years with T score ≤ -2.5	Bazedoxifene vs. raloxifene	Bazedoxifene is cos-effective, and even dominant compared with raloxifene	84.50	77.08
36 Moriwaki [83], 2013	Osteopenic postmenopausal women aged over 65 years without a history of fracture	Alendronate vs. no treatment	Cost-effectiveness, preventive alendronate treatment should be considered for a more selected population on the basis of age, BMD, and number of CRFs.	89.00	79.17
37 Parthan [38], 2013	Cost effectiveness of denosumab versus oral bisphosphonates for postmenopausal osteoporosis in the US	Denosumab vs. generic alendronate, branded risedronate and branded ibandronate	Denosumab is cost-effective or dominant compared with generic alendronate	75.50	83.33
38 Ström [84], 2013	Postmenopausal women aged over 50 years at different degrees of osteoporotic fracture risk	Denosumab vs. no treatment, generic alendronate, risedronate and strontium ranelate	Denosumab is a cost-effective	75.00	77.08
39 Kim [41], 2014	Postmenopausal women aged over 55 years using FRAX	Bazedoxifene vs. raloxifene	Bazedoxifene is cos-effective compared with raloxifene	95.00	81.25
40 Darbà [35], 2015	Osteoporotic postmenopausal women	Denosumab vs. no treatment, generic bisphosphonates, and strontium ranelate	Denosumab is cost-effective	79.00	79.17
41 Mori [33], 2016	Women without prior major osteoporotic fractures	Combined oral bisphosphonate therapy vs. oral bisphosphonate therapy alone	Oral bisphosphonate therapy is cost-effective compared with oral bisphosphonate therapy only	78.00	70.83
42 Golmohamdi [28], 2016	Postmenopausal osteoporosis	Zoledronic acid vs. routine medical treatment	Zoledronic acid is a cost-effective and dominant	83.00	70.83
43 Karnon [85], 2016	Women with mean age 72 years (range, 60–90 years), mean BMD T score at the femoral neck of -2.15	Denosumab vs. generic alendronate	Denosumab would provide value for money	74.00	72.63
44 Mori [86], 2017	Women without prior hip or vertebral fracture	Subcutaneous denosumab vs. oral alendronate	Denosumab is cost-effective and cost-saving compared with alendronate	78.50	66.67
45 O'Hanlon [46], 2017	70-year-old female patients with T scores below -2.5 and a previous vertebral fracture.	Romozosumab and abaloparatide vs. teriparatide	New bone-forming agents (romozosumab and abaloparatide) is a cost-saving, can provide onset and efficacy improvements over teriparatide	47.00	58.33
46 Moriwaki [44], 2017	70-year-old women with a femoral neck BMD T score of -2.5 ($= 0.565 \text{ g/cm}^2$)	zoledronic acid + basic treatment (once-a-year injection of zoledronic acid 5 mg + calcium + vitamin D supplement) vs. alendronate + basic treatment (once-weekly alendronate 35 mg + calcium + vitamin D supplement) or basic treatment alone (calcium + vitamin D supplement)	Considering the advantage of annual zoledronic acid treatment in compliance and persistence, zoledronic acid may be a cost-effective treatment option compared to alendronate	80.50	95.83
47 Ito [47], 2018	Women aged 85 years who resided in nursing homes with low BMD (a T score of ≤ -2.0) at the spine, hip or radius	Zoledronic acid vs. usual care	Routine administration of single-dose zoledronic acid in nursing home residents with osteoporosis is not a cost-effective use of resources in the USA but could be justifiable in those with a favorable life expectancy	84.00	75.93
48 Yoshizawa [87], 2018	Women aged 75 years with a BMD of 65% of the YAM (T score, -2.87) and a history of previous vertebral body fracture	Denosumab vs. alendronate	Denosumab treatment might be more cost-effective than alendronate for patients with a BMD of 65% of YAM or lower among over 75 years of age	79.50	71.83
49 Hiligsmann [48], 2019	Women 60–80 years of age, with a BMD T score ≤ -2.5 and/or prevalent vertebral fractures	Alendronate vs. generic risedronate	GR risedronate is a cost-effective compared with weekly alendronate and generic risedronate	84.50	93.78

FRAX, fracture risk assessment tool; PTH, parathyroid hormone; SOTI, Spinal Osteoporosis Therapeutic Intervention; TROPOS, Treatment of Peripheral Osteoporosis; PVF, prevalent vertebral fracture; BMD, bone mineral density; CRFs, clinical risk factors; YAM, young adult mean.

woman at higher risk of fracture [39–41]. Strontium ranelate was cost-effective compared with risedronate [32], whereas risedronate was cost-effective compared with generic alendronate [42,43]. Studies showed that treatment with zoledronic acid is considered to be cost-effective approach compared with branded bisphosphonates and routine medical treatment respectively [1,28,29,44], while Murphy and coworkers reported that treatment with teriparatide was cost-effective when compared with oral bisphosphonates in severe postmenopausal osteoporosis [45]. The new bone-forming agent romosozumab and abaloparatide was more effective compared to teriparatide [46]. Routine administration of single-dose zoledronic acid was not a cost-effective treatment among women aged 85 years with low BMD, resided in nursing home in the USA but could be justifiable in those with a favorable life expectancy [47].

Most recent, a study suggests that gastro-resistant (GR) risedronate is a cost-effective treatment compared with weekly dose of alendronate and generic risedronate [48].

3.3. Overall quality of economic evaluations

3.3.1. CHEERS

Among 49 studies, only 9 studies (18.36%) scored the high-quality threshold of 85%, those analyses CEA. Several studies scored slightly below the high-quality threshold, while the remaining 37 studies (75.5%) scored below the high-quality threshold [29,41,49]. In addition, the average score of reported studies was 17.94 out of 24 maximum score. A total of 33 studies published between 2008 and 2012 were found with a higher average score of 17.90, whereas 16 studies were published between 2013 and 2017 with an average score of 18.04. Overall, the mean CHEERS checklist scores of included studies was 75.03 ± 11.21 . Only 50% of included studies were reporting fully satisfied for item 2, where comparators were considered without proper justification. Similarly, the justification for time horizon, discount rates, and choice for health outcomes were also not provided in all articles. Various studies were not reported completely all the parameters, considering a description of approaches used to estimate resources and costs, as well as the reporting of study parameters. Across all the studies items 'measurement of effectiveness' '11a' and '11b' (description of the methods used for the identification of studies used for effectiveness) were partially or not reported, 97.7% of studies were partially reported for item '12' 'measurement and valuation of preferences-based outcomes' (description of the population and methods used to elicit preferences for outcomes; item '12').

Most of the studies partially fulfilled the criteria for item '14' of currency, price date and conversion' (reporting of the dates of the estimated resource quantities and unit costs and description of the methods for adjusting estimated unit costs to the year of reported costs) and item '17' 'analytic methods' (description of all structural or other assumptions underpinning the decision-analytic model). Several studies were not satisfactory to fulfill the following criteria; incremental costs and outcomes (item 19), characterized uncertainty and heterogeneity (items 20 and 21), and discussed the key findings, limitations, generalizability, and how the findings fit with current knowledge (item 22), especially item '20a' completely not full fill these criteria overall studies. Item 21 'Source of funding' information (the role of the funder in the identification, design, conduct, and reporting of the analysis) were not fully reported in about 63% studies.

3.3.2. QHES

Overall, 38 studies (77.5%) met the 75-point threshold (highest category; category-4) for high-quality economic studies which

examined the CEA, whereas Tosteson 2008, and Wasserfallen 2008 [50,51] achieved high-quality economic studies examined both CEA, budget impact analysis, and CEA, CUA respectively. Nine studies were scored in category-3, while remaining 2 studies scored in category-2. none of the studies scored in category-1 (lowest category) [52]. According to the QHES checklist, in terms of the discussion of direction and magnitude of potential bias (item 14) was relatively low in majority of studies. Thirty-five studies were found to be industry-funded with higher QHES mean (82.44 ± 8.69) as compared with 11 non-industry funding studies with mean 72.22 ± 17.67 . Overall, the mean QHES scores of all included studies was 79.06 ± 11.84 out of 100.

All studies presented their objectives in clear, specific and measurable manner (item 1) except a single study [53]. Out of 49, majority of studies 48 (97.9%) clearly mentioned the perspective analysis (item 2), however the reason for selection was not always clearly stated but the perspectives have not differed from their respective country's recommendations [54]. All studies described the methodology for data abstraction (item 7). Seven studies (14.28%) have not stated clear justification for the discount rate and did not allow analytic horizon for all relevant and important outcomes (item 8). Most of studies were reported the measurement of costs appropriate and the method for the estimation of quantities and unit cost (item 9), and outcomes (item 10) was also clearly described (item 9). Various studies 36 (73.46%) did not explicit stated the direction and magnitude of potential biases (item 14).

All the studies reported that their intervention was cost-effective when compared with a comparator, but justification was not clearly stated by the result (item 15). Forty-one studies (83.67%) have disclosed the source of funding (item 16), where 35 studies (71.42%) were funded by the pharmaceutical company.

3.3.3. QHES vs. CHEERS

The resulted average CHEERS score was 75.03% following the average QHES score was 79.06%. QHES score found higher mean as compared to CHEERS although the statistical pairwise comparison between CHEERS mean (75.03 ± 11.21) and QHES mean (79.06 ± 11.84) did not found statistically significant difference ($P = 0.10$).

3.4. Key findings for drivers of cost-effectiveness

There are several key drivers of cost-effectiveness were found, and it differ widely among included studies.

3.5. Fracture risk and age

Fracture risk was one of the important drivers of cost-effectiveness, whereas age was a significant but not a key determinant [55].

The cost-effectiveness of osteoporotic drugs improved with increasing patient age and fracture risk. Hilgsmann and Reginster [48] suggests that cost-effectiveness of GR risedronate improved with increasing fracture risk and age of the patients at baseline, as the benefits remains improved when increasing the fracture risk of the population. The GR risedronate was dominant/cost-saving in women with ≥ 80 years age was estimated at €60,000 per QALY gained compared to all comparators. At the age of 70 years with BMD T score ≤ -2.5 or prevalent vertebral fractures only, GR risedronate became cost saving by cost per QALY gained decrease below €25,000 for all comparators.

The use of clinical risk factors across the populations identifies the future fractures risks, that may treat cost-effectively [31]. A study showed that, at a willingness-to-pay threshold of €20,000 per QALY gained, denosumab was probably to cost-effective

compared to alendronate or no treatment. Incremental cost-effectiveness ratio (ICER) of denosumab versus no treatment, alendronate, risedronate, and ibandronate was €6823, €16,294, €4895, and €2205 per QALY gained, respectively according to BMD T score and the estimated ICER reduced the fracture risk in future [35].

Including fracture risk, age, clinical risk factors, treatment efficacy and severity of menopausal symptoms considered as the key drivers for cost-effectiveness.

3.6. Medication adherence

Medication adherence has critically incorporated as important determinants, which affects the cost-effectiveness results [56,57]. Nonadherence to osteoporosis therapy results potential changes in cost-effectiveness and worsening of health outcomes [58]. The costs per QALY gained for branded bisphosphonates were estimated at €19,069, €32,278, and €64,052 (year 2006 values) according to adherence levels 100%, 80%, and 60%, respectively [59].

A better adherence decreased the costs per QALY gained at 70 years to €35,993 at the 10% threshold [60].

Consequently, study suggested that denosumab would be cost-effective and favorable compared with oral bisphosphonates, if medication adherence was included. Therefore, nonadherence to osteoporotic therapy must be examined and should be an essential part of economic evaluations [59].

3.7. Comparators

An extensive number of HES analyses the active treatment as a comparator for postmenopausal osteoporosis. The cost-effectiveness of an osteoporotic treatments can be varying according to the selected comparator.

In the overall simulated population, GR risedronate was cost-effective compared with generic risedronate, alendronate, and no treatment at a threshold of €60,000 per QALY gained [48]. Similarly, denosumab was dominant as compared with risedronate and ibandronate, while the cost-effectiveness was less favorable when compared with generic alendronate [38]. Therefore, justification of the comparators is important.

3.8. Country-specific analyses

The cost effectiveness of bazedoxifene showed large variations across countries. Among the 6 European countries, the highest ICER was reported in Spain (€105,450) to the cost-savings in Sweden (year 2008 values) [61]. There are several determinants like event incidences, drug prices, event-related costs and normal population utility are responsible for extensive variations in geographical results. Additionally, medication adherence also varied between the countries resulting significant changes in cost-effectiveness of drug therapies. The reported drug costs per year ranged between €325–€540, where Germany contributing the higher cost and United Kingdom to lower cost [61]. With considering the similar determinants, the annual costs of bazedoxifene or raloxifene was higher in Belgium (€552) and lower in Ireland (€320), while the costs of hip fracture were ranged between €19,142 and €10,502 (year 2008 values) [41].

4. Discussions

This systematic review evaluated the quality of HES, reporting cost-effectiveness of drugs used in postmenopausal osteoporosis. Of the 49 eligible studies, most of the studies were on high to moderate quality according to QHES and CHEERS scores

respectively.

In order to support decision-making in healthcare, the evidence on health economic evaluations (HEEs) for interventions and technologies needs to be reliable and of good quality. In addition to, it may ensure by means of transparent methodology, traceable sources and a justifiable selection of data inputs. There are different types of HEEs instruments are available to evaluate the quality of HEEs, including QHES and CHEERS, checklist incorporating the elements required for transparent reporting. Since, this systematic review examined 49 published economic evaluations of drugs used in postmenopausal osteoporosis. In drugs for postmenopausal osteoporosis, such a qualitative review of CEAs has previously been performed, evaluating in compliance with the CHEERS checklist [15]. In different, with previous study, here we used CHEERS and QHES instrument to evaluate the quality of HEEs and compared both the instrument respectively.

On the basis of QHES scores, this review found 38 studies (77.5%) were graded as high quality, while, on the basis of CHEERS scores, only 9 studies (18.36%) were marked with the high-quality score.

In our studies, according to CHEERS scores, most of studies were graded as moderate quality due to lack of information regarding study methods, especially the cost measurement perspective, model or calculation justification and anticipated bias magnitude and direction. However, several included studies showed higher QHES quality scores due to transparent justification for conclusions.

Our findings are in line with the previous study conducted by Hilgsmann et al. [15]. These authors reviewed economic analyses drugs related to postmenopausal osteoporosis in multiple countries. While their results demonstrated a substantial number of published cost-effectiveness analyses of drugs over time, the existing body of literature did not offer specific public policy or practice implications at that time. Therefore, they suggested that critical appraisal of these articles may help decision makers when prioritizing health interventions and can inform the development of future economic evaluations [15].

The published studies shown active osteoporotic drugs were generally cost-effective, in postmenopausal women aged more than 60–65 years with low bone mass, especially in patients with prior vertebral fractures. It is cost effective at commonly accepted threshold for cost-effectiveness (about €45,000 per QALY gained) [15].

Previous review of economic studies conducted for the prevention and treatment of osteoporosis reported that oral bisphosphonates considered as a cost-effective drug in osteoporosis with women aged over 70 years, especially those with additional risk factors [62,63]. Additionally, this review also suggested that oral bisphosphonates along with new alternative intervention such as denosumab, strontium ranelate, bazedoxifene, zoledronic acid, new bone-forming agent (romosozumab and abaloparatide) were cost-effective.

Si et al. [64], conducted a systematic review of the evolution of health economic models used in cost-effectiveness analyses of preventing osteoporotic fractures. But in this review, we restricted our study to drug therapies, reported and discussed the results, conclusion of the studies, and critically appraised the all included articles [64]. Several key drivers of the cost-effectiveness were reported in our systematic review, such as patients age, fracture risk, comparators and country specific analysis. The development of various fracture risk algorithms, for example FRAX® tool allow the evaluation of cost-effectiveness in different kinds of patients with additional clinical risk factors. Medication adherence significantly added as determinants which affects the cost-effectiveness of drugs used in osteoporosis and it should be considered in future HES. The cost effectiveness of treatment extensively varying according to the selected comparators and across the countries.

In order to reporting the quality of included health economic evaluations, although the fact that HEEs have been conducted in accordance with guidelines which is widely available for many years. The previous review has already highlighted the lacking of high standard methodological quality of reported studies, in regard to model perspective where some studies failed to describe the perspective of the evaluation and the studies on societal perspective have not considered indirect costs. However, studies on societal perspective must include direct and indirect costs [64]. We observed that the quality of reporting was still mainly scarce for several articles and many other items were either partially or not reported by most of the articles.

Availability of several instruments such as QHES, CHEERS [12,14] evaluating the quality of HES have been developed. CHEERS is a comprehensive checklist incorporating the most essential elements required for improving quality and transparent reporting of economic evaluations of osteoporosis.

In spite of conducting the quality assessment of HES there may have been some potential limitations in our study. The potential limitations may be due to, first, many researchers were engaged in to review the quality of reporting assessment and discrepancy in scoring due to reviewer's interpretation. Sometimes, while assigning scores, there is difficulty to differentiate the partially or fully reported for individual items. Second, we assigned a score of 0.5 for partial reporting which might be questionable and lead to an upgrade of the overall score of the studies or would have decreased the overall reporting quality while using binary rating 'yes' for item was adequately reported and otherwise 'no.' Third, the level of quality might be underrated for the studies in which some of the items were not easily accounted somewhere else.

Fourth, it should be addressed that low-quality reporting does not lead to poor quality and results bias.

Of 49 studies, 35 studies were funded by pharmaceutical company, and it is found that industry-funded studies were more possibly to consider favorable cost-effectiveness ratios [65]. In contrast, a review conducted by Fleurence et al. [66] suggested that funding source (industry versus nonindustry) have not significantly influence the reporting of favorable cost-effectiveness for bisphosphonates in treatment of osteoporosis. This review could play an important role in decision-making to prioritize the health interventions.

Due to humanistic and economic constraint of osteoporosis, the health economic evidences could be used in health care decision-making for the purpose of reimbursement of drugs cost. In line with cost-effectiveness, affordability could also play an important role in reimbursement decisions. A discrete-choice experiment reported that patients could have preferences for characteristics of osteoporosis drug therapy and the patient's preferences should be considered along with medical and economic considerations [67].

Increasing number of cost-effectiveness studies of drug therapy used for osteoporosis, there is a lack of specific strategies for decision makers. However, compare specific strategies which would be advisable because of cost-effective, as well in a reimbursement as in real cost-based setting. A quantitative evaluation with adequate thresholds could be high quality to a purely qualitative approach.

The QHES checklist is a validated instrument, is often used as quantitative benchmarking. Whereas, the CHEERS checklist was not considered as quantitative benchmarking. The QHES scores are based on transparency evaluation (formal presence of data) with quality appreciation (appropriateness of choices made), with several attributes and various items.

Si et al. [64], documented that by capturing all possible costs and cost-effectiveness, the time horizon must be long term, therefore lifetime horizon should be preferable. The cost-effectiveness

modeling could consistently play a significant role in HEEs of osteoporotic fracture prevention.

5. Conclusions

This review evaluated an extensive number of published HEEs of drugs used for postmenopausal osteoporosis. The overall quality of the published literatures was relatively few high-quality HEE demonstrating the cost-effectiveness of drugs for postmenopausal osteoporosis, and the majority of the literature suggests that methodological shortcoming. Therefore, further reliable cost-effectiveness result is required to ensure the health care resource allocation with considering data sources, demographic heterogeneity, sensitivity analysis and threshold selection.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

CRedit author statement

Md Azharuddin: Conceptualization, Methodology, Formal analysis, Data Curation, Writing – Original Draft. **Mohammad Adil:** Conceptualization, Methodology, Formal analysis, Data Curation, Writing – Review & Editing. **Rashid Ali Khan:** Formal analysis, Data Curation. **Pinaki Ghosh:** Formal analysis, Writing – Review & Editing. **Prem Kapur:** Writing – Review & Editing. **Manju Sharma:** Writing – Review & Editing.

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References

- [1] Fardellone P, Cortet B, Legrand E, Bresse X, Bisot-Locard S, Vigneron AM, et al. Cost-effectiveness model of using zoledronic acid once a year versus current treatment strategies in postmenopausal osteoporosis. *Joint Bone Spine* 2010;77:53–7.
- [2] Cooper C, Campion G, Melton 3rd LJ. Hip fractures in the elderly: a world-wide projection. *Osteoporos Int* 1992;2:285–9.
- [3] Melton 3rd LJ, Chrischilles EA, Cooper C, Lane AW, Riggs BL. How many women have osteoporosis? *JBM* anniversary classic. *JBM*, volume 7, number 9, 1992. *J Bone Miner Res* 2005;20:886–92.
- [4] 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;22:465–75.
- [5] Hiligsmann M, Kanis JA, Compston J, Cooper C, Flaminio B, Bergmann P, et al. Health technology assessment in osteoporosis. *Calcif Tissue Int* 2013;93:1–14.
- [6] Kanis JA, McCloskey EV, Johansson H, Cooper C, Rizzoli R, Reginster JY, et al. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Osteoporos Int* 2013;24:23–57.
- [7] Püntmann I, Schmacke N, Melander A, Lindberg G, Mühlbauer B. EVITA: a tool for the early evaluation of pharmaceutical innovations with regard to therapeutic advantage. *BMC Clin Pharmacol* 2010;10:5.
- [8] Williams IP, Bryan S. Cost-effectiveness analysis and formulary decision making in England: findings from research. *Soc Sci Med* 2007;65:2116–29.
- [9] Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the *BMJ*. The *BMJ* Economic Evaluation Working Party. *BMJ* 1996;313:275–83.
- [10] Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. *Methods for the economic evaluation of health care programmes*. Oxford: Oxford university press; 2015.

- [11] Evers S, Goossens M, de Vet H, van Tulder M, Ament A. Criteria list for assessment of methodological quality of economic evaluations: Consensus on Health Economic Criteria. *Int J Technol Assess Health Care* 2005;21:240–5.
- [12] Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated health economic evaluation reporting standards (CHEERS)—explanation and elaboration: a report of the ISPOR health economic evaluation publication guidelines good reporting practices task force. *Value Health* 2013;16:231–50.
- [13] Chiou CF, Hay JW, Wallace JF, Bloom BS, Neumann PJ, Sullivan SD, et al. Development and validation of a grading system for the quality of cost-effectiveness studies. *Med Care* 2003;41:32–44.
- [14] Ofman JJ, Sullivan SD, Neumann PJ, Chiou CF, Henning JM, Wade SW, et al. Examining the value and quality of health economic analyses: implications of utilizing the QHES. *J Manag Care Pharm* 2003;9:53–61.
- [15] Hiligsmann M, Evers SM, Ben Sedrine W, Kanis JA, Ramaekers B, Reginster JY, et al. A systematic review of cost-effectiveness analyses of drugs for postmenopausal osteoporosis. *Pharmacoeconomics* 2015;33:205–24.
- [16] Monten C, Veldeman L, Verhaeghe N, Lievens Y. A systematic review of health economic evaluation in adjuvant breast radiotherapy: quality counted by numbers. *Radiother Oncol* 2017;125:186–92.
- [17] Azharuddin M, Adil M, Ghosh P, Sharma M. Assessing the quality of economic evaluation of treatment options for Parkinson's disease using the quality of health economic studies (QHES) Scale. In: 2018 international congress. Movement disorders; monday, 2018 Oct 8. New Delhi, India. Hoboken (NJ): WILEY; 2018. 5836.
- [18] Nwachukwu BU, Schairer WW, Bernstein JL, Dodwell ER, Marx RG, Allen AA. Cost-effectiveness analyses in orthopaedic sports medicine: a systematic review. *Am J Sports Med* 2015;43:1530–7.
- [19] Azar FE, Azami-Aghdash S, Pournaghi-Azar F, Mazdaki A, Rezapour A, Ebrahimi P, et al. Cost-effectiveness of lung cancer screening and treatment methods: a systematic review of systematic reviews. *BMC Health Serv Res* 2017;17:413.
- [20] Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009;151:264–9. W64.
- [21] Geng J, Yu H, Mao Y, Zhang P, Chen Y. Cost effectiveness of dipeptidyl peptidase-4 inhibitors for type 2 diabetes. *Pharmacoeconomics* 2015;33:581–97.
- [22] Hamberg-van Reenen HH, Proper KI, van den Berg M. Worksite mental health interventions: a systematic review of economic evaluations. *Occup Environ Med* 2012;69:837–45.
- [23] Plumpton CO, Roberts D, Pirmohamed M, Hughes DA. A systematic review of economic evaluations of pharmacogenetic testing for prevention of adverse drug reactions. *Pharmacoeconomics* 2016;34:771–93.
- [24] Au F, Prahardhi S, Shiell A. Reliability of two instruments for critical assessment of economic evaluations. *Value Health* 2008;11:435–9.
- [25] Walker DG, Wilson RF, Sharma R, Bridges J, Niessen L, Bass EB, et al. Best practices for conducting economic evaluations in health care: a systematic review of quality assessment tools. Rockville (MD): Agency for Healthcare Research and Quality (US); 2012 Oct. Report No.: 12(13)-EHC132-EF.
- [26] Campbell JD, Spackman DE, Sullivan SD. Health economics of asthma: assessing the value of asthma interventions. *Allergy* 2008;63:1581–92.
- [27] Monten C, Lievens Y. Adjuvant breast radiotherapy: how to trade-off cost and effectiveness? *Radiother Oncol* 2018;126:132–8.
- [28] 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. *Electron Physician* 2016;8:3434–40.
- [29] Akehurst R, Brereton N, Ariely R, Lusa T, Groot M, Foss P, et al. The cost effectiveness of zoledronic acid 5 mg for the management of postmenopausal osteoporosis in women with prior fractures: evidence from Finland, Norway and The Netherlands. *J Med Econ* 2011;14:53–64.
- [30] Kanis JA. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: synopsis of a WHO report. WHO Study Group. *Osteoporos Int* 1994;4:368–81.
- [31] Kanis JA, McCloskey EV, Johansson H, Strom O, Borgstrom F, Oden A, et al. Case finding for the management of osteoporosis with FRAX—assessment and intervention thresholds for the UK. *Osteoporos Int* 2008;19:1395–408.
- [32] Hiligsmann M, Bruyere O, Reginster JY. Cost-effectiveness of strontium ranelate versus risedronate in the treatment of postmenopausal osteoporotic women aged over 75 years. *Bone* 2010;46:440–6.
- [33] Mori T, Crandall CJ, Ganz DA. Cost-effectiveness of combined oral bisphosphonate therapy and falls prevention exercise for fracture prevention in the USA. *Osteoporos Int* 2017;28:585–95.
- [34] Chau D, Becker DL, Coombes ME, Ioannidis G, Adachi JD, Goeree R. Cost-effectiveness of denosumab in the treatment of postmenopausal osteoporosis in Canada. *J Med Econ* 2012;15(Suppl 1):3–14.
- [35] Darbà J, Kaskens L, Sorio Vilela F, Lothgren M. Cost-utility of denosumab for the treatment of postmenopausal osteoporosis in Spain. *Clinicoecon Outcomes Res* 2015;7:105–17.
- [36] Hiligsmann M, Reginster JY. Cost effectiveness of denosumab compared with oral bisphosphonates in the treatment of post-menopausal osteoporotic women in Belgium. *Pharmacoeconomics* 2011;29:895–911.
- [37] Jönsson B, Ström O, Eisman JA, Papaioannou A, Siris ES, Tosteson A, et al. Cost-effectiveness of Denosumab for the treatment of postmenopausal osteoporosis. *Osteoporos Int* 2011;22:967–82.
- [38] 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. *Appl Health Econ Health Pol* 2013;11:485–97.
- [39] Darbà J, Pérez-Álvarez N, Kaskens L, Holgado-Pérez S, Racketa J, Rejas J. Cost-effectiveness of bazedoxifene versus raloxifene in the treatment of postmenopausal women in Spain. *Clinicoecon Outcomes Res* 2013;5:327–36.
- [40] Hiligsmann M, Ben Sedrine W, Reginster JY. Cost-effectiveness of bazedoxifene compared with raloxifene in the treatment of postmenopausal osteoporotic women. *J Bone Miner Res* 2013;28:807–15.
- [41] Kim K, Svedbom A, Luo X, Sutradhar S, Kanis JA. Comparative cost-effectiveness of bazedoxifene and raloxifene in the treatment of postmenopausal osteoporosis in Europe, using the FRAX algorithm. *Osteoporos Int* 2014;25:325–37.
- [42] Berto P, Maggi S, Noale M, Lopatriello S. Risedronate versus alendronate in older patients with osteoporosis at high risk of fracture: an Italian cost-effectiveness analysis. *Aging Clin Exp Res* 2010;22:179–88.
- [43] Thompson M, Pasquale M, Grima D, Moehrke W, Kruse HP. The impact of fewer hip fractures with risedronate versus alendronate in the first year of treatment: modeled German cost-effectiveness analysis. *Value Health* 2010;13:46–54.
- [44] Moriwaki K, Mouri M, Hagino H. Cost-effectiveness analysis of once-yearly injection of zoledronic acid for the treatment of osteoporosis in Japan. *Osteoporos Int* 2017;28:1939–50.
- [45] Murphy DR, Smolen LJ, Klein TM, Klein RW. The cost effectiveness of teriparatide as a first-line treatment for glucocorticoid-induced and postmenopausal osteoporosis patients in Sweden. *BMC Musculoskel Disord* 2012;13:213.
- [46] O'Hanlon CE, Parthan A, Kruse M, Cartier S, Stollenwerk B, Jiang Y, et al. 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. *Clin Therapeut* 2017;39:1276–90.
- [47] Ito K. Cost-effectiveness of single-dose zoledronic acid for nursing home residents with osteoporosis in the USA. *BMJ Open* 2018;8. e022585.
- [48] Hiligsmann M, Reginster JY. Cost-effectiveness of gastro-resistant risedronate tablets for the treatment of postmenopausal women with osteoporosis in France. *Osteoporos Int* 2019;30:649–58.
- [49] Jansen JP, Gaugris S, Bergman G, Sen SS. Cost-effectiveness of a fixed dose combination of alendronate and cholecalciferol in the treatment and prevention of osteoporosis in the United Kingdom and The Netherlands. *Curr Med Res Opin* 2008;24:671–84.
- [50] Tosteson AN, Burge RT, Marshall DA, Lindsay R. Therapies for treatment of osteoporosis in US women: cost-effectiveness and budget impact considerations. *Am J Manag Care* 2008;14:605–15.
- [51] Wasserfallen JB, Krieg MA, Greiner RA, Lamy O. Cost effectiveness and cost utility of risedronate for osteoporosis treatment and fracture prevention in women: a Swiss perspective. *J Med Econ* 2008;11:499–523.
- [52] van der Schans S, Goossens LMA, Boland MRS, Kocks JWH, Postma MJ, van Boven JFM, et al. Systematic review and quality appraisal of cost-effectiveness analyses of pharmacologic maintenance treatment for chronic obstructive pulmonary disease: methodological considerations and recommendations. *Pharmacoeconomics* 2017;35:43–63.
- [53] Kanis JA, Adams J, Borgström F, Cooper C, Jönsson B, Preedy D, et al. The cost-effectiveness of alendronate in the management of osteoporosis. *Bone* 2008;42:4–15.
- [54] International Society for Pharmacoeconomics and Outcomes Research, Inc. Pharmacoeconomic guidelines around the world [Internet]. Lawrenceville (NJ): International Society for Pharmacoeconomics and Outcomes Research, Inc.; c2020 [cited 2020-february-18]. <https://tools.ispor.org/peguidelines/>.
- [55] Ivergård M, Ström O, Borgström F, Burge RT, Tosteson AN, Kanis J, et al. Identifying cost-effective treatment with raloxifene in postmenopausal women using risk algorithms for fractures and invasive breast cancer. *Bone* 2010;47:966–74.
- [56] Hiligsmann M, Boonen A, Rabenda V, Reginster JY. The importance of integrating medication adherence into pharmacoeconomic analyses: the example of osteoporosis. *Expert Rev Pharmacoecon Outcomes Res* 2012;12:159–66.
- [57] Kanis JA, Cooper C, Hiligsmann M, Rabenda V, Reginster JY, Rizzoli R. Partial adherence: a new perspective on health economic assessment in osteoporosis. *Osteoporos Int* 2011;22:2565–73.
- [58] Rabenda V, Hiligsmann M, Reginster JY. Poor adherence to oral bisphosphonate treatment and its consequences: a review of the evidence. *Expert Opin Pharmacother* 2009;10:2303–15.
- [59] Hiligsmann M, Rabenda V, Gathon HJ, Ethgen O, Reginster JY. Potential clinical and economic impact of nonadherence with osteoporosis medications. *Calcif Tissue Int* 2010;86:202–10.
- [60] Alzahouri K, Bahrami S, Durand-Zaleski I, Guillemin F, Roux C. Cost-effectiveness of osteoporosis treatments in postmenopausal women using FRAX™ thresholds for decision. *Joint Bone Spine* 2013;80:64–9.
- [61] Borgström F, Ström O, Kleman M, McCloskey E, Johansson H, Odén A, et al. Cost-effectiveness of bazedoxifene incorporating the FRAX® algorithm in a European perspective. *Osteoporos Int* 2011;22:955–65.
- [62] Fleurence RL, Iglesias CP, Torgerson DJ. Economic evaluations of interventions for the prevention and treatment of osteoporosis: a structured review of the literature. *Osteoporos Int* 2006;17:29–40.
- [63] Zethraeus N, Borgström F, Ström O, Kanis JA, Jönsson B. Cost-effectiveness of the treatment and prevention of osteoporosis—a review of the literature and a

- reference model. *Osteoporos Int* 2007;18:9–23.
- [64] Si L, Winzenberg TM, Palmer AJ. A systematic review of models used in cost-effectiveness analyses of preventing osteoporotic fractures. *Osteoporos Int* 2014;25:51–60.
- [65] Bell CM, Urbach DR, Ray JG, Bayoumi A, Rosen AB, Greenberg D, et al. Bias in published cost effectiveness studies: systematic review. *BMJ* 2006;332:699–703.
- [66] Fleurence RL, Spackman DE, Hollenbeck C. Does the funding source influence the results in economic evaluations? A case study in bisphosphonates for the treatment of osteoporosis. *Pharmacoeconomics* 2010;28:295–306.
- [67] Hiligsmann M, Dellaert BG, Dirksen CD, van der Weijden T, Goemaere S, Reginster JY, et al. Patients' preferences for osteoporosis drug treatment: a discrete-choice experiment. *Arthritis Res Ther* 2014;16:R36.
- [68] Lekander I, Borgström F, Ström O, Zethraeus N, Kanis JA. Cost effectiveness of hormone therapy in women at high risks of fracture in Sweden, the US and the UK—results based on the Women's Health Initiative randomised controlled trial. *Bone* 2008;42:294–306.
- [69] Ding H, Koinuma N, Stevenson M, Ito M, Monma Y. The cost-effectiveness of risedronate treatment in Japanese women with osteoporosis. *J Bone Miner Metabol* 2008;26:34–41.
- [70] Grima DT, Papaioannou A, Thompson MF, Pasquale MK, Adachi JD. Greater first year effectiveness drives favorable cost-effectiveness of brand risedronate versus generic or brand alendronate: modeled Canadian analysis. *Osteoporos Int* 2008;19:687–97.
- [71] Hiligsmann M, Ethgen O, Bruyère O, Richey F, Gathion HJ, Reginster JY. Development and validation of a Markov microsimulation model for the economic evaluation of treatments in osteoporosis. *Value Health* 2009;12:687–96.
- [72] Salpeter SR, Buckley NS, Liu H, Salpeter EE. The cost-effectiveness of hormone therapy in younger and older postmenopausal women. *Am J Med* 2009;122:42–52.
- [73] Lekander I, Borgström F, Ström O, Zethraeus N, Kanis JA. Cost-effectiveness of hormone therapy in the United States. *J Womens Health* 2009;18:1669–77.
- [74] Borgström F, Ström O, Coelho J, Johansson H, Odén A, McCloskey E, et al. The cost-effectiveness of strontium ranelate in the UK for the management of osteoporosis. *Osteoporos Int* 2010;21:339–49.
- [75] Borgström F, Ström O, Coelho J, Johansson H, Odén A, McCloskey EV, et al. The cost-effectiveness of risedronate in the UK for the management of osteoporosis using the FRAX®. *Osteoporos Int* 2010;21:495–505.
- [76] Borgström F, Ström O, Marin F, Kutahov A, Ljunggren Ö. Cost effectiveness of teriparatide and PTH (1-84) in the treatment of postmenopausal osteoporosis. *J Med Econ* 2010;13:381–92.
- [77] Hiligsmann M, Bruyère O, Reginster JY. Cost-utility of long-term strontium ranelate treatment for postmenopausal osteoporotic women. *Osteoporos Int* 2010;21:157.
- [78] Hiligsmann M, Reginster JY. Potential cost-effectiveness of denosumab for the treatment of postmenopausal osteoporotic women. *Bone* 2010;47:34–40.
- [79] Seeman E, Boonen S, Borgström F, Vellas B, Aquino JP, Semler J, et al. Five years treatment with strontium ranelate reduces vertebral and nonvertebral fractures and increases the number and quality of remaining life-years in women over 80 years of age. *Bone* 2010;46:1038–42.
- [80] Ström O, Borgström F, Kleman M, McCloskey E, Oden A, Johansson H, et al. FRAX® and its applications in health economics—cost-effectiveness and intervention thresholds using bazedoxifene in a Swedish setting as an example. *Bone* 2010;47:430–7.
- [81] Pham AN, Datta SK, Weber TJ, Walter LC, Colón-Emeric CS. Cost-effectiveness of oral bisphosphonates for osteoporosis at different ages and levels of life expectancy. *J Am Geriatr Soc* 2011;59:1642–9.
- [82] 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;23:2579–89.
- [83] Moriwaki K, Komaba H, Noto S, Yanagisawa S, Takiguchi T, Inoue H, et al. Cost-effectiveness of alendronate for the treatment of osteopenic postmenopausal women in Japan. *J Bone Miner Res* 2013;28:395–403.
- [84] Ström O, Jönsson B, Kanis JA. Intervention thresholds for denosumab in the UK using a FRAX®-based cost-effectiveness analysis. *Osteoporos Int* 2013;24:1491–502.
- [85] 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 Eff Resour Alloc* 2016;14:11.
- [86] Mori T, Crandall CJ, Ganz DA. Cost-effectiveness of denosumab versus oral alendronate for elderly osteoporotic women in Japan. *Osteoporos Int* 2017;28:1733–44.
- [87] 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. *Arch Osteoporos* 2018;13:94.