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REVIEW

Economic evaluations of interventions for the prevention and treatment of osteoporosis: a structured review of the literature

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Abstract Economic evaluations are increasingly being used by decision-makers to estimate the cost-effectiveness of interventions. The objective of this study was to conduct a structured review of economic evaluations of interventions to prevent and treat osteoporosis. Articles were identified independently by two reviewers through searches on MEDLINE, the bibliographies of reviews and identified economic models, and expert opinion, using predefined inclusion and exclusion criteria. Data on country, type and level of interventions, type of fractures, interventions, study population and the authors' stated conclusions were extracted. Forty-two relevant studies were identified. The majority of studies (71%) were conducted in Sweden, the UK and the US. The main interventions investigated were hormone replacement therapy (27%), bisphosphonates (17%) and combinations of vitamin D and calcium (16%). In 38% of studies, hip fracture was the sole fracture outcome. Eighty-eight percent (88%) of studies investigated female populations only. A relatively large number of economic evaluations were identified in the field of osteoporosis. Major changes have recently occurred in the treatment of this disease, following the publication of the results of the Women's Health Initiative trial. Methodological developments in economic evaluations, such as the use of probabilistic sensitivity analysis and cost-effectiveness acceptability curves, have also taken place. Such changes are reflected in the studies that were reviewed. The development of economic models should be an iterative process that incorporates new information, whether clinical or methodological, as it becomes available.

Keywords Cost-effectiveness · Economics · Fractures · Model · Osteoporosis · Review

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Introduction

Economic evaluations are increasingly being used by decision-makers to evaluate the cost-effectiveness of treatments. In Australia and in the Canadian province of Ontario, economic evaluations are mandatory components of the pharmaceutical licensing process [1]. In the UK, the National Institute for Clinical Excellence (NICE) requires an economic evaluation as part of its submission procedures for the appraisal of new technologies (www.nice.org.uk). In the USA, the Academy for Managed Care Pharmacy (AMCP) has developed submission guidelines that require evidence of cost-effectiveness of new treatments for the inclusion on pharmacy formularies (www.amcp.org).

Economic evaluations can be conducted alongside clinical trials where economic data are collected at the same time as clinical data. Often, however, economic evaluations are conducted using models that explicitly combine available information in a formal framework. These models enable the combination of evidence from a variety of sources in order to explore scenarios that for different reasons have not been empirically tested. For example, results from studies with relatively short follow-up periods can be extrapolated to longer time periods that are more relevant to policy-makers. Economic models can also explore the long-term effectiveness and cost-effectiveness of treatments in populations at different risk.

A number of interventions are available to prevent and treat osteoporosis [2, 3]. However, recommendations

for the treatment and prevention of osteoporosis have changed radically in the last few years. In 2002, the Women's Health Initiative trial was stopped early because of the excess risk in cardiovascular events that were observed in women taking estrogen and progestin [4, 5]. The segment of the study investigating the effects of estrogen alone in women without a uterus was also stopped early due to the increase in observed strokes [6]. Following these results, treatment with hormone replacement therapy (HRT) for long-term prevention is no longer recommended. However, newer therapies such as bisphosphonates and raloxifene have been shown to be effective in clinical trials. Less expensive therapies with no known adverse side effects such as vitamin D with or without calcium supplements and hip protectors are also being investigated [7, 8, 9, 10].

A number of economic evaluations have been conducted in the field of osteoporosis and have investigated the cost-effectiveness of interventions in a variety of settings and study populations. A review of models by Zethreaus et al. published in this journal in 2002 described some of these models [11]. Because of the increase in cost-effectiveness studies, and the rapid changes in the use of treatments for osteoporosis, we conducted an updated structured review of economic evaluations of interventions relating to the prevention and treatment of osteoporosis.

Materials and methods

Two reviewers (RF and CI) conducted the search independently according to predefined inclusion and exclusion criteria. The inclusion criteria for the structured review were: economic evaluations of interventions to prevent or treat osteoporosis; economic evaluations could be modeling studies as well as economic evaluations of clinical study data; study populations could include elderly men as well as postmenopausal or elderly women; interventions included any treatment or device used to prevent or treat osteoporosis or osteoporotic fractures, with or without prior screening of bone mineral density (BMD); economic evaluation outcomes were cost per quality-adjusted life year (QALY) and cost per fracture avoided; the languages were English, French and Spanish (languages spoken by the reviewers).

The exclusion criteria for the structured review were: cost of illness and burden of disease studies; cost studies, such as retrospective claims analyses; editorials and reviews; any study describing a model, but not presenting results; economic evaluations of interventions to treat glucocorticoid-induced osteoporosis.

The search for papers was up to December 2004. Four broad search strategies were used to identify economic models of interventions to prevent and treat osteoporosis: a search on MEDLINE, a search of the bibliographies of relevant review articles, a search of the bibliographies of identified economic models of osteoporosis and a request for further references from expert opinion.

Both reviewers (CI and RF) conducted the search independently. The literature search on MEDLINE used combinations of the following Mesh terms: ''Osteoporosis,'' ''Fractures,'' ''Economics,'' ''Cost-Benefit Analysis,'' ''Costs,'' ''Model'' and ''Models.'' We also used the ''Related Articles'' function available in MEDLINE to identify any additional studies. Abstracts of papers from these searches were analyzed, and any potential study meeting the inclusion and exclusion criteria was obtained for further investigation. Bibliographies of review articles were analyzed to search for additional references [11, 12, 13, 14, 15, 16]. Bibliographies of identified economic models in osteoporosis were checked for any additional references that could have been missed from the other search strategies. At this stage, both reviewers compared their potential lists of studies to be included, and a single list was created. Any discrepancy was resolved through discussion between the reviewers. Finally, the third author (DT) reviewed our list to identify any potentially missing study.

Relevant information from each included study was extracted according to a predefined grid. Information included: study reference, country to which economic evaluation refers, type of fractures included, type of prevention or treatment (primary, secondary or treatment), interventions and control, study population and authors' stated conclusions. Primary prevention is used for asymptomatic populations with no apparent osteoporosis or elevated risk of the condition to reduce their risk of onset in later life. Secondary prevention is used for asymptomatic patients who have been shown to have BMD sufficiently low to place them at elevated risk of fracture, to slow down the decline (or restore) BMD and hence reduce the risk of fracture. Treatment is used for patients known to have osteoporosis and who have already experienced one or more fractures to reduce their risk of further fractures [14].

Results

Forty-two (42) economic evaluations of interventions for the prevention or treatment of osteoporosis met the specified inclusion and exclusion criteria. A summary of the models by author, country, type of fracture, level of intervention (primary, secondary or treatment), intervention and control, study population and authors' stated conclusions is presented in Table 1.

Twenty-nine percent (12) of the economic evaluations were set in the UK, 21% (9) were set in the USA and Sweden, respectively, 7% (3) were set in Canada, 5% (2) were set in Australia, Germany, and Spain, respectively, and 2% (1) were set in Italy, Japan, and Denmark, respectively. Three countries were associated with 71% of the economic evaluations, Sweden, the UK and the USA, reflecting the concern over the large burden of osteoporosis in these countries.

The main intervention investigated was HRT (in which we include Estrogen Replacement Therapy or

Table 1 Economic evaluations for the prevention and treatment of osteoporosis. *BMD* bone mineral density, *CE* cost-effectiveness, *CHD* coronary heart disease, *CRT* combined replacement therapy, *ERT* estrogen replacement therapy, *HRT* hormone replacement therapy, *OHT* ovarian hormone therapy, *QALY* quality-adjusted life year, *QoL* quality of life

Authors' names	Country, type of fracture, type of prevention	Interventions and control	Study population	Authors' conclusions
Ankjaer-Jensen A and Johnell O (1996) [48]	Denmark, hip, wrist and vertebral, primary and secondary	Calcium, etidronate and calcitonin. Comparator: HRT	Healthy women aged 50 years and high-risk women identified with BMD screening	There were large differences in the cost-effectiveness of different treatments. Treatment will be more cost-effective in higher risk groups. Prevention of osteoporosis through screening for low BMD should not be recommended
Armstrong K et al. (2001) [49]	US, hip, wrist and vertebral, primary	HRT and raloxifene. Comparator: no treatment	Healthy postmenopausal women aged 50	Assuming a benefit of HRT in CHD prevention, long-term HRT is the most cost-effective alternative for women at average breast cancer and CHD risk. Raloxifene is the more cost-effective alternative for women at average CHD risk with one or more major breast cancer risk factors
Borgstrom F (2004) [30]	Sweden, hip, wrist and vertebral, treatment	Alendronate. Comparator: no treatment	Cohort of 71-year-old Swedish men with low BMD and prior vertebral fracture	Under the assumption that the Fracture Intervention Trial (FIT) results were also applicable to men, alendronate is cost-effective in elderly men with low bone mass and prior vertebral fractures
Brecht J (2003) [50]	Germany, hip, wrist, vertebral and other, treatment	Risedronate. Comparator: standard treatment	70-year-old women with low BMD and a prevalent vertebral fracture	Risedronate is a cost-effective treatment for postmenopausal osteoporosis
Brecht J (2004) [51]	Germany, hip, wrist, vertebral and other, treatment	Risedronate, alendronate and Raloxifene. Comparator: standard treatment	70-year-old women with low BMD and a prevalent vertebral fracture	Bisphosphonates are cost-effective. Risedronate dominates treatment for postmenopausal osteoporosis within the German health care system
Cheung A and Wren B (1992) [17]	Australia, hip and wrist, primary	ERT or CRT. Comparator: no treatment	Simulated cohort of 27,021 perimenopausal women in New South Wales. Women were followed from age 50 to death	HRT for symptomatic women is cost-effective. Short-term treatment of asymptomatic women for prevention of osteoporotic fractures and myocardial infarction is an inefficient use of resources. Cost-effectiveness of HRT in asymptomatic women is dependent on the magnitude of the cardiac benefits associated with hormone use and the treatment duration
Colon-Emeric C (2003) [52]	US, hip, primary	External hip protectors. Comparator: no treatment	Nursing facility residents	Using external hip protectors in nursing facilities is cost saving or economically attractive over a wide range of cost and utility assumptions

Table 1 (Contd.)

Authors' names	Country, type of fracture, type of prevention	Interventions and control	Study population	Authors' conclusions
Coyle D et al. (2001) [53]	Canada, hip, wrist and vertebral, treatment	Nasal calcitonin. Comparator: alendronate, etidronate and no treatment	Postmenopausal women aged 65 with previous osteoporotic fracture	Nasal calcitonin can be considered at the margins of being cost-effective when compared with no therapy. Compared with active therapy, nasal calcitonin can be considered more cost-effective than etidronate, but its cost-effectiveness versus alendronate is inconclusive
Daly E et al. (1992) [54]	UK, hip, wrist and vertebral, primary	ERT for women with a hysterectomy. HRT for women with or without a hysterectomy. Comparator: no treatment	Hypothetical cohorts of women with and without a hysterectomy starting at age 50	There are substantial benefits to hysterectomized women taking ERT, particularly in relation to cardiovascular disease. Offering treatment to both hysterectomized women and to those with severe menopausal symptoms might be cost-effective
Daly E et al. (1996) [55]	UK, hip, wrist and vertebral, primary	ERT for women with a hysterectomy. HRT for women without a hysterectomy. Comparator: no treatment	Hypothetical cohorts of women with and without a hysterectomy starting at age 50	If estrogen has a cardioprotective effect, long-term prophylactic treatment of hysterectomized women would be relatively cost-effective. Treatment of symptomatic menopausal women for any period of time appears to be cost effective. Firm conclusions about the CE of treating non-hysterectomized asymptomatic women cannot be drawn because of the uncertainty surrounding ERT/HRT and cardioprotection
Fleurence R et al. (2002) [26]	UK, hip, leg, wrist, arm, ankle and other, secondary	HRT. Comparator: no treatment	A cohort of 3,645 perimenopausal women who had a BMD measurement with recommendation to use HRT if low BMD was present	HRT is cost effective in high-risk populations with low BMD
Fleurence R (2004) [31]	UK, hip, wrist, vertebral and other, primary and treatment	Vitamin D and calcium. Hip protectors. Vitamin D and calcium + hip protectors. Comparator: no treatment	UK male and female population over 70 at high and general risk of fracture	At the decision-maker's ceiling ratio of $20,000 per QALY, hip protectors are cost-effective in the general female population and high-risk male population, and cost saving in the high-risk female population, despite the low compliance rate with the treatment
Francis R et al. (1995) [56]	UK, vertebral, treatment	HRT, etidronate and salmon calcitonin. Comparator: no treatment	Post-menopausal women with vertebral established osteoporosis	Further vertebral fractures may be averted at relatively low cost by the use of HRT or etidronate in women with established vertebral osteoporosis. Salmon calcitonin should be reserved for the situation where HRT and cyclical etidronate are inappropriate

Garton M et al. (1997) [57]	UK, hip, wrist and vertebral, primary and secondary	BMD screening followed by HRT when appropriate. Comparator: universal recommendation of HRT without prior screening	Hypothetical cohort of 100,000 British women aged 45 years at beginning of follow-up	If BMD measurement does not influence compliance, then universal treatment with HRT is likely to prevent more fractures than selective therapy. However, if BMD screening leads to increased compliance, then screening has a favorable impact on the numbers and/or net cost of fractures prevented
Geelhoed E et al. (1994) [58]	Australia, hip, primary	ORT and a lifetime regimen of calcium supplements and exercise. Comparator: universal recommendation of HRT without prior screening	Caucasian healthy women aged 50 years or over	Treatment with estrogen from 65 years of age was the most cost-effective option to prevent hip fractures in Caucasian women. Further research is needed to establish whether there is an optimal age in terms of cost-effectiveness
Hart W et al. (2002) [59]	Spain, hip, vertebral, primay and secondary	Risedronate and alendronate. Comparator: no treatment	Hypothetical cohort of 70-year-old women with and without vertebral fracture	Risedronate was associated both with a lower cost per hip fracture avoided and a lower cost per quality-adjusted life year. In patients with or without previous vertebral fracture, risedronate is more cost-effective than weekly alendronate
Iglesias C et al. (2002) [32]	UK, hip, wrist and vertebral, treatment	Risedronate. Comparator: no treatment	75-year-old women with low BMD and previous fracture	Risedronate treatment for women aged ≥75, who have low BMD and a previous vertebral fracture, not only improves quality of life by reducing fractures, but also leads to lower net cost
Johnell O et al. (2003) [60]	Sweden, hip, wrist and vertebral, treatment	Alendronate. Comparator: no treatment	Hypothetical cohort of women aged 71 and over with low bone mass and at least one prior spine fracture	Treating older osteoporotic women and women with prior spine fracture was more cost-effective. However, cost per QALY gained for all populations studied were below generally accepted thresholds for cost-effectiveness
Jonsson B (1998) [61]	Sweden, hip, primary	Hypothetical intervention aiming to prevent hip fractures. Comparator: no treatment	Women aged 50 years or over	Targeting high-risk populations is radically important for the identification of cost-effective interventions. The cost-effectiveness of interventions aiming to reduce the risk of osteoporotic fracture improves with the age at intervention
Jonsson B et al. (1995) [62]	Sweden, hip, wrist, vertebral and shoulder, secondary	Treatment interventions for prevention of fractures (no actual treatments specified). Comparator: no treatment	Hypothetical cohort of women with established osteoporosis aged 62 with BMD below 1 SD of the mean	The cost per QALY associated with the treatment of osteoporotic patients is similar to that associated with the treatment of patients with hypertension. Given the limited evidence available, no clear conclusion regarding the cost-effectiveness of the treatment of osteoporosis is provided

Table 1 (Contd.)

Authors' names	Country, type of fracture, type of prevention	Interventions and control	Study population	Authors' conclusions
Jonsson B et al. (1999) [23]	Sweden, hip, primary, secondary and treatment	Hypothetical intervention to prevent hip fractures. Comparator: no treatment	Women aged 50 years or over	The cost-effectiveness of interventions aiming to reduce the risk of osteoporotic fracture improves with the age at intervention. The cost-effectiveness heavily relies on the offset period of the intervention's associated effect
Kanis J et al. (2002) [63]	UK, hip, spine, wrist, humerus, secondary, treatment	Bisphosphonates, vitamin D, 1-alpha hydroxylated derivatives of vitamin D, calcitonin, calcium, estrogens, estrogen like agents, anabolic steroids, fluoride salts, thiazide diuretics, raloxifene, vitamin K2, protein supplements and exercise. Comparator: no treatment	UK female population with established osteoporosis aged 50, 60, 70 and 80 years	At age 50, only HRT and calcium plus vitamin D were cost-effective. At age 80, HRT, calcium with or without vitamin D, alfacalcidol, alendronate and 'bisphosphonate' treatment were all cost-effective
Kanis J et al. (2005) [34]	UK, vertebral, secondary and treatment	Raloxifene. Comparator: no treatment	UK female population aged 50 or more with low bone mineral density or with a prior vertebral fracture	Raloxifene is cost-effective in the treatment of postmenopausal women at an increased risk of vertebral fractures in the UK
Kanis J et al. (2004) [33]	UK, hip, wrist, vertebral, secondary and treatment	Risedronate. Comparator: no treatment	Postmenopausal women from 60 to 80 years old with a variety of risk factors for fractures	Interventions with risedronate were cost-effective in women aged 60 years and older
Kanis J et al. (2001) [24]	Sweden, hip, primary	Interventions by cost of intervention (representing approximately vitamin D and calcium, bisphosphonates or estrogens). Comparator: not clear, presumably no treatment	Female population at average risk of hip fracture at any given age	Reasonable cost-effectiveness was shown even with relatively high intervention costs for women at average risk at the age of 84 years or more. For the cheapest interventions, cost-effectiveness could be found from the age of 53 years
Nagata-Kobayashi S et al. (2002) [64]	Japan, hip, primary and secondary	Screening and no screening followed by HRT. Comparator: no treatment	Asymptomatic postmenopausal women aged 50	HRT for patients with osteoporosis after screening was the most cost-effective strategy, but screening Japanese women may not be cost-effective compared to other screening interventions
Rodriguez C et al. (1999) [65]	Spain, hip, treatment	Alendronate, calcium and vitamin D. Comparator: calcium and vitamin D	Women with established osteoporosis	Alendronate to prevent hip fractures in postmenopausal women with established osteoporosis is not cost-effective
Rosner A et al. (1998) [66]	Canada, vertebral, secondary	Sequences of treatment including calcium, etidronate, alendronate, OHT (either ERT or HRT). Comparator: no treatment	Women with established osteoporosis, with and without a hysterectomy, with average age 72 years	Four treatment strategies, 'calcium → no therapy,' 'OHT → calcium → no therapy' 'OHT → etidronate → calcium no therapy,' 'OHT → alendronate calcium → no therapy,' were potentially cost-effective

Segui-Gomez M et al. (2002) [45]	US, hip, primary	Hip protectors. Comparator: vitamin D and calcium	Men and women aged 65 +	Use of hip protectors among women is associated with costs savings and QALY gains. Hip protectors are also associated with cost savings in men, but there are net losses of QALYs because of the inconveniences associated with the protectors
Singh S et al. (2004) [67]	Canada, hip, primary	Hip protectors. Comparator: no treatment, and vitamin D and calcium	Nursing home residents with average age 85 years old	Hip protector use was found to be a dominant strategy compared to no treatment and to calcium and vitamin D supplements
Torgerson D and Kanis J (1995) [68]	UK, hip, primary and secondary	Parenteral vitamin D. Comparator: oral vitamin D and calcium	Women with low BMI in the community, women in nursing homes, women with low BMI in nursing homes and all elderly women	Parenteral administration of vitamin D is a potentially cost-effective strategy for the prevention of hip fractures for women in the community and nursing homes
Torgerson D et al. (1996) [69]	UK, hip, primary	HRT (Premique), thiazide, vitamin D injection, oral vitamin D and calcium, calcium alone, calcitonin. Comparator: vitamin D injection	Hypothetical cohort of women aged 80	Vitamin D injection proved to be the most potentially cost-effective treatment. By contrast, the most expensive therapy was calcitonin
Tosteson A and Weinstein M (1991) [19]	US, hip, primary and secondary	ERT or HRT. Comparator: no treatment	Hypothetical cohort of perimenopausal women with and without a hysterectomy, starting age 50	ERT is cost-effective in hysterectomized women. HRT was found to be more expensive and would probably only be cost-effective if it is used in women at high risk of hip fracture
Tosteson A et al. (1990) [18]	US, hip, primary and secondary	BMD followed by selective, long-term HRT. Universal HRT. Comparator: no treatment, universal treatment	Hypothetical cohort of perimenopausal asymptomatic white women with intact uteri starting age 50	Screening asymptomatic perimenopausal white women to detect low bone mass and to target HRT at women who are at the greatest risk for fracture is a reasonably cost-effective use of health care resources
Visentin P et al. (1997) [70]	Italy, hip, primary and secondary	Calcitonin. Comparator: no treatment	Italian women over 50 years	Calcitonin is a costly strategy for the prevention of hip fractures in Italian women over 50, and its prescription should be considered only in women who are at high risk of hip fracture. HRT seems to be the best option for the prevention of hip fractures
Waldegger L et al. (2003) [71]	Canada, hip, wrist, vertebral, secondary prevention	Hip protectors	Women aged 82 in institutional dwelling with a previous fracture	There is sufficient evidence to support the use of hip protectors for institutional dwelling elderly, but further evidence for use in community-dwelling elderly populations is required

Table 1 (Contd.)

Authors' names	Country, type of fracture, type of prevention	Interventions and control	Study population	Authors' conclusions
Weinstein M (1980) [20]	US, hip, wrist, primary and secondary	ERT. Comparator: no treatment	Postmenopausal women aged 50 over, with or without intact uterus	Treatment appears to be relatively cost-effective in menopausal women with prior hysterectomy or osteoporosis, but does not appear to be cost-effective as a prophylactic measure in asymptomatic women with intact uteri
Weinstein M and Schiff I (1983) [21]	US, hip, wrist, primary	ERT and HRT. Comparator: no treatment	Postmenopausal women aged 50 and over with intact uterus	Overall HRT appears to be cost-effective, except in women who consider the adverse effects of menstruation to offset the relief of menopausal symptoms
Weinstein M and Tosteson A (1990) [22]	US, hip, primary	ERT and HRT. Comparator: no treatment	Hypothetical cohort of postmenopausal women aged 50, with and without menopausal symptoms	An estimated gain in life expectancy with HRT compared to ERT alone may be partly offset by a perceived reduction in the QoL owing to prolongation of menstruation in women receiving progestin. HRT is less costly on average than ERT, mainly as a consequence of reduced costs of endometrial monitoring. ERT/HRT compares favorably with many accepted clinical practices
Willis M et al. (2001) [72]	Sweden, hip, wrist, vertebral, secondary	Tibolone. Comparator: no treatment	Postmenopausal women at risk for osteoporosis-related bone fractures aged 53 +	Tibolone is cost-effective relative to no treatment in Sweden for the prevention of fractures in women with low bone mass, especially when treatment is initiated around the onset of menopause and is administered for 5 years
Willis M (2002) [73]	Sweden, hip, primary and treatment	Calcium and vitamin D3. Comparator: no treatment	Hypothetical cohorts of post-menopausal women aged 50 and older	Results suggest a lifetime treatment in older women with calcium and vitamin D3. Treatment may also be cost-effective for cohorts of high-risk 50- and particularly 60-year-old women, in particular those with osteoporosis or a maternal family history of hip fracture
Zethraeus N et al. (1999) [25]	Sweden	ERT and HRT. Comparator: no treatment	Hypothetical cohort of average asymptomatic women at the age of 50, 60 and 70 years, with and without a hysterectomy	Treating women who had had a hysterectomy with estrogen-only therapy was associated with lower CE ratios compared with treating intact women with combined therapy for all ages and risk reductions. However, uncertainty surrounding the long-term effects of HRT means that CE estimates should be interpreted carefully

ERT) with 27% (17) of studies investigating its cost-effectiveness. Bisphosphonates represented 17% (11) of the interventions, calcium and/or vitamin D 16% (10), calcitonin 9% (6), hypothetical interventions and hip protectors 8% (5) each, raloxifene 6% (4), and exercise, steroids and other, 3% (2) each. The numbers add to more than 42 as some studies investigate multiple therapies. It should be noted that seven of the HRT/ERT studies were conducted before 1994. In recent years, newer interventions such as bisphosphonates and raloxifene as well as cheaper interventions with no known side-effects such as vitamin D and calcium and hip protectors have been more readily investigated.

In 38% (16) of studies, hip fractures were the sole fracture outcome. Twenty-nine percent, 29% (12) investigated hip, wrist and vertebral fractures, 17% (7) hip, wrist, vertebral and other fractures (often proxied by shoulder fracture), 7% (3) analyzed hip and wrist fractures and 7% (3) vertebral fractures alone. Two percent 2% (1) investigated hip and vertebral fractures. Thirty-one percent (13) of the reviewed studies looked at primary intervention, 17% (7) at secondary intervention and 19% (8) investigated treatment. The remainder, 33% (14), analyzed various combinations of intervention levels. Finally 88% (37) of the studies investigated female populations. Only five studies included men in their analyses (although two of these studies questionably used general rates of fracture for both men and women).

Discussion

This structured review of economic evaluations for the prevention and treatment of osteoporosis identified 42 studies. The studies identified were published between 1980 and 2004 and span 24 years of research in the field of economic evaluation of interventions for the prevention and treatment of osteoporosis. Initially, the area was dominated by variations of a model developed in the USA, investigating the use of ERT and HRT in women with and without hysterectomy. Screening policies were also investigated to evaluate the cost-effectiveness of BMD measurements followed by HRT compared with universal HRT treatment [17, 18, 19, 20, 21, 22]. More recently, a model developed in Sweden has been employed a number of times to investigate various hypothetical interventions, at different costs, effectiveness and offset times [23, 24, 25]. Other models have been developed to investigate the cost-effectiveness of bisphosphonates and raloxifene following the results of clinical trials published in that area (FIT and MORE). Recently, a number of new models have also been published, investigating interventions such as vitamin D and calcium and hip protectors.

Despite the variety of interventions and populations considered, all but one of the reviewed studies employed cost-effectiveness models (one study provided an analysis based on economic data collected alongside clinical data [26]). The use of models is indicated in conditions such as osteoporosis because of the need to model long-term costs and effects that are not always available from trial or even observational data. In the absence of available data, decision-makers need formal frameworks on which to base their decisions, and such models can provide such as a basis when they are well conducted, transparent and explicit [27].

The quality of models in the field is variable [11, 14]. For example, some of the earlier studies made questionable use of cost-effectiveness decision rules [14]. However, the quality of the methodology and the reporting in publications is on average increasing, reflecting the availability of structured guidelines for developing and reporting cost-effectiveness models [28]. Most studies are explicit about the inputs and structure of the model. A number of models now include vertebral and wrist fractures as well as hip fractures. Some studies also include other fractures, sometimes proxied by shoulder fractures. Recently, much effort has been devoted to validating the models by providing explicit internal and external validity checks [29]. In addition, Zethreaus et al. have proposed making their model available to researchers in the field [11].

With the large number of assumptions that such models rely on, quantifying the uncertainty associated with the estimates is essential for the validity of the models. Although single and multi-way sensitivity analysis may be used to investigate the effect of different model parameters, only full probabilistic models allow the exploration of the interaction of different sources of uncertainty present within a model [28]. In these models, each input parameter is assigned an appropriate statistical distribution and a 95% confidence interval, representing a range of plausible values obtained from the literature. A Monte-Carlo simulation is then run to obtain a large number of iterations of the model. These results are used to obtain cost-effectiveness acceptability curves that show the probability that an intervention is cost-effective as a function of the decision-maker's ceiling cost-effectiveness ratio (this ceiling will vary according to the resources available for health care and is in general unknown to the analyst). An increasing number of economic evaluations are using probabilistic sensitivity analyses and cost-effectiveness acceptability curves to investigate uncertainty in the model parameters and to present this to decision-makers (for example, [26, 30, 31, 32, 33, 34]).

Several specific trends were identified from the analysis of the studies included in the structured review: first, there is a major shift away from investigating the cost-effectiveness of HRT. While the reduction in fractures following HRT use has been established through trials [35], in earlier economic evaluations, a number of assumptions were made on the potential cardioprotective effect of HRT. Because of the high absolute risk of coronary heart disease (CHD), such assumptions had large impacts on the results. However, the results of the Women's Health Initiative trial have radically challenged this approach [5, 6, 36]. With the current recommendations that HRT be

used only for the short-term relief of menopausal symptoms, and the sharp drop in prescription and use of HRT [37], the long-term use of HRT for the prevention of fractures is no longer recommended [38]. Reflecting this major shift, no economic evaluations analyzing HRT have been published since 2002.

Second, the shift away from HRT has brought other therapies to the forefront. Bisphosphonates, such as alendronate, etidronate and risedronate, and raloxifene have been investigated following the results of large clinical trials [39, 40, 41, 42, 43]. Cheaper therapies with no side effects have also been investigated: vitamin D with or without calcium and hip protectors. These interventions have also been investigated in clinical trials, or are currently being investigated [7, 8, 9, 10].

Third, there has been a shift from investigating postmenopausal women only to also investigating the cost-effectiveness of treatments in elderly men. The interest in male osteoporosis has only recently been reflected in economic evaluations, as these all date from 2003 and 2004. It has been reported that actually one-third of hip fractures will occur in men [44]. Two studies investigated male and female populations [31, 45]. One study investigated alendronate in men only [30]. Two studies did not investigate men and women separately, although this may be problematic as hip fracture rates are different in both populations.

Finally, there has been a shift away from using BMD-based measures to predict the risk of fractures to using measures of fracture risk that are age dependent. It has been argued that they more accurately predict the risk of fracture than BMD-based measures [11, 29, 46].

There have been major developments in the treatment of osteoporosis in the last few years with the publication of the results of the Women's Health Initiative on ERT and HRT, but also a number of clinical trials of other treatments for osteoporosis such as bisphosphonates, raloxifene, vitamin D and calcium and hip protectors. This shift of focus in treatments is reflected in the cost-effectiveness models that have been developed and subsequently published that have been described in this article. While a number of particular assumptions, such as the putative cardioprotective effect of HRT in these models may be obsolete, this does not make the models themselves obsolete. Methodological developments, such as the use of probabilistic sensitivity analysis and cost-effectiveness acceptability curves have also taken place. Such changes are reflected in the studies that were reviewed. If economic evaluations are to be useful decision-making tools, their development should follow an iterative process that incorporates new information, whether clinical or methodological, as it becomes available.

This structured review has provided an update and an extension to the review published by Zethreaus in 2002 [11]. It uses different inclusion and exclusion criteria from that study. For example, it does not include articles that described models without providing results [29, 47]. On the other hand, it includes studies that present cost per fracture as an outcome, while Zethreaus et al. did not. In this study, accepted methodologies for conducting systematic reviews were used. The search strategy was predefined, and data were extracted using predefined evidence tables. However, we did not provide a critical appraisal of the quality of theses economic evaluations, which would be necessary for it to qualify as a full systematic review. Future work should build on these initial results to provide a structured appraisal of the quality of the economic evaluations identified. Such work will provide researchers with additional information to build and develop future cost-effectiveness models that will provide economic and clinical evidence to decision-makers on treatment and prevention options for patients with osteoporosis.

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