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Original Article

Prevention of Osteoporosis: Cost-effectiveness of Different Pharmaceutical Treatments

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Abstract. The cost-effectiveness of different pharmaceutical programmes to prevent osteoporosis has been compared. The following pharmaceutical treatments were analysed and compared: calcium supplementation, etidronate and calcitonin. As a benchmark for comparison, oestrogen replacement therapy, in the form of both pills and plaster, was also included in the analysis. The cost-effectiveness of different strategies for particular age groups was analysed. Finally, the cost-effectiveness of population-based prevention programmes was compared with the cost-effectiveness of programmes based on screening followed by treatment of women with low bone mineral density (BMD). A cost-effectiveness analysis (CEA) was carried out. The cost/effectiveness ratio computed was net costs per hip fracture avoided. The evaluation was based on a simulation model in which 1000 women were followed from the age of 50 years. The model was based on Danish epidemiological data and Danish health care cost figures. Assumptions concerning the health effect of the pharmaceutical methods of prevention were based on results from existing studies. As different results have been reported, 'optimistic' and 'pessimistic' alternatives were simulated in the model. The analysis revealed large differences in the cost-effectiveness of different pharmaceutical methods; however, the cost-effectiveness is highly sensitive to the treatment effect assumed. Treatment will be more cost-effective the higher the fracture risk of the group treated, so cost-effectiveness will therefore increase the later in life the intervention takes place, and if only women screened for low BMD are treated. However, the overall effect from a general screening programme will be low and highly sensitive to compliance. As compliance with pharmaceutical treatment seems to be low, and as the effectiveness – and thereby the cost-effectiveness – is encumbered with much uncertainty, prevention of osteoporosis through screening for low BMD should not be recommended at present.

Keywords: Cost-effectiveness; Fracture; Osteoporosis; Pharmaceutical; Prevention

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Introduction

Bone fractures in elderly people – especially hip fractures, vertebral fractures and fractures of the distal end of the forearm – are a major health problem in Western countries [1]. In Denmark, patients over 65 years of age with bone fractures account for 6% of all annual bed-days in acute hospitals. Osteoporosis is assumed to be the main cause of these bone fractures. Programmes to prevent osteoporosis may therefore potentially lead to large savings in human as well as societal costs and, consequently, in many countries there has been a growing debate concerning whether – and how – to implement such programmes.

A decision to introduce a programme to prevent osteoporosis, among other things, has to be based on information on outcome and cost of different ways of organizing such programmes. The objective of this paper is to compare the cost-effectiveness of different pharmaceutical programmes to prevent osteoporosis. The analysis will be carried out in a Danish context.

Previous studies have analysed the cost-effectiveness of hormone replacement therapy (HRT) [2–5], but so far no study has analysed and compared the cost-

effectiveness of other pharmaceutical methods to prevent osteoporosis [6]. In this study, the cost-effectiveness of the following pharmaceutical preventive methods will be analysed: calcium supplementation, etidronate and calcitonin. As a benchmark, HRT, in the form of both pills and plaster, has been included in the analysis as well. However, because of the extraskeletal effects of HRT (effect on cardiovascular disease and breast cancer) a direct comparison between HRT and the other pharmaceuticals is difficult.

The risk of osteoporotic fractures increases sharply with age. In Denmark, the incidence for women (number of hip fractures per 1000) at the age of 50 years is about 0.5, at the age of 70 years about 3.5, and at the age of 80 years about 11.5 (unpublished data, DHI). As the effect of pharmaceutical prevention will decline after withdrawal of treatment, the question is when to start preventive treatment. This paper analyses the cost-effectiveness of different strategies regarding which age groups to treat.

Instead of a population approach aimed at preventing osteoporosis of the population as a whole, intervention can be restricted to a high-risk group. Identification of those at risk could be based on criteria generally accepted to be associated with an increased risk of osteoporotic fractures such as early menopause, low muscle strength, prolonged immobility and positive family history [7–9]. Alternatively, high-risk individuals could be identified by measurement of bone mineral density (BMD). If prevention is restricted to individuals with a high risk of bone fracture, the benefit of the programme may be expected to increase. However, this benefit may be outweighed by the costs associated with the screening programme. In the analysis, the cost-effectiveness of population-based prevention programmes will be compared with the cost-effectiveness of prevention programmes based on screening of all women followed by treatment of women with a low BMD.

Economic Evaluation

Since resources are limited, economic evaluation aims to maximize benefit (health/quality of life) within resources available. In economic evaluation of a health care programme, the resources consumed by the programme (the costs) are compared with health improvement. The benefit of the health programme can be measured in either physical units (e.g. life-years gained, number of cases avoided), Quality-Adjusted Life-Years (QALY) or monetary terms, depending on the purpose of the evaluation. Which costs to include in the evaluation depend on the scope of the analysis (societal viewpoint, health care sector, etc.). However, costs can be of the following types: *direct costs* of the programme (e.g. costs of physician, consumables and drugs), *indirect costs*, which are the cost of morbidity (e.g. time lost from work) and mortality (e.g. premature death leading to removal from the workforce), and *intangible costs* of the programme (the pain and suffering of the patient and the relatives). Any savings in direct or indirect costs due to the programme should be deducted from the cost of the programme. Finally, the costs/savings due to any side effects should be included in the cost analysis [10–13].

Method

The present study is a cost-effectiveness analysis (CEA), a method of economic evaluation where the health improvement of the health care programme is measured in physical units. The physical unit chosen (*effect-measure*) should reflect the health effect most relevant to the objective of a programme. An intermediate effect-measure for a programme with the aim of preventing osteoporosis could be increased BMD, or reduced loss of BMD. However, as it is not the reduced BMD *per se* but associated bone fractures that incur the human and societal costs of osteoporosis, the final effect-measure should be reduction in number of bone fractures. As a programme to prevent osteoporosis may lead to a reduction in several types of bone fractures, different outcome measures may be chosen in the CEA. However, as only one measure of effect can be included in the CEA (at a time), and as hip fractures seem to have the most serious human as well as societal costs, reduction in number of hip fractures was chosen as effect-measure.

The *direct costs* of a pharmaceutical programme to prevent osteoporosis consist of the medical direct costs (e.g. costs of medication, cost of GP consultations) and non-medical direct costs (e.g. transportation costs). These costs will be partially offset by savings in health care etc., due to a reduction in the number of bone fractures. *Indirect costs* may be incurred because of production loss due to time spent visiting a GP or participating in a screening programme. Indirect costs may be offset by production gain due to fewer bone fractures (less absence from work or fewer people being disabled). Finally, *intangible costs* may occur as a result of participating in a screening programme for low BMD (i.e. the anxiety caused to patients identified as having low BMD). Prevention of osteoporosis with HRT reduces the risk of cardiovascular diseases but increases the risk of breast cancer. The economic consequences of these side effects have to be included in the CEA of HRT.

The analysis is restricted to hip fractures, fracture of the forearm and vertebral fractures, as these are the most frequent osteoporotic fractures. As many of the persons involved in this programme will be retired from the labour force, indirect costs are not included in this analysis. Further, only medical direct costs have been included, while non-medical direct costs, such as transportation costs and personal costs due to HRT (sanitary protection), have not been included.

The CEA presented in this paper was carried out from a societal perspective. Both costs and effectiveness are measured as 'net' changes from a baseline programme which is no intervention. The cost-effectiveness ratio determined is

$$\frac{C-B}{E}$$

where C is medication costs, costs of GP visits, costs of diagnostic tests due to treatment; E is the number of hip fractures avoided; and B is the change in cost due to hip fractures, forearm fractures and vertebral fractures avoided. (For HRT; the change in cost due to changes in the incidence of cardiovascular disease and number of breast cancers.)

Because of the existence of time preference due to likely future growth, risk and uncertainty, future costs have to be discounted to present value. Further, some economists advise discounting of future benefit [14] while others argue against [15]. In this study, future costs are discounted, but not future benefits (hip fractures). On the advice of the Ministry of Finance in Denmark a discount rate of 5% was chosen. To illustrate the effect of discounting benefits, the cost-effectiveness of HRT with and without discounting future hip fractures has been compared.

As women have a higher risk of osteoporotic fractures (although the difference between men and women has decreased in recent years: unpublished data, DHI), this evaluation includes programmes for women only.

Simulation Model

The evaluation was based on a simulation model in which a cohort of 1000 50-year-old women was followed. Different scenarios were simulated: number of bone fractures without treatment, number of bone fractures with treatment under different assumptions concerning treatment efficiency and under different assumptions concerning age at treatment. Also risk of side effects (cardiovascular disease and breast cancer in the case of HRT) with and without treatment, and the effect of using BMD measurement for selection of patients at high risk of fracture, was simulated in the model. Each simulation allowed calculation of outcome – measured as the reduced number of bone fractures, etc. – for each 1-year age group. Further, treatment costs and savings due to number of bone fractures and economic consequences of side effects could be calculated on the basis of the model.

The model is constructed as a Quattro-Pro spreadsheet program.

Epidemiological Parameters

The cohort was reduced by the age-specific mortality rates for women (based on data from the Danish Bureau of Statistics).

Incidence of hip fracture (Table 1) was taken from the National Patient Register for 1993 in the following way: all patients with a first admission for hip fractures (ICD-8 code 820) for each 1-year age group were related to the mid-year population of that specific age group.

As no Danish data concerning age-specific incidence of fractures of the distal end of the forearm exist, and as data cannot be gathered from the National Patient Register (most patients with a fracture of the forearm are treated as outpatients), data from an English study [16] were used.

As vertebral fractures may occur with few or no symptoms there are problems in identifying the frequency of those fractures [17,18]. The analysis is based on the simple assumption that a 50-year-old woman will have a 15% lifetime risk of having a clinically diagnosed fracture [19], meaning that 150 vertebral fractures in total will occur among the cohort of 1000 women included in our model.

Age-specific incidence of breast cancer (Table 1) was gathered from the Danish Register of Cancer.

Occurrence of cardiovascular diseases (CVD) was based on prevalence data (Table 1) instead of incidence data. The risk of admission for CVD for each 5-year age group of women was calculated by relating the number of admissions for CVD (ICD-8 codes 410–414) among women to the female population in the same age groups.

Table 1. Age-specific incidence of hip fractures and breast cancer and age-specific admission rates for cardiovascular disease (CVD) among women in Denmark

Age-group (years)	Hip fractures per 1000 women[a]	Breast cancer incidence per 1000 women[b]	CVD admissions per 1000 women[c]
50–54	0.51	1.99	5.3
55–59	0.94	2.31	8.4
60–64	1.86	2.48	11.7
65–69	3.07	2.54	15.4
70–74	5.70	2.78	18.5
75–79	10.86	2.90	22.5
80–84	18.00	3.07	27.3
85–89	29.83	3.16	28.2
90–94	39.39	3.16	25.5
95–99	45.92	3.16	25.5

[a] Based on the National Patient Register for 1993. All patients with a first admission for hip fracture (ICD-8 code 820) related to mid-year population of that specific age group.
[b] Based on the Danish Register of Cancer, 1988–90.
[c] Based on the National Patient Register, 1993.

Treatment Efficiency

Different results concerning the health effect of the pharmaceutical methods of prevention included in the study have been reported. Therefore, we have chosen to illustrate the possible range of the cost-effectiveness by including two alternatives concerning treatment efficiency: an 'optimistic' alternative showing the cost-effectiveness under an optimistic expectation of treatment efficiency (including side effects), and a 'pessimistic' alternative showing the cost-effectiveness under a pessimistic expectation of treatment efficiency (including side effects). For HRT, a third 'realistic' alternative based on a recent meta-study by Johnell [7] was also included.

Table 2. Assumptions concerning treatment efficiency (RR), duration of treatment and duration of effect

Treatment	Health effect	Optimistic assumption (RR)	Pessimistic assumption (RR)	Realistic assumption (RR)
Calcitonin, 5 years	Fracture[a]	0.23 remainder of one's life	0–5 years: 0.70 5+ years: linear decrease[b]	
Etidronate, 5 years	Fracture[a]	0.5 remainder of one's life	0–5 years: 0.50 5+ years: linear decrease[b]	
Calcium, 5 years	Fracture[a]	0.5 remainder of one's life	0–5 yeara: 0.75 5+ years: linear decrease[b]	
HRT (pills+plaster) treatment, 10 years	Fracture[a]	0–30 years:0.50	0–10 years: 0.75 10–15 years 0.85	0–10 years: 0.50 10–35 years: linear decrease
	Breast cancer	0–10 years: 0 10–20 years: 130 20+ years 0	0–10 years: linear increase 10–20 years: 1.30 20+ years: 0	0–10 years: 0 10–20 years 1.30 20+ years: 0
	CVD	0–30 years: 0.50	0–10 years: 0.65 10–15 years: 0.75	0–30 years: 0.65

Sources: [7,20–23,35,38].
[a]Same reduction in risk of hip, forearm and vertebral fracture assumed.
[b]No effect reached after 25 years.

Calcitonin, Etidronate, Calcium: Different effects are reported for the pharmaceutical methods included in the study [7,19]. We have chosen to include two assumptions concerning reduced risk of bone fracture for each pharmaceutical method. For calcitonin, data from Overgaard et al. [20] and the MEDOS study [21] were used. For etidronate, data from Watts et al. [22] were used. They conducted a follow-up after 3 years, and those with a high risk had 228 fractures per 1000 patient years compared with 412 fractures for non-etidronate-treated women. For calcium, data from the MEDOS study [21] were used. Duration of treatment is assumed to be 5 years according to present recommendations. As the effect of many of these drugs are expected to persist after treatment is stopped [19], two assumptions concerning duration of protective effect are made: unchanged effect for the remainder of one's life, and a linear decreasing effect with no effect reached after 25 years.

Hormone Replacement Therapy: Several articles review the effect of HRT on postmenopausal women [7,23–27].

Studies of the protective effect on *bone fracture* reveal a relative risk varying from RR = 1.0 to RR = 0.2, most estimates being around 0.5–0.8. As an 'optimistic' assumption it was chosen to operate with an effect of RR = 0.5, which is generally made assumption concerning the effect on bone fractures. As an alternative 'pessimistic' assumption, an effect of RR = 0.75 was chosen based on a meta-analysis by Grady et al. [23]. It was assumed that there was the same protective effect on hip fractures as on forearm fractures and vertebral fractures.

Studies have shown that the protective effect of HRT will diminish after withdrawal of treatment [28], and after a number of years the difference in BMD between those who have taken HRT and those who have not will disappear. To provide maximal protection, treatment may have to be started at the time of menopause and never stopped. In the analysis we have assumed a treatment period of 10 years, while alternative assumptions concerning duration of the protective effect after withdrawal were made.

Most studies concerning the relationship between HRT and *cardiovascular disease* show reductions in CVD risks [29]. In the analysis we chose as a 'positive' assumption RR = 0.5 [30,31] and as a 'pessimistic' assumption RR = 0.65 [23]. In the study we have made different assumptions concerning the duration of the protective effect after withdrawal of treatment.

The effect on *breast cancer* risk is unclear [23,32–34]. However, several studies suggest an increase in risk of 30% [33,34]. Most studies also suggest increased risk with increased duration of treatment. In the study we have assumed either a linear increase in risk or no increased risk until after 10 years of use. The increased risk was assumed to persist 10 years after treatment withdrawal.

An overview of the assumptions made about treatment efficiency is shown in Table 2.

Cost Estimates

The correct costs to include in a CEA are the incremental/decremental costs associated with the health programme in question [11]. Only costs directly attributed to the programme – representing resources which could have been spent for an alternative purpose – should be considered. These costs include nursing time, physician time, diagnostic and therapeutic services plus 'hotel' costs such as patient diet, linen and porters' services. Patient-indirect hospital costs such as administration, building maintenance and depreciation of existing equipment should not be included if they will not be affected by the programme. This again depends on the size of change in activity. In this case, the reduced number of bone fractures will be spread over a number of hospitals and will not influence the patient indirect costs of the individual hospital. If the programme necessitates purchasing extra equipment, i.e. a bone-

mass scanner, in cases where screening programmes are introduced, the depreciation, maintenance, etc. of such equipment should be included in the programme costs.

Programme Costs: Estimated direct treatment costs per year for each treatment programme are shown in Table 3. The costs consist of drug expenses (based on Danish prices including public subsidy, if any) plus one GP consultation. In Denmark, GPs are reimbursed partly on a per capita basis, partly on a fee-for-service basis. For an ordinary consultation the GP is reimbursed 82 DKK. The incremental costs per consultation are therefore equal 82 DKK. Because of the increased risk of breast cancer, and as regular mammography examinations are not current practice in Denmark, one mammography examination every second year is included in the treatment costs for HRT.

Table 3. Programme costs

Treatment	Dose	Cost per year (DKK)
Calcitonin (nasal)	100 IU/day	8,975
Etidronate	400 mg/day for 15 days per quarter	1,919
Calcium[a]	1000 mg/day	2,369
HRT, pills (Trisekvens)	2 mg/day	1,061
HRT, plaster	50 µg/day	1,748

[a]There are large variations in the price of different calcium supplements. The costs presented here are based on the price of calcium as a pharmaceutical. However, calcium as a dietary supplement can be bought at a much lower price.

The total programme costs equal treatment costs per year multiplied by the recommended number of years of treatment. Present value of treatment costs is found by discounting future costs by 5%.

Costs of Hip Fractures: Based on a Danish study [36] the total patient direct costs per hip fracture are estimated at DKK 146 641. As shown in Table 4, the costs consist of treatment, rehabilitation, etc., during the first year plus costs induced by increased need of care due to the hip fracture for an estimated 4 years.

Table 4. Average incremental costs per hip fracture in Denmark (only variable costs included)

	Average costs (DKK)
First year	
Admission (operation, 21 bed-days, home visit, etc.)	35 000
Re-operation (10%)	3 500
Rehabilitation in primary care (40%)	3 000
Aids/alterations of home	5 000
Increased need for home care/nursing	20 570
Total first year	67 070
Following years	
Increased need for home care/nursing per year	22 440
Total cost per hip fracture (undiscounted)	156 580
Total cost per hip fracture (discounted)	146 641

Source: [36].

Costs of Fracture of the Forearm: Most patients with fracture of the forearm are treated as outpatients at an estimated cost of DKK 700 (including X-ray examination). It is assumed that 25% of the patients will be admitted and operated on at an estimated cost of DKK 22 000 (average length of stay 9.6 days). Further, it is assumed that 25% will receive physiotherapy. Cost per fracture on average is DKK 6592.

Costs of Vertebral Fracture: Most patients with a vertebral fracture will never receive medical attention (estimated 50%). Some will be treated by the GP, and about 10% [19] will be admitted to hospital (average length of stay 16.9 days). Estimated cost per patient on average is DKK 3794.

Costs of Cardiovascular Diseases: The economic consequences of a reduced number of cases of CVD due to HRT will depend on which cases are avoided: Will some cases be avoided or will the cases just be less severe? Will there be a reduced number of patients needing heart surgery (i.e. by-pass operations)? Will there be a reduction in drug expenses? As described earlier we have based our calculation concerning CVD on prevalence data rather than incidence data, taking into account only resource use in hospitals. It is assumed that a reduction in the risk of CVD of, for example, 50% will reduce the number of admissions and bed-days due to CVD by an equivalent 50% per year. It is assumed that the first day of each admission will be spent in a special coronary care unit at a cost of DKK 8400 per day. Cost of remaining bed-days per admission is estimated at DKK 2000 per day (average length of stay for women in each age group based on data from the National Patient Register). As the economic consequences of a reduction in CVD are expected to have a major impact on the cost-effectiveness of HRT, a sensitivity analysis is carried out for different assumptions about savings due to reduced CVD.

Costs of Breast Cancer: Costs per case of breast cancer are based on the treatment protocol introduced by the Danish Breast Cancer Group. Besides the examinations prior to the admission it consists of admission (with surgery), post-surgical treatment (chemotherapy, radiation therapy, etc.) and controls for the following 10 years. It is assumed that 45% will have a relapse within 10 years (average hospitalization 3 months). Total cost per case on average: DKK 127 402 (undiscounted) and DKK 96 129 (discounted).

Costs of Screening: Introduction of a programme to measure bone mass for all postmenopausal women in Denmark would require purchasing of a number of bone mass scanners. The cost per woman screened will consist of staffing, consumables, costs associated with maintaining and depreciation of scanners, and follow-up on women identified as having low bone mass. The size of the costs will depend on which technique of measurement is used and on utilization of the equip-

ment. In the analysis two assumptions concerning cost of screening have been made: DKK 1000 per person screened and DKK 2000 per person screened.

Results

Population Approach (No BMD Screening)

Comparison of Different Pharmaceutical Treatments: Table 5 shows programme cost, economic benefit and net cost per hip fracture avoided for the pharmaceutical treatments included in the analysis, assuming that treatment is started at the age of 70 years in all women. This age of treatment onset was chosen because most of the studies (apart from some studies on oestrogen) have data from the mean age of 70 years. Table 5 also shows the possible range of cost per hip fracture avoided for each pharmaceutical treatment.

It appears that there are large differences between different pharmaceutical treatments, with etidronate being the most cost-effective and calcitonin the least cost-effective. It also appears that the cost-effectiveness is extremely sensitive to assumptions concerning treatment efficiency (RR) as well as to assumptions concerning duration of treatment efficiency. For calcitonin, the cost varies from DKK 140 000 to DKK 870 000 per hip fracture avoided. For etidronate, the cost per hip

Table 5. Programme costs, economic benefit, number of hip fractures avoided and net costs on average per individual treated for different pharmaceutical treatments under different assumptions concerning treatment efficiency [a] and treatment onset at 70 years

	Optimistic assumption	Pessimistic assumption	Realistic assumption
Calcitonin			
Programme costs (C), DKK	38 842	38 842	
Economic benefit (B), DKK			
Hip fractures	−14 132	−3 900	
Forearm fractures	−340	−115	
Vertebral fractures	−179	−59	
Net costs ($C-B$), DKK	24 191	34 678	
Hip fractures avoided (E)	0.17	0.04	
$(C-B)/E$	142 300	866 950	
Etidronate			
Programme costs (C), DKK	8 307	8 307	
Economic benefit (B), DKK			
Hip fractures	−9 176	−6 348	
Forearm fractures	−220	−186	
Vertebral fractures	−106	−64	
Net costs ($C-B$), DKK	1 195	1 709	
Hip fractures avoided (E)	0.11	0.07	
$(C-B)/E$	−10 864	24 414	
Calcium supplement			
Programme costs (C), DKK	10 252	10 252	
Economic benefit (B), DKK			
Hip fractures	−9 084	−3 260	
Forearm fractures	−220	−94	
Vertebral fractures	−111	−49	
Net costs ($C-B$), DKK	837	6 849	
Hip fractures avoided (E)	0.11	0.03	
$(C-B)/E$	7 609	228 300	
HRT, pills			
Programme costs (C), DKK	7 628	7 628	7 628
Economic benefit (B), DKK			
Hip fractures	−9 176	−2 719	−7 357
Forearm fractures	−221	−92	−204
Vertebral fractures	−117	−47	−108
CVD	−2 260	−932	−1 803
Breast cancer	+266	+505	+226
Net costs ($C-B$), DKK	−4 280	5 343	−1 618
Hip fractures avoided (E)	0.11	0.03	0.08
$(C-B)/E$	−38 909	178 100	−20 225
HRT, plaster [b]			
Programme costs (C), DKK	12 570	12 570	12 570
Net costs ($C-B$), DKK	662	9 285	3 324
$(C-B)/E$	6 018	309 500	41 550

[a] Assumptions concerning treatment efficiency duration and duration of effect are shown in Table 1.
[b] Same health effects as assumed for HRT, pills.

fracture avoided varies from a net *saving* of DKK 11 000 per hip fracture to a net *cost* of DKK 25 000 per hip fracture avoided. A further analysis of the sensitivity to assumptions concerning duration of effect after treatment has stopped, showed that if assumptions concerning duration of effect in the case of calcium (pessimistic assumption) are changed from 25 years to 10 years, the cost per hip fracture avoided increases from DKK 228 000 to DKK 480 000.

Sensitivity to Cost Estimates: The costs of vertebral fractures have been crudely estimated. A sensitivity analysis, however, shows that the costs of vertebral fractures have a small impact on the cost-effectiveness of pharmaceutical treatment of osteoporosis. Under the assumption that the cost of a vertebral fracture was increased by 100%, the cost-effectiveness of calcium supplementation will decrease from DKK 228 000 per hip fracture avoided to DKK 227 000 per hip fracture avoided (pessimistic assumption). The cost of hip fracture has a larger impact on the cost-effectiveness of osteoporosis prevention. If the cost per hip fracture is reduced by 50%, the cost-effectiveness of calcium supplementation will decrease from DKK 228 000 to DKK 283 000 per hip fracture avoided (pessimistic assumption).

The sensitivity to programme costs has been analysed. A 50% reduction in the market price of the pharmaceuticals will result in the following improvement in the cost-effectiveness (pessimistic assumption, 70 years at treatment onset):

	Present market prices	*50% reduction*
Calcitonin	866 950	355 634
Etidronate	24 414	−36 357
Calcium supplement	228 300	49 422

Sensitivity to Different Assumptions Concerning Discounting: As discounting of benefit implies a reduction in the size of the denominator, the effect of discounting benefit depends on the sign of the net cost: if the net cost has a positive sign, the cost-effectiveness will be significantly reduced, while if the net cost has a negative sign, the cost-effectiveness will be improved. The cost-effectiveness of HRT (pessimistic assumption) will decrease from DKK 178 000 per hip fracture avoided, when only costs are discounted, to DKK 234 000 per hip fracture avoided if both costs and effectiveness are discounted (treatment onset at 70 years). However, under the realistic assumption concerning the health effect of HRT, the cost-effectiveness will increase from DKK −20 000 per hip fracture avoided to DKK −32 000 per hip fracture avoided if both cost and effectiveness are discounted.

When to Treat: Assuming the same reduction in fracture risk for all age groups, the cost-effectiveness of treatment will increase, the later in life the intervention starts. The cost-effectiveness of treatment with calcitonin, etidronate and calcium will increase from respectively DKK 808 000, 25 000 and 194 000 per hip fracture avoided to DKK 555 000, −34 000 and 85 000 per hip fracture avoided if the treatment onset is changed from 70 years to 80 years. This increase is due to the fact that the fracture risk increases sharply in the age groups above 80 years.

Screening with BMD

According to Nevitt et al. [37], women with the lowest bone mass (lowest quartile) have a 2.2 times higher risk of hip fracture than the group on average. Table 6

Table 6. Net costs and number of hip fractures avoided on average per individual included in a screening programme: pessimistic assumption, 70 years at screening and treatment onset

	Net costs per individual (*C*)	Hip fractures avoided (*E*)	*C/E*	Increased costs *MC*	Increased no. of hip fractures avoided (*ME*)	Incremental costs per hip fracture avoided (*MC/ME*)
(*a*) *100% compliance*						
Calcitonin						
Screening	8 354	0.02	417 700			
Population-based	34 678	0.04	866 950	26 324	0.02	1 136 200
Editronate						
Screening	−618	0.04	−15 450			
Population-based	1 709	0.07	24 414	2 327	0.03	77 567
Calcium						
Screening	1 626	0.02	81 300			
Population-based	6 849	0.03	228 300	5 223	0.01	522 300
(*b*) *50% compliance*						
Calcitonin						
Screening	4 644	0.01	464 400			
Population-based	34 678	0.04	866 950	30 034	0.03	1 001 133
Editronate						
Screening	160	0.02	8 000			
Population-based	1 709	0.07	24 414	1 549	0.05	30 980
Calcium						
Screening	1 283	0.01	128 300			
Population-based	6 849	0.03	228 300	5 566	0.02	278 300

compares the cost per hip fracture avoided under a screening programme versus a population-based programme, assuming the same reduction in fracture risk for women with low BMD as for the group as a whole. In both alternatives it is assumed that screening – and possible treatment – is taking place at the age of 70 years. The table also shows the cost per hip fracture avoided for 100% and 50% compliance.

It appears from Table 6 that a population-based programme will result in the prevention of a higher number of hip fractures than a programme consisting of screening all individuals followed by treatment of the identified high-risk group. However, the programme costs will also be higher in the population-based programme. The incremental cost-effectiveness ratio (the cost per extra hip fracture avoided) is also shown in Table 6. It appears that the cost per extra hip fracture avoided, going from a screening programme to a population-based programme, in the case of calcium will be DKK 500 000. All in all, the screening programme will be more cost-effective than the population-based programme. Even if compliance is only 50% (Table 6*b*) the screening programme will be more cost-effective.

The cost-effectiveness of a screening programme is sensitive to screening costs. A sensitivity analysis showed that an increase in the screening costs from DKK 1000 to DKK 2000 per individual will result in a decreased cost-effectiveness of etidronate from DKK −15 450 per hip fracture avoided to DKK +8.518 per hip fracture avoided (pessimistic assumption, 100% compliance). However, as it appears from Table 6*a*, even in that case the screening programme will be cost-effective than the population-based programme.

Discussion

The analysis carried out in this paper gives the impression that an estimation of the cost-effectiveness of pharmaceutical prevention of osteoporosis is subject to much uncertainty – mostly concerning the clinical effectiveness of treatment in reducing fracture risk but also regarding the duration of treatment effect. However, a CEA can give important information about the relative cost-effectiveness of different ways of organizing prevention, i.e. how to prevent (which pharmaceutical treatment), when to treat and whom to treat. Firstly, the analysis shows that there are large differences in the cost-effectiveness of different pharmaceutical treatments. Secondly, given that preventive treatment is undertaken for only a limited number of years, and that the preventive effect will decrease after withdrawal of treatment, prevention will be more cost-effective the later in life treatment takes place. Thirdly, treatment will be most cost-effective the higher the fracture risk of the group treated; therefore screening for BMD will increase cost-effectiveness even when screening costs are taken into account.

Factors other than treatment outcome, however, are subject to uncertainty in a cost-effectiveness analysis of osteoporosis prevention. The costs of vertebral fractures have been little studied; however, a sensitivity analysis showed that costs of vertebral fractures have little impact on the cost-effectiveness, while the costs of hip fractures have a larger impact on the results.

Of course economic evaluation of a pharmaceutical is very sensitive to the market price of that pharmaceutical. A change in the market price will change the cost-effectiveness of the product in question relative to alternative methods of treatment. Concerning the pharmaceutical prevention of osteoporosis, a 50% reduction in the price of calcium will improve the cost-effectiveness of prevention by calcium supplement from DKK 230 000 per hip fracture avoided to DKK 50 000 per hip fracture avoided (treatment onset at 70 years, pessimistic assumption), thus bringing the cost-effectiveness of this method of prevention in line with the cost-effectiveness of prevention by etidronate.

The economic evaluation presented in this article is carried out in a Danish context and therefore based on Danish drug prices and Danish health care costs. Drug prices are known to vary a great deal among countries (e.g. the price in Sweden for the drugs included in this study is about 50% lower than in Denmark). However, prices cannot be compared directly among countries, but have to be adjusted for differences in purchasing power, wages, etc. A comparison of the cost-effectiveness of a drug between different countries therefore has to adjust not only for differences in drug prices but also for differences in the other components included in the evaluation, such as cost of medical care avoided because of the intervention.

The analysis is based on the assumption that treatment would result in the same reduction in risk of hip, forearm and vertebral fractures. For some of the pharmaceutical treatments included in the study, however, the documented risk reduction is subject to some uncertainty. For etidronate, only data on the protective effect on vertebral fractures exist [22,38,39]. However, major studies with hip fractures as their endpoint are under way. The results from these studies will be available in the years to come. For calcitonin, prospective data concerning vertebral fractures and 'all fractures' exist [20]. Further, one major epidemiological study shows a reduction in risk of hip fracture.

CEA is relevant when the purpose of the economic evaluation is to compare alternative programmes that have the same objective and whose effect can therefore be measured in the same terms. However, as the numerator is measured in currency, and the denominator is measured in physical units, CEA is not very helpful if the question is *whether* to implement a preventive programme for osteoporosis. In that case, the relevant type of analysis would be a cost–benefit analysis (CBA) where both the numerator and the denominator are measured in monetary terms. Furthermore, CEA is not very helpful when the choice is between health programmes with different objectives and therefore measured in different effect-measures, e.g. whether to prevent osteoporosis or high blood

pressure). For such purposes, cost–utility analysis (CUA), where the benefit is measured in QALY – a unit of measure which allows comparison across programmes with different objectives – is the relevant analysis to apply.

Another advantage of QALY over effect in physical units is that it allows analysis of programmes which have several types of effects. This is the case with HRT which, besides its effect on bone fractures, has an effect on CVD and breast cancer. Furthermore, the effect of a programme to prevent osteoporosis may be a reduction of several types of bone fractures, which have different health implications.

It may, therefore, be concluded that the ideal outcome measure to choose in economic evaluation of programmes for osteoporosis prevention would be QALY. However, a problem is the lack of valid and reliable quality-of-life weight. Previous economic evaluations of osteoporosis prevention [2–5,40,41] have been carried out as CUA, but with the use of arbitrary weights. Because of the difficulty of obtaining weights empirically which take into account the combined effect on quality of life of reduced risk of bone fracture, reduced risk of CVD and an increased risk of breast cancer, and because a reduction in number of bone fractures is assumed to be the main objective of the programme, it was decided to carry out this analysis with the use of a simpler measure of effect: number of hip fractures avoided. However, due to the lack of inclusion of the extraskeletal effects of HRT in the outcome measure, the results concerning HRT cannot be compared with those on other pharmaceutical preventive treatments included in the study. Furthermore, the resulting cost-effectiveness ratios cannot be used in a comparison with other health programmes.

As previous studies concerning the cost-effectiveness of osteoporosis have used QALY as outcome measure, the comparability of the results from our study with those of other studies is limited. However, in a recent study by Jönsson et al. [40], the cost per hip fracture avoided under different assumptions concerning treatment cost, health effect and treatment duration has been calculated. Jönsson et al. found that the cost-effectiveness of treatment of a 62-year-old woman with a BMD 1 SD below the mean is SEK 1 000 000 per hip fracture avoided under the assumption of a reduction in annual fracture rate of 30% and an annual treatment cost of SEK 9000. Under the assumption of an annual treatment cost of SEK 3000, the cost per hip fracture avoided was found to be SEK 280 000. These results may be compared with the results in our study concerning screening and treatment of a 70-year-old woman with calcitonin and calcium under a pessimistic assumption. In our study the cost per hip fracture avoided is found to be DKK 354 000 for calcitonin and DKK 84 000 for calcium. The higher cost-effectiveness found in our study may be explained by differences in the age group treated, as our study has shown that the cost-effectiveness is extremely sensitive to age at treatment onset. Further, the differences may be explained by different assumptions concerning duration of effect after treatment has stopped, as it is not clear from Jönsson et al.'s study for how long the protective effect is assumed to exist after treatment has stopped.

In a Swedish study [42], total cost per hip fracture was estimated at SEK 150 000, which at the current exchange rate is equivalent to DKK 112 500. A study from the United States [43] estimates the average cost per hip fracture at $19 174, which at the current exchange rate is about DKK 105 457. Both cost estimates are below the results from the Danish cost study included in this evaluation. Besides differences in price level, organization and quantity of services offered between the three countries, this difference may be explained by the fact that the Danish study has included an increase in home care/nursing for 4 years after the hip fracture.

Seen from a cost-effectiveness point of view alone, screening for BMD would be the optimal policy on pharmaceutical prevention of osteoporosis. However, the full effect of a screening programme presupposes that individuals actually attend the screening, and that individuals identified as being in the high-risk group comply with the treatment programme recommended. In respect of compliance, experience from several studies are discouraging. Results from the Humberside experiment in the United Kingdom [19] show that among 310 women screened and identified as being in the low BMD quartile and offered HRT by their GP, only 242 (66.4%) accepted the offer, of whom 209 (57.4%) were compliant after 3 months.

A population-based intervention will have the same (or greater) problems with compliance. The results concerning effectiveness of population-based prevention therefore cannot be extended to a programme covering the whole population. Instead our results illustrate the net cost and outcome, given that a cohort with an average risk of hip fracture etc. is treated, and given 100% compliance. In the case of less than 100%

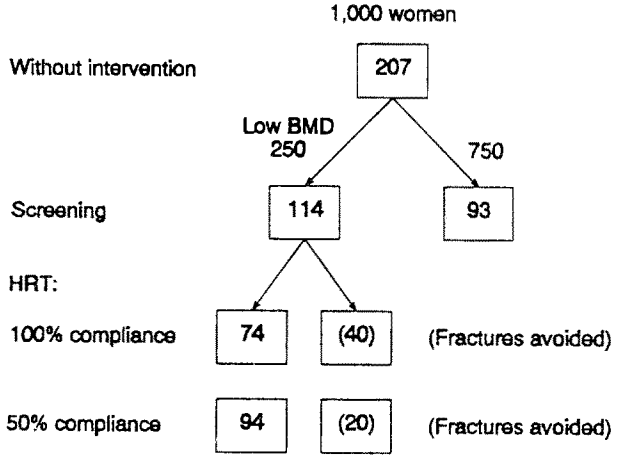

Fig. 1. Number of hip fractures without intervention, number of hip fractures that will occur among women with low BMD, and number of hip fractures among women with low BMD on HRT (prevention onset at 70 years), assuming 100% or 50% compliance.

compliance, the programme cost as well as the outcome will be reduced.

As illustrated in Fig. 1, the consequence of low compliance will be an overall small reduction in the number of hip fractures. It appears that among the 207 hip fractures that will occur in a cohort of 1000 50-year-old women (without intervention), only 20 will be avoided as a consequence of a screening programme at the age of 70 years followed by 10 years of HRT with 50% compliance.

Conclusion

Our analysis has shown large differences in the cost-effectiveness of different pharmaceutical preventive treatments. Further, our analysis showed that the cost-effectiveness of osteoporosis prevention improves, the higher the fracture risk of the group treated. However, as compliance with pharmaceutical treatment seems to be low, and as the effectiveness – and thereby the cost-effectiveness – is encumbered with much uncertainty, prevention through screening for low BMD is not recommended. Further scientific programmes need to be performed to clarify the efficiency of different prevention programmes, including those based on screening for BMD. In addition, improved methods for measuring the impact on quality of life of different prevention programmes should be developed. Finally, strategies to prevent osteoporosis by change of *lifestyle* such as increased exercise, avoidance of smoking and a change of diet with an increased intake of calcium or vitamin D – which have little or no cost to society – should be tested in a clinical trial.

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