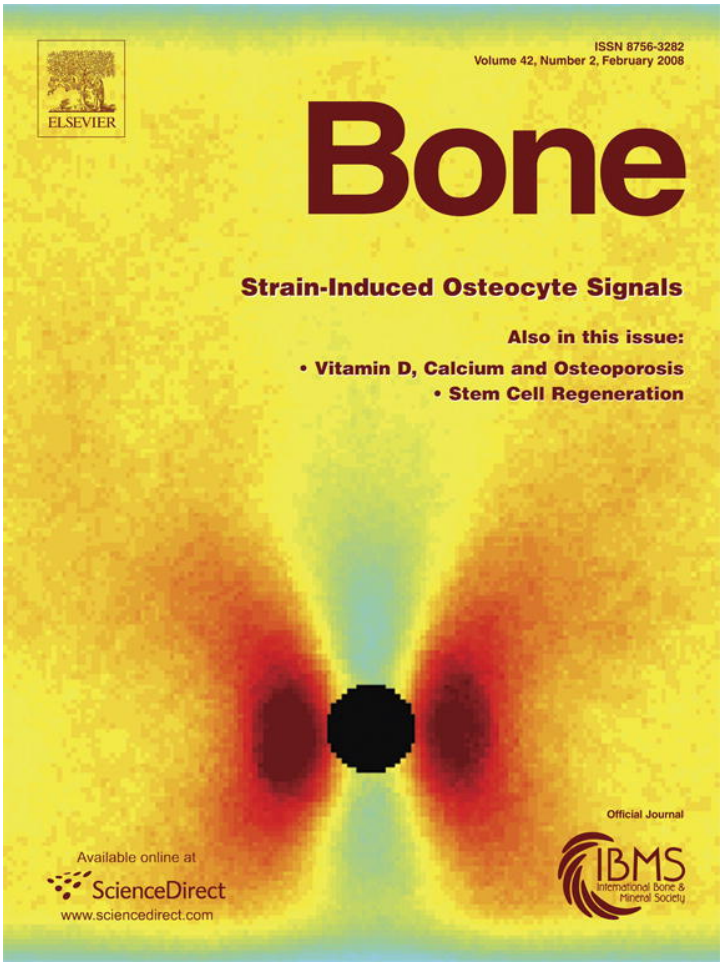

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Cost effectiveness of hormone therapy in women at high risks of fracture in Sweden, the US and the UK—Results based on the Women's Health Initiative randomised controlled trial ☆

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Abstract

Objective: The purpose of the study was to assess the cost effectiveness of hormone therapy (HT) for postmenopausal women without menopausal symptoms at an increased risk of fracture in Sweden, the UK and the US.
Methods: Using a state-transition model, the cost effectiveness of 50 year old women was assessed based on a societal perspective and the medical evidence found in the Women Health Initiative (WHI) trials. The model had a lifetime horizon divided into cycle lengths of 1 year and comprised the following disease states: hip fracture, vertebral fracture, wrist fracture, breast cancer, colorectal cancer, coronary heart disease, stroke and venous thromboembolic events. An intervention was modelled by its impact on the disease risks during and after the cessation of treatment. The model required data on clinical effects, risks, mortality rates, quality of life weights and costs valid for Sweden, the UK and the US. The main outcome of the model was cost per QALY gained of HT compared to no treatment.
Results: The results indicated that HT compared to no treatment was cost-effective for most sub-groups of hysterectomised women, whereas for women with an intact uterus without a previous fracture, HT was commonly dominated by no treatment. Fracture risks were the single most important determinant of the cost effectiveness results.
Conclusions: HT is cost-effective in women with a hysterectomy irrespective of prior fracture status. In women with an intact uterus, opposed HT was cost-effective in those with a prior vertebral fracture, but cost-ineffective in women without a prior vertebral fracture. Even though HT is found cost-effective for a selection of osteoporotic women, it is unlikely to be considered for first-line therapy for osteoporosis because bisphosphonates have shown a similar reduction in fracture risks but without an increased risk of adverse events.

Keywords: HT; Osteoporosis; Hysterectomy; WHI

Introduction

Hormone therapy (HT) was for many years recommended as a first-line treatment for osteoporosis because randomised controlled studies had showed that HT prevented bone loss at the time of menopause and in later life. In addition, observational studies [1–3] showed that the use of HT was associated with a decrease in fracture risk. Enthusiasm for HT was further bolstered by information from observational studies showing lower risks of cardiovascular disease in women treated with HT, but offset by inconsistent reports that HT was associated with an increased risk of breast cancer [2,4–7]. For non-hysterectomised women taking oestrogens only therapy, an increased risk of endometrial cancer was established, but the increase in risk was eliminated by the addition of a progestin [6]. Thus oestrogen only therapy was given to hysterectomised women, whilst women with an intact uterus were recommended oestrogen combined with a progestin.

Concerns over the safety of HT grew with the publication of several influential studies. The Heart and Estrogen/Progestin

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Replacement Study (HERS) showed a short-term increase in cardiovascular risk in women selected for being at high risk [8] and the Million Women Study (MWS) reported a significant association of HT use with breast cancer [4]. Consistent with these findings, the Women's Health Initiative (WHI) [3,6,9] found an increased risk of coronary heart disease (CHD) and breast cancer for women given opposed (oestrogen plus progestins) HT. In contrast, the WHI also found a decreased hazard ratio for breast cancer in hysterectomised women on oestrogen alone, although the confidence intervals crossed unity [3]. The WHI study [6] also showed that HT increased the risk of stroke and venous thromboembolic events (VTE) but decreased the risk of osteoporotic fractures and colorectal cancer (with opposed HT).

In assessing the overall risks and benefits of HT, the Data Safety and Monitoring Board of the WHI devised a Global Index to measure the overall balance of risks and benefits of HT [3,6,9]. The Global Index, based on counting the number of adverse and beneficial effects, showed a net risk for opposed HT (Hazard ratio (HR) = 1.15, 95% CI = 1.03–1.28) and a neutral effect of oestrogen alone in hysterectomised women (HR = 1.01, 95% CI = 0.91–1.12). Consequently, regulatory authorities have advised that HT should not be used as a first-line treatment for osteoporosis and many now consider that the risks outweigh the benefits to the extent that HT can no longer be recommended at all for the management of osteoporosis. This view is reflected by a decrease in use [10] and sales of HT by more than 40% worldwide.

There are, however, problems with the use of the Global Index as a measure of the overall balance of risks and benefits of HT [3,6,9]. First, the index does not include fractures other than hip fractures, although these too incur major mortality and morbidity, particularly clinical spine fractures. If all fractures were counted as benefits, the Global Index would find very much in favour of both opposed and unopposed oestrogen. Second, the Global Index is applied to a population of women at average or lower than average risk of fracture. Targeting HT to women at high risk of fracture is likely to alter the Global Index since more fractures would be saved for the same number of adverse events. Third, the Global Index does not take account of the morbidity consequences of events. Thus a VTE is accorded the same weight as a case of breast cancer. In order to make a fair and balanced assessment of the health impact of HT, it is appropriate to quantify these outcomes with a common metric such as quality-adjusted life years (QALYs). An extension of this method is a cost effectiveness analysis, which considers the whole effect profile of HT and therefore also can be used to inform payers and policy makers.

Given the new evidence in WHI, it has been found that there is still a high probability that HT is a cost-effective strategy for women with menopausal symptoms [11]. However, there is still a need to further investigate the cost effectiveness of HT for women without menopausal symptoms but at an increased risk of fractures.

The aim of the present study was to undertake a cost effectiveness analysis to investigate whether the risks of HT outweighed the benefits when targeted to women without menopausal symptoms and at an increased risk of fractures in Sweden, the UK and the US.

Methods

Cost effectiveness analysis

Cost effectiveness analysis (CEA) is a method for assessing costs and benefits of alternative ways of allocating resources to assist decisions aiming to improve efficiency. CEA is based on maximising health effects subject to a cost constraint, where costs are measured in monetary units and health effects in non-monetary units such as life years or QALYs. The incremental cost effectiveness ratio (ICER) can then be calculated, defined as the cost per gained unit of effectiveness, e.g. cost per QALY gained.

The cost effectiveness of HT was compared to no treatment in postmenopausal women at the threshold of osteoporosis (femoral neck *T*-score = −2.5 SD) in Sweden, the US and the UK. A lower *T*-score (<−2.5) would increase the fracture risk and thereby make the results more favourable for HT. The analysis was based on a societal perspective including costs associated with a change in the expected length of life and on the clinical findings as reported by the WHI [3,6,9]. The evaluation was carried out in 12 independent patient groups dependent on nationality, uterine status (intact uterus or hysterectomised) and previous vertebral fracture status (yes or no). Women were aged 60 years and those with an intact uterus were assigned to combined therapy and hysterectomised women were assigned to oestrogen only therapy.

Model

To assess the cost effectiveness of HT, modelling was necessary because clinical trials do not provide all the information needed for economic evaluation, i.e. cost and effectiveness information in a long run perspective were missing. The cost effectiveness model used in this study was based on a previously developed model, which has been extensively described elsewhere [11,12]. The model used was an individual state-transition model that keeps track of the patient's disease history. Patients were in any state permitted to transit to all disease states, staying or dying. The model included the following disease events: stroke, VTE, breast cancer, colorectal cancer, hip fracture, vertebral fracture, wrist fracture and CHD. CHD was defined by three disease states in the model: acute myocardial infarction (AMI), angina and coronary insufficiency (Fig. 1). The WHI trial defined CHD as death from CHD and non-fatal MI (acute and silent MI) and was assumed to be valid for the three disease states in the model.

A patient started a model simulation in a *Well/No event* state and passed through the model in yearly cycles between the different health states until 100 years of age or death. In each cycle it was possible to incur any disease event and throughout the simulation, the number and time of events for each patient

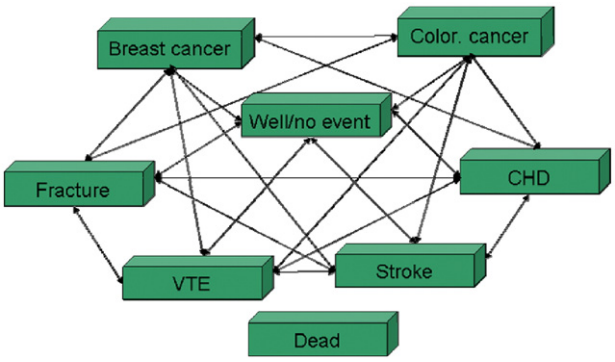

Fig. 1. The structure of the model. Note: The model shows all permitted transitions in each cycle. It is also possible to transit to the dead state in each cycle but these arrows are excluded to simplify the model.

were recorded. The events were assumed to be mutually exclusive, i.e. only one event could occur in each cycle, which may have led to a slight underestimation of the number of disease events. However, there are no data on the effects of combined events and the chosen model was therefore designed to reflect a more conservative scenario.

The main output from the model was costs and QALYs, from which the ICER of different treatment alternatives was computed, in this case, HT compared to no treatment. Some of the diseases had related costs and effects that lasted longer than 1 year, which were accounted for by the memory functionality.

Since an intervention is modelled by its impact on the disease risks during therapy and possibly also after stopping treatment, a remaining therapeutic effect during an offset period of time was added in the model. For example, a remaining effect on fracture risk after cessation of treatment was modelled as a linear decline in the effect for a given offset time period, e.g. 5 years.

Sensitivity analyses

The input data in the model are surrounded by uncertainty. Sensitivity analyses were done for all input parameters considered to have a potential impact on the results.

Probabilistic sensitivity analysis

To assess the uncertainty surrounding a model, a probabilistic sensitivity analysis can be done, where the uncertainty in the relevant underlying parameters is taken into account by allowing some or preferably all of them to vary over a given range with a given distribution. One possible option for analysing the uncertainty, which have been used in this study, is acceptability curves [13].

Data

The data for the model were based on available evidence for risks, mortality rates, quality of life weights and costs for Sweden, the US and the UK. Incidence, cost and quality of life data were based on published empirical studies. Mortality rates were obtained from national registers and epidemiological studies.

The effect of HT

The effects of HT on disease risks during therapy were taken from the WHI study [3,6,9]. Although a few point estimates were borderline significant or not significant, these estimates were used in the model to get the best available estimates for the base case scenario. Non-significant estimates were excluded in sensitivity analysis. Duration of HT treatment was set to 3 years, and a remaining effect of 5 years was assumed for fractures, consistent with recent analyses of osteoporotic treatments [11,14]. Studies of osteoporotic treatments suggest that the remaining effect may even be longer than this [15–19]. However, the evidence is not consistent so that the remaining effect on fractures was varied in a sensitivity analysis. No other remaining effects are assumed to exist [4,11].

For women taking oestrogen plus progestin, HT was assumed to decrease the risk of hip fracture (RR=0.66 CI: 0.5–0.98), vertebral fracture (RR=0.66, CI: 0.44–0.98), wrist fracture (RR=0.77, CI: 0.69–0.86) and colorectal cancer (RR=0.63 CI: 0.43–0.92) but increase the risk of breast cancer (RR=1.26, CI: 1.00–1.59), stroke (RR=1.41, CI: 1.07–1.85), VTE (RR=2.11, CI: 1.58–2.82) and CHD (RR=1.24, CI: 1.00–1.54).

In women with a prior hysterectomy, HT was assumed to decrease the risk of hip fracture (RR=0.65, CI: 0.45–0.94), vertebral fracture (RR=0.64, CI: 0.44–0.93), wrist fracture (RR=0.58, CI: 0.47–0.72), breast cancer (RR=0.77, CI: 0.59–1.01) and CHD (RR=0.91, CI: 0.75–1.12) but increase the risk of colorectal cancer (RR=1.08, CI: 0.75–1.55), stroke (RR=1.39, CI: 1.10–1.77) and VTE (RR=1.33).

Disease risks

The risks of disease events for the general population of each country were derived from previous studies and inpatient registers (Table 1). Since the target patient group of this study was women with osteoporosis, the fracture risks were adjusted to reflect the increased fracture risk for women at the threshold for osteoporosis compared to the general population. The method used to calculate the age differentiated relative risk of fractures has previously been described in Kanis et al. and De Laet et al. [20,21]. The relative risks were calculated from the bone mineral density (BMD) and the prevalence of vertebral fractures in the patient groups. Because these relative risk calculations are associated with a fair amount of uncertainty, the relative risks of fractures were varied in a sensitivity analysis (*T*-score=−1 and −4 SD).

Other disease event risks were assumed not to be affected by osteoporosis. However, results from previous studies [22,23] indicate a decreased risk of breast cancer for osteoporotic women, but evidence in published literature is inconclusive [24,25]. For this reason, we assumed a 20% lower breast cancer risk than the average population risk [23] only in a sensitivity analysis.

Mortality rates

The age specific annual mortality rates were from national mortality databases and published literature (Table 1). Mortality rates based on inpatient and death registers were estimated using logistic regression [26] (first year mortality rates) and Weibull survival regression [27] (subsequent years). Mortality rates were missing for some events in the UK and US. These were therefore imputed based on the Swedish mortality rates by taking the age differentiated relative risk of dying after an event (i.e. event mortality divided by normal mortality) multiplied with the US and UK normal mortality rates.

Some alterations to the data have been made. To fit the model structure, normal mortality rates were adjusted to exclude the risk of dying from disease events already included in the model [11]. This was calculated as normal mortality multiplied by the share of all causes of death [28–30] that were not explained by CHD, stroke, breast cancer or colorectal cancer. Also, due to co-morbid conditions, the excess mortality after fracture cannot be entirely ascribed to the fracture event [31]. Results from previous studies of hip and vertebral fracture patients have estimated that 17%–42% [31–33] of all deaths were considered to be causally related to the fracture event. Consistent with these findings we assumed that 30% of the observed excess mortality after a hip or vertebral fracture was associated with the fracture

Table 1
Values and sources for input data in the model

Item	Sweden	UK	US
Disease risks (per 1000)			
Hip fracture	0.63–77.08 [51]	0.37–55.94 [52]	0.52–41.78 [53]
Vertebral fracture	1.62–28.84 [51]	0.95–20.93 [54]	0.44–14.17 [55]
Wrist fracture	4.01–18.52 [51]	2.08–7.87 [52]	2.4–7.94 [53]
Breast cancer	3.13–1.76 [56]	2.36–4.2 [57]	2.18–3.11 [58]
Colorectal cancer	0.22–1.52 [56]	0.15–2.33 [57]	0.23–1.88 [58]
AMI	0.62–14.17 [56]	0.69–0.17 [59–62]	1.17–0.29 [59,60,63]
Angina	1.15–7.89 [56]	1.66–0.17 [59–62]	2.8–0.29 [59,60,63]
Coronary insufficiency	0.46–1.54 [56]	0.28–0.04 [59–62]	0.47–0.07 [59,60,63]
Stroke	0.97–24.47 [56]	0.54–15.08 [64]	1.32–40.28 [65]
VTE	0.72–4.79 [56]	0.83–8.29 [66]	0.63–8.13 [66]
Mortality (per 1000)			
Normal	2.4–347.9 [28]	2.8–417.0 [29]	3.1–316.5 [30,67]
Hip fracture	31.3–525.7 [68]	NA	NA
Vertebral fracture	35.0–338.7 [35]	NA	NA
Breast cancer	74.6–365.8 [56]	NA	20.3–455.2 [69]
Colorectal cancer	78.4–630.7 [56]	NA	113.9–1000 [69]
AMI	54.5–772.1 [56]	102.0–1000 [59]	10–464.2 [59]
Angina	6.3–471.6 [56]	8.5–489.9 [59]	7.5–430.9 [59]
Coronary insufficiency	12.3–537.6 [56]	11.4–527.7 [59]	10–464.2 [59]
Stroke	103.3–695.2 [56]	NA	NA
VTE	113.5–701.3 [56]	NA	NA
Direct costs (1st year, US $ 2006)			
Hip fracture	11,961–15,162 [70–72]	14,467–24,376 [70,73–75]	13,620 [76,77]
Vertebral fracture	1959–12,101 [70]	1853–3376 [73]	5571 [76,77]
Wrist fracture	2717 [70]	971 [73]	3024 [76,77]
Breast cancer	9000–7533 [56]	19,348 [78]	13,473–8160 [79]
Colorectal cancer	16,828–14,262 [56]	23,945 [80]	24,889–23,477 [81]
AMI	7223 [82]	5525 [83,84]	20,645 [85,86]
Angina	7010 [82]	7727 [83]	3207 [85,86]
Coronary insufficiency	14,084 [82]	7727 [83]	15,055 [85]
Stroke	23,219 [87]	17,519 [88]	38,141–16,648 [89]
VTE	4929 [56]	2727–1887 National Schedule of Reference Costs	19,421 [90]
Indirect costs (1st year, US $ 2006)			
Hip fracture	115 [70]	NA	NA
Vertebral fracture	4461 [91]		
Wrist fracture	193 [70]		
Breast cancer	12,818 [92]	NA	NA
Stroke	16,281 [93]	NA	NA
CHD	13,898 [94]	NA	NA
Cost added life years (CALY, US $ 2006)			
	−9318 to 36,238 [95]	NA	−10,823 to 25,394 [96]
*Quality of life**	*All countries 1st year*		
Hip fracture	0.8 [70,97,98]		
Vertebral fracture	0.65 [70,97,98]		
Wrist fracture	0.93 [70,97,98]		
Breast cancer	0.8 [99]		
Colorectal cancer	NA		
Stroke	0.74 [36,100]		
CHD	0.73 [101,102]		
VTE	NA		

Note: Due to space limits, all age-adjusted data could not be shown; only the ranges for ages 50–100 are shown. If only one figure is showing, it is used for all age groups. Where the ranges seem low, it is possible that the maximum value is in the middle of the age range and therefore not shown. See under "data" in the Methods section for details and assumptions made on missing data.
*Data represent multipliers for each disease event. For country specific utilities per event, these values were related to the utility of the general population.
NA—not available, these costs and mortality rates have been imputed based on Swedish data in the model.
CHD—coronary heart disease, VTE—venous thromboembolic event, CALY—cost added life years.

event. Wrist fracture was assumed not to be associated with any excess mortality [34,35].

In all the estimated functions, the mortality rate decreased for each year that passed after the event. Because of insufficient follow-up data on these patients, the long-term trend is extrapolated from the decreasing trend found in the mortality function. In some instances, when many years have passed, the estimated mortality can be lower than population mortality, which is not reasonable. Therefore, if the estimated mortality risk was lower than population mortality, the population mortality was used.

Quality of life

For comparability, the quality of life estimates derived from empirical studies were all estimated using the EuroQol-5D (EQ-5D) instrument. An exception was the quality of life estimates for stroke, which were derived from a meta-analysis, which included different estimation methods [36]. The quality of life estimates were used to derive multipliers for each disease, based on utility estimates of the general population in each specific country of study (Table 1). The multipliers were then applied to utility estimates of the general population for Sweden, UK and US [37–39]. It was hence assumed that the quality of life effects of a specific disease event were equal across the investigated countries.

There is, however, a lack of quality of life data, especially with regard to non-skeletal events. Therefore some assumptions had to been made in the model. VTE was assumed not to be associated with any quality of life reduction after the first year. First year quality of life loss for colorectal cancer and VTE as well as quality of life reductions after the first year for stroke and CHD were assumed to be 10%, i.e. a multiplier of 0.9. Previous studies [11,12] have assumed a utility loss of 0.1 for these outcomes. We have chosen to be consistent with the other estimates and used multipliers instead of a fixed reduction. This gives more conservative estimates of the utility loss compared to the previous studies.

The estimation of the gain in quality of life of menopausal symptom relief with HT is based on a Swedish empirical study

Table 2
Base case results life years and QALY gained for 60 year old osteoporotic (*T*-score=−2.5SD) women, discounted (undiscounted)

		Intact uterus		Hysterectomised	
		No previous fracture	Previous fracture	No previous fracture	Previous fracture
Sweden	Life years	−0.0344 (−0.0534)	0.0056 (0.013)	0.0482 (0.086)	0.0669 (0.113)
	QALYs	−0.018 (−0.028)	0.0316 (0.044)	0.054 (0.087)	0.083 (0.125)
UK	Life years	−0.0457 (−0.0718)	0.0094 (0.0226)	0.0073 (0.0151)	0.0457 (0.078)
	QALYs	−0.0323 (−0.0496)	0.0192 (0.0318)	0.0132 (0.0213)	0.052 (0.0792)
US	Life years	−0.0581 (−0.091)	−0.0086 (−0.011)	−0.00632 (−0.0067)	0.0321 (0.0563)
	QALYs	−0.0388 (−0.0605)	0.0238 (0.0301)	0.0128 (0.0182)	0.0646 (0.092)

Note: The table presents the base case results of life years gained and quality-adjusted life years (QALYs), discounted (undiscounted) for all patient groups included (different fracture risks and uterus status). Women with intact uterus were given combination therapy whereas hysterectomised women were taken oestrogen only.

[40], where, depending on severity, the quality of life loss from menopausal symptoms ranged from 0.18 to 0.42. In sensitivity analysis, the mean quality of life loss from the study, i.e. 0.29, was used.

Costs

Direct intervention, morbidity related and mortality costs were accounted for in the model. All costs were expressed in US dollar prices of 2006. Where appropriate, the costs were inflated using national inflation rates. In the base case, a 3% discount rate was used on both costs and effects.

The annual intervention cost for women on combination therapy (with intact uterus) was estimated at $426 for Sweden, $279 for the UK and $717 for the US. This included drug costs, 0.5 BMD examinations and 1.5 General Practitioner (GP) consultations [2]. The corresponding annual intervention cost for women on oestrogen only therapy (with a hysterectomy) was estimated at $249 for Sweden, $167 for the UK and $205 for the US. This included drug costs, 0.5 BMD examinations and 1 GP consultation [2]. The drug prices used in the calculations were from a selection of drugs comparable between the countries.

The direct costs of an event can be divided into acute costs, which occur in the first year following the event, and the long-term costs, which can persist several years after the event or even for the remaining lifetime of the patient. The sources for all cost estimates are listed in Table 1. However, some calculations and assumptions need explanation.

In the model, it was conservatively assumed that VTE, vertebral and wrist fractures were not associated with any long-term costs. Where long-term costs were missing, i.e. for breast cancer, colorectal cancer and stroke in UK, it was assumed that the costs constituted 10% of first year costs. This assumption was based on the relationship between costs in the first and subsequent years for Sweden and the US. The long-term hip fractures costs were assumed to be relative to the age differentiated proportion of hip fracture patients staying at nursing homes. The rates varied from 6.7% for 50–59 year old women to 22.6% for 90 year olds [41].

Some of the costs were based on inpatient registers. It should, however, be noted that these cost estimates did not reflect the full potential direct cost effects because of the conservative assumption of only including the cost of inpatient care.

Indirect costs for UK and US as well as cost in added life years (CALY) for the UK were missing. These costs were therefore imputed based on the Swedish data, using Purchasing Power Parities (PPP), and added in a sensitivity analysis.

Results

Health outcomes and costs

HT was associated with a loss in life years (LY) in women with an intact uterus and without a previous fracture in all countries (Table 2). The mean decrease in expected life years was 0.03–0.06, depending on the country, which corresponds to a loss of 13–21 days. For this group of women, there was also a decrease, as expected, in QALYs between −0.02 and −0.04 due to HT use (Table 3). Women with a previous fracture in US also had a loss in life years, whereas for women in Sweden and UK, there was a small gain in life years. For women with an intact

Table 3
Base case results of cost effectiveness analyses of 60 year old osteoporotic (*T*-score=−2.5 SD) women (US $ 2006)

		Intact uterus			Hysterectomised		
		Incremental cost	QALY gained	Cost/QALY gained	Incremental cost	QALY gained	Cost/QALY gained
No previous fracture	Sweden	408	−0.018	HT dominated	1439	0.054	26,644
	UK	793	−0.032	HT dominated	254	0.013	19,265
	US	1129	−0.039	HT dominated	206	0.013	16,059
Previous fracture	Sweden	526	0.032	16,616	1183	0.083	14,163
	UK	560	0.019	29,132	107	0.052	2054
	US	1 180	0.024	49,539	215	0.065	3326

Note: Cost effectiveness results of the base case analyses displaying the incremental costs, the incremental quality-adjusted life years (QALYs) and the cost per QALY gained, i.e. the incremental cost effectiveness ratio (ICER). These results are valid for an osteoporotic woman at a *T*-score equal to −2.5 SD. A higher *T*-score would make the ICER more favourable for HT.

Table 4
Sensitivity analyses of cost per QALY gained of HT compared to no treatment for women with intact uterus

	Sweden		UK		US	
	No previous fracture	Previous fracture	No previous fracture	Previous fracture	No previous fracture	Previous fracture
Base case	HT dominated	16 616	HT dominated	29 132	HT dominated	49 539
Sensitivity analysis						
50 year olds	HT dominated	30 125	HT dominated	1628	HT dominated	115,370
70 year olds	26,636*	Cost saving	HT dominated	Cost saving	8246*	10,683*
With CALY**	HT dominated	13,171	2359	46,067	HT dominated	49,539
With indirect costs**	HT dominated	9126	HT dominated	34,171	HT dominated	54,489
Menopausal symptoms	602	723	1195	785	1725	1644
Treatment duration 1 year	38,037	15,992	HT dominated	2814	HT dominated	12,379
Treatment duration 5 years	HT dominated	19,374	HT dominated	89,050	HT dominated	230,255
No offset time on fractures	HT dominated	HT dominated	HT dominated	HT dominated	HT dominated	HT dominated
Offset time on fractures=3 years	HT dominated	29,735	HT dominated	55,596	HT dominated	100,620
T-score=−1	HT dominated	HT dominated	HT dominated	HT dominated	HT dominated	HT dominated
T-score=−4	196	Cost saving	18,125	Cost saving	26,198	Cost saving
20% decreased risk of BC	HT dominated	20,402	HT dominated	36,535	HT dominated	44,854
No HT effect on						
Fractures	HT dominated	HT dominated	HT dominated	HT dominated	HT dominated	HT dominated

The patients are 60 year old osteoporotic women (*T*-score=−2.5 SD), with or without a previous fracture.
Note: The table shows the results from the sensitivity analysis which had significant impact on the results or were motivated for some other reason. The values in the table should be compared to the base case results at the top of the table.
*The value represents the ICER for "no treatment" compared to HT, i.e. HT is not the most favourable treatment option.
**In base case, only costs valid for each country are included. Therefore, one analysis was made where CALY (imputed values for UK) was included in all country specific assessments and one with indirect costs (imputed values for UK and US) included.
CALY—cost added life years, HT—hormone therapy.

uterus and a previous vertebral fracture, HT increased the QALYs compared to no treatment for all groups in base case. The QALY effects for this group were between 0.02 and 0.03.

HT was associated with a gain in life years in hysterectomised women with and without previous fracture in Sweden and UK. The mean gain in life expectancy was 0.007–0.07, which

Table 5
Sensitivity analyses of cost per QALY gained of HT compared to no treatment for hysterectomised women

	Sweden		UK		US	
	No previous fracture	Previous fracture	No previous fracture	Previous fracture	No previous fracture	Previous fracture
Base case	26,644	14,163	19,265	2054	16,059	3326
Sensitivity analysis						
50 year olds	26,805	12,572	763	184	34,733	8200
70 year olds	14,861	10,492	Cost saving	Cost saving	47,960*	Cost saving
With CALY**	28,060	15,778	35,519	21,751	16,059	3326
With indirect costs**	3631	Cost saving	16,550	536	15,364	Cost saving
Menopausal symptoms	1919	1518	359	144	291	283
Treatment duration 1 year	19,134	14,326	3186	Cost saving	Cost saving	3488
Treatment duration 5 years	33,211	15,307	28,115	4382	30,400	4568
No offset time on fractures	46,441	27,377	60,374	12,121	121,846	8374
Offset time on fractures=3 years	31,170	18,844	24,833	3127	27,126	5030
T-score=−1	97,313	34,078	88,205	11,443	117,643	26,402
T-score=−4	4663	Cost saving	Cost saving	Cost saving	506	Cost saving
20% decreased risk of BC	25,517	15,833	24,656	2339	25,351	2952
No HT effect on						
Fractures	1,594,154	HT dominated	2,383,970	HT dominated	HT dominated	HT dominated
BC, CC, CHD, VTE***	29,172	13,762	59,304	3509	29,830	4012

The patients are 60 year old osteoporotic women (*T*-score=−2.5 SD), with or without a previous fracture.
Note: The table shows the results from the sensitivity analysis which had significant impact on the results or were motivated for some other reason. The values in the table should be compared to the base case results at the top of the table.
*The value represents the ICER for "no treatment" compared to HT, i.e. HT is not the most favourable treatment option.
**In base case, only costs valid for each country are included. Therefore, one analysis was made where CALY (imputed values for UK) was included in all country specific assessments and one with indirect costs (imputed values for UK and US) included.
***The effects were not significant and in sensitivity analysis the treatment effect was set to zero.
CALY—cost added life years, HT—hormone therapy, BC—breast cancer, CC—colorectal cancer, CHD—coronary heart disease, VTE—venous thromboembolic event.

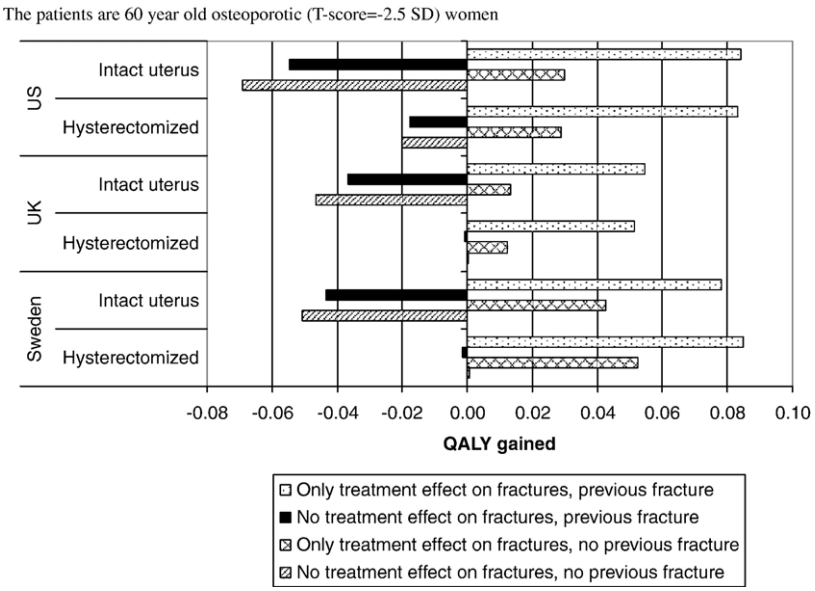

Fig. 2. Difference in QALY gained between only including treatment effect on fractures and no treatment effect on fractures. The patients are 60 year old osteoporotic (*T*-score = −2.5 SD) women. Note: The figure illustrates the effect on the incremental QALYs when only including the effect of HT on fractures and only including the effects on other disease events in the model. In almost all cases, only including the treatment effect on fractures gives a net gain in QALYs whereas only including the other events gives a net loss. The results represent the minimum value for osteoporotic women since the women are defined at the lower *T*-score threshold value.

corresponds to 3–25 days (Table 2). HT was also associated with an increase in expected QALYs compared to no treatment between 0.01 and 0.08 (Table 3). The life year and QALY effects varied with regard to US women. The effects on life years ranging from −0.006 to 0.03 and QALYs from 0.013 to 0.065.

The health effects were discounted in base case. The undiscounted values of life years gained and QALYs (Table 2) were found to be greater, which increased the difference between the effects on different patient populations.

In the base case, the cost difference of HT compared to no treatment was positive for all patient groups and countries. The cost differences for women with intact uterus were between $400 and $1200. For hysterectomised women, the cost difference ranged from $100 to $1400 (Table 3).

Cost effectiveness

The base case scenarios for 60 year old women indicated that the ICER for HT in hysterectomised women and women with intact uterus and a previous fracture ranged from $150 to $50,000. For patients with an intact uterus and without a previous fracture, “no treatment” was the preferred treatment option in all countries (Table 3). The results also indicated that the ICER was lower in older age groups than in younger (Tables 4

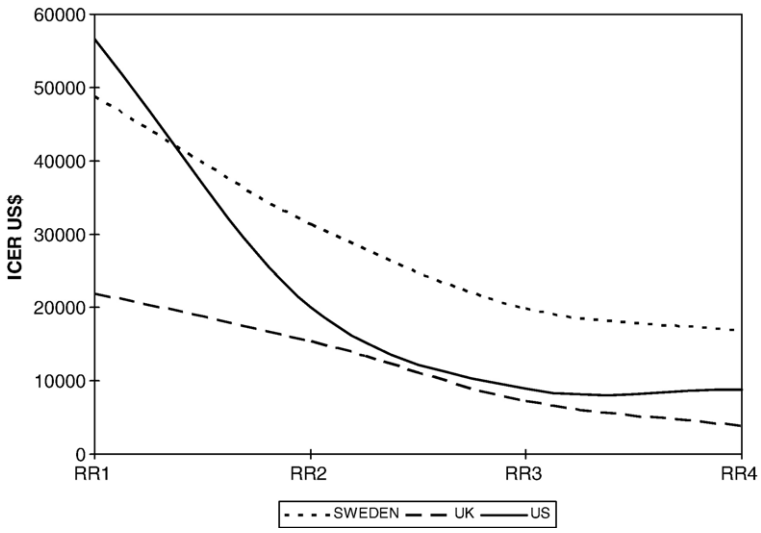

Fig. 3. Threshold analysis of relative risk (RR) of fracture for hysterectomised women. Note: The figure illustrates the different ICERs, or cost per gained QALY, for different abstract levels of relative risk of fracture compared to the general population. The increased risk of fractures can be due to many factors, not just BMD, and are set as a fixed rate irrespective of age.

and 5). The inclusion of different cost items did not significantly change the results in most cases, but inclusion of indirect costs had the greatest effect, making HT a more favourable treatment option (Tables 4 and 5).

The cost effectiveness ratios were lower for women with a previous fracture, irrespective of uterus status, which was directly related to the difference in fracture risk between patient groups. Sensitivity analyses confirmed the impact of fracture

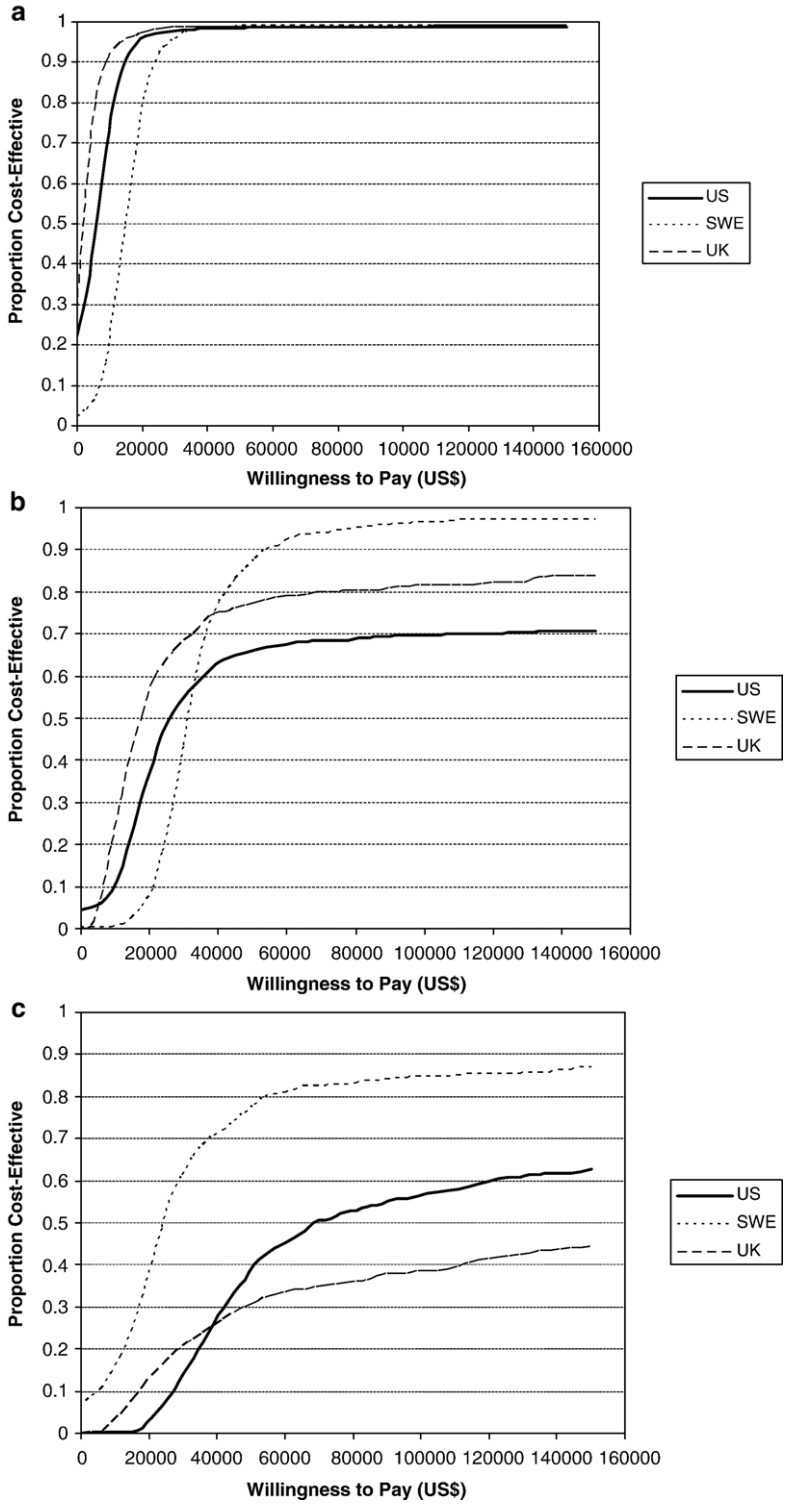

Fig. 4. Acceptability curves for 60 year old osteoporotic (*T*-score = −2.5 SD) women. (a) Hysterectomised women with a previous fracture. (b) Hysterectomised women without a previous fracture. (c) Women with intact uterus and a previous fracture. Note: These figures illustrate the results from the probabilistic analyses. The results represent the proportion of ICERs that fall below different values of willingness to pay (WTP). The WTP sets the threshold value for when an intervention is deemed cost-effective. The results illustrated in panel a have, for example, a higher probability of falling below smaller values of WTP than the results in panel c.

risks on the results. By setting the HT effect on fractures to zero, the ICER for HT treatment became very high or even dominated by no treatment. The same pattern was found when the offset time for fractures was reduced to 3 years in one analysis and set to zero in another analysis (Tables 4 and 5). The impact of the other disorders included in the model was not as significant. In a separate analysis, the health effects (QALY) of fractures versus the other disorders were assessed (Fig. 2). For all but two patient groups, the QALY effects were positive when only including treatment effects on fractures whereas the QALY effects were negative when excluding the fractures. For example, in the US population of women with intact uterus and a previous vertebral fracture (Fig. 2), there was a QALY gain of 0.08 when only including the treatment effect on fractures, but a QALY loss of 0.055 when including the effects on all disorders except fractures. The net effect for this group of women was hence positive. For all groups of women, the QALY gains outweighed the QALY losses, except for women with intact uterus and no previous fracture, where the opposite prevailed.

Some of the results from the WHI trial were of borderline significance or not significant. In a sensitivity analysis, the treatment effects, which were not significant, were therefore set to zero (only relevant for unopposed oestrogen). The results indicated that, when these effects were excluded, the ICER increased, especially in the absence of a previous vertebral fracture, even though it was balanced by competing risks of the different disease events (Table 5).

The *T*-score also had a significant effect on the cost effectiveness of HT (Tables 4 and 5). This finding was consistent with the results from the threshold analysis of the relative risks (RR) of fracture (Fig. 3), indicating a decreasing ICER with increasing RR for hysterectomised women. The same analysis was done on women with intact uterus, showing an increased incremental effect as RR increased. However, even at higher RR of fracture, the incremental effect was still negative, resulting in no actual change in the ICER (HT still dominated by no treatment).

Sensitivity analysis also showed that the duration of treatment with HT affected the results. A shorter duration (1 year) was cost-effective or even cost saving, whereas a longer treatment duration (5 years) affected the results in the opposite direction. These results were primarily driven by much higher incremental costs as the duration of treatment increased. The incremental effect also changed with duration of treatment, but the differences were too small to balance the increasing costs. Other variables, such as the treatment effect on other events than fractures, were also varied in sensitivity analyses but were found to only marginally impact the results and the data are therefore not shown.

The estimated acceptability curves showed that a high proportion of the ICERs falls below commonly used threshold values in hysterectomised women (Figs. 4a and b), particularly for those women who also have had a previous fracture. At a willingness to pay $75,000 and at the age of 60 years, treatment of women with a vertebral fracture with unopposed HT was cost-effective in 99% of simulations for all countries (Fig. 4a). For women with an intact uterus, the corresponding figures for the US, UK and Sweden were 52, 35, and 83%, respectively (Fig. 4c). For women with an intact uterus and no previous fracture, even at a WTP of $150,000, the proportion of cost-effective ICERs was still close to zero (data not shown).

Discussion

Previous studies have demonstrated the necessity of modelling when evaluating the long-term cost effectiveness of HT [42–44]. The results of previous assessments almost invariably indicate that HT is cost-effective for the treatment of menopausal symptoms [11,44]. However, the aim of the present study was to determine whether it was also cost-effective to treat postmenopausal women with an increased risk of fracture and without menopausal symptoms. The analysis was undertaken for a female population in Sweden, UK and the US, based on a societal perspective.

In the countries modelled there were, as expected, differences in ICERs, but several findings were invariant between countries. It was not cost-effective to treat asymptomatic women with an intact uterus and a fracture risk equal to that of the general population. Indeed, the risk outweighed any potential benefits. In contrast, it was on average cost-effective to treat women at high risk of fracture and very cost-effective in all women with menopausal symptoms irrespective of baseline risk of fracture.

However, the ICER varied between different groups of patients dependent on age, hysterectomy, previous fracture and country. The base case results indicated that HT was potentially cost-effective in patients with an increased risk of fracture, this was more evident in hysterectomised women than in women with an intact uterus, especially in women with a prior vertebral fracture. These findings were robust to sensitivity analysis. The benefits also outweighed the risks in all groups of women except those with an intact uterus and no previous fracture. In women with an intact uterus and with a prior vertebral fracture, the difference in effect between HT and no treatment was minor (close to zero), which made the ICER very sensitive to small changes in the incremental effect. This was confirmed in the probabilistic sensitivity analyses, which gave large spreads in the ICERs.

The implication of the base case results was that, if HT were considered for the management of patients with osteoporosis, then it is important to determine at what risk of fracture HT becomes cost-effective. The threshold analysis on different relative risks (RR) of fractures (Fig. 3) indicated that the use of HT for hysterectomised women even with normal fracture risks (RR = 1) was cost-effective and that there was a decreasing trend in the ICER as the relative risk of fracture increased. The trend was not as obvious for women with intact uterus where HT was dominated by no treatment. The results from sensitivity analyses also indicated that for women with a higher *T*-score, it was potentially more cost-effective to use HT. Additionally, when the offset time for fractures was set to zero, HT became less cost-effective or even dominated by no treatment. Nevertheless, evidence suggests [16] that there is a finite offset time for fractures after stopping HT treatment, which, even with a shorter offset time, makes the results favourable for HT.

Several studies have indicated that menopausal symptoms decrease quality of life [40] and that the potential gain in quality of life of using HT is significant. It has also been noted that women with severe menopausal symptoms have a higher risk of fracture than asymptomatic women [45,46]. The implication of this is that osteoporotic women with symptoms should be treated with HT. However, since it is already established that it is cost-effective to treat symptomatic women with HT [11,44], it does not matter if they are osteoporotic or not. If women are both symptomatic and osteoporotic, the use of HT is very cost-effective or even cost saving for all patient groups, as shown in sensitivity analyses.

The base case results varied across the investigated countries, which could partially be explained by differences in costs included in the model. However, changing different cost items presented in this report in the analysis did not significantly change the results. Any initial screening to identify the patients was not included in the model and the cost per QALY may therefore not fully reflect clinical practice. The impact of the omitted costs is uncertain because of the unknown trade-off between the increased costs from the screening and the increased fracture risk when assessing all osteoporotic women (not just at a *T*-score = −2.5 as in this assessment). However, the current results are valid in a situation where an osteoporotic patient has already been identified since the costs for regular per patient BMD examinations were included.

There were differences in risks and mortality rates between the countries, which also affected the results. For example, the risk of hip fracture and CHD was higher in Sweden, the latter specifically in older ages. For UK and US, the method of estimating the risks of CHD resulted in a function where the risk increased up to the age of 70 and thereafter decreased, whereas the Swedish risks increased continuously with age. The data entered into the model hence imposed certain problems for comparability. Nevertheless, since all health effects in the results were close to zero, the difference between the countries cannot be considered significant.

The model used in this study was based on a previous model that has been well validated [11,12]. Nevertheless, some of the data used in the model are based on assumptions. There is, in particular, a lack of empirically based long-term quality of life estimates related to non-skeletal disease events. For this reason, we used conservative assumptions for quality of life reductions. It was also assumed that the results of the WHI were transferable to other countries and patients, i.e. to Sweden, UK and osteoporotic women, even though the WHI trials were based on a healthy US population. It is therefore unsure whether the WHI effects of HT hold for women at an increased risk of fracture. To what extent the assumptions made holds true and whether the benefits on the skeletal system in individuals at high risk outweigh adverse effects requires reexamination. Nevertheless, in this present study, we used the data from the WHI with a fracture risk adjustment [20,21] to account for the increased risk for osteoporotic women.

The sensitivity analyses showed that the effect of HT on fractures had a significant effect on the cost effectiveness results. In a separate analysis it was evident that the positive impact on QALYs due to HT use (by decreasing fracture risks) in most cases outweighed the negative impact on QALYs through increased risks of adverse events. This contrasts with the conclusions from the WHI trial where the negative effects outweighed the positive. This indicates that the effects of morbidity and the inclusion of vertebral and wrist fractures in the evaluation of HT have a significant impact, especially in women at increased risk of fracture. The Global Index used in the WHI trial did not include this information and it is questionable, therefore, whether it provides enough information to adequately evaluate the complete outcome profile of HT.

There are also three major limitations in the data on treatment effects, which impose constraints on the applicability of the results. First, the treatment effects taken from the WHI trial were not corrected for previous HT use. The only exception was for breast cancer with combination therapy (used in sensitivity analysis, data not shown). The adjusted data for breast cancer [47] indicated that the negative effects of HT use increased if the patient had previously taken HT. It would therefore be of interest to have adjusted effects for all the outcomes included in the model. The effects of HT can also be highly time-dependent as shown in a recent report from the WMS, where a significantly increased risk of ovarian cancer was found when HT treatment duration was longer than 5 years [48]. There are also indications in the WHI that adverse effects can be time and age dependent. For example, the results from the WHI indicated that women who initiated HT close to menopause had a reduced CHD risk compared to an increase for women further from menopause [49]. This makes analysis of short-term treatment in younger individuals highly relevant. It was, however, not possible to model this accurately in our analysis because of the instability of the relative risks reported or the absence of relevant analyses in both wings of the WHI. In sensitivity analyses, it was confirmed that duration of treatment with HT had impact on the results, if the effects reported in the WHI study are also valid for longer treatment duration. Since we do not know the magnitude or impact of previous HT use or the age and time dependent effects, it was difficult to draw any stable conclusions based on treatment duration.

Second, the specific composition of hormones used in WHI may have an impact on the effect of HT treatment and therefore also the results. The combination therapy used in the WHI trial consisted of conjugated equine oestrogen (CEE) 0.625 mg alone in hysterectomised women and medroxyprogesterone acetate 2.5 mg with CEE 0.625 mg in women with an intact uterus. However, these are not the most common doses or combination used for HT today in many countries [50]. It is therefore questionable whether the treatment effects of HT as presented in the WHI trial are applicable to current clinical practice.

Third, HT was not directly compared to another osteoporotic treatment, mainly because there are no direct head to head studies between HT and other treatment options, making assumptions about the relative effect quite arbitrary and uncertain. Nevertheless, based on the study results, HT could be considered as one of several cost-effective treatments compared to no treatment. In certain situations, for example at significantly increased risk of fracture and for a short treatment duration, HT could be considered relevant in clinical practice. Whether HT could be considered a first-line treatment of osteoporosis is

quite doubtful since bisphosphonates have shown a similar or higher fracture risk reduction but without the increased risk of adverse events.

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