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Original article

Cost-effectiveness of hormone replacement therapy for menopausal symptoms in the UK

Ingrid Lekander,* Fredrik Borgström,* Oskar Ström,* Niklas Zethraeus† and John A Kanis‡

*i3 Innovus, Stockholm, Sweden; †Stockholm School of Economics, Stockholm, Sweden; ‡WHO Collaborating Centre for Metabolic Bone Diseases, University of Sheffield Medical School, Sheffield, UK

Correspondence: Ingrid Lekander, i3 Innovus, Klarabergsviadukten 90 Hus D, SE-111 64 Stockholm, Sweden. Email: ingrid.lekander@i3innovus.com

Abstract

Objective. To estimate the cost-effectiveness of five-year treatment of hormone replacement therapy (HRT) compared with no treatment for women with menopausal symptoms in the UK.

Method. A Markov cohort simulation model with tunnel techniques was used to assess the cost-effectiveness of HRT in women aged 50 years. For the clinical effects of HRT we used, where possible, results taken from the Women's Health Initiative (WHI). The model had a life-time horizon with cycle lengths of one year and contained 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 stopping treatment. The model was populated with UK-specific data on risks, mortality rates, quality-of-life weights and costs. The main outcome of the model was cost per quality-adjusted life year (QALY) gained of HRT compared with no treatment.

Results. The results indicated that it was cost-effective to treat women with menopausal symptoms with HRT in the UK. The severity of menopausal symptoms was the single most important determinant of cost-effectiveness, but HRT remained cost-effective even where symptoms were mild or effects on symptom relief were small.

Conclusions. Treatment of women with menopausal symptoms with HRT is cost-effective.

Keywords: Menopausal symptoms, HRT, Women's Health Initiative, WHI, Markov model

Introduction

Women in the industrialized world are today living more than one-third of their life after menopause. At menopause, which occurs on average at the age of 51 years, approximately 75% of women experience menopausal symptoms such as sleep disturbance, hot flushes, night sweats and atrophy-related symptoms of the urogenital tract.[1] Menopausal symptoms may persist for many years with a substantial impact on the quality of life.[2,3] The use of hormone replacement therapy (HRT) can mitigate or eliminate menopausal symptoms and thereby significantly improve the quality of life for menopausal women with symptoms.[2,3]

Concerns over the safety of HRT have, however, grown with the publication of several influential studies. The Heart and Estrogen/progestin Replacement Study showed a short-term increase in cardiovascular risk in women selected for being at high risk of cardiovascular disease[4] and the Million Women Study reported a significant association of the use of HRT with breast cancer.[5] Consistent with these findings, the Women's Health Initiative (WHI)[6,7] found an increased risk of coronary heart disease (CHD) and breast cancer for women given combined (estrogen plus progestin) HRT. Recent statements from the International Menopause Society declared, however, that properly timed HRT is safe for healthy women in their early postmenopause.[8] This statement was based on more recent WHI publications, including one which indicated that HRT was not associated with an increased cardiovascular risk if initiated in younger women (50–59) close to menopause.[9] If the risks of HRT are less than previously perceived for this patient population, it may hence be beneficial to treat younger women with HRT. In particular, it is possible that HRT is a cost-effective strategy for younger women with

menopausal symptoms. Zethraeus *et al.*[10] showed that the value of the positive effects for Swedish women with menopausal symptoms in terms of symptom relief clearly outweighed the negative effects of HRT. In the light of the findings of the WHI, the aim of the present study is to evaluate the cost-effectiveness of HRT in women with menopausal symptoms in a UK setting. A comparison is also made to the results from a recent US assessment[11] of the same basic model as used in this study as well as previously published Swedish results.[10]

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 aimed to improve efficiency. CEA is based on maximizing 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 quality-adjusted life years (QALYs). The incremental cost-effectiveness ratio (ICER) can then be calculated, defined as the cost per gained unit of effectiveness, i.e. cost per QALY gained. A commonly used threshold for cost-effectiveness is £30,000/QALY gained.[12] Thus an intervention with an ICER of less than £30,000 was considered to be cost-effective.

In this study, the cost-effectiveness of HRT was compared with no treatment in menopausal women in the UK. The CEA was based on the adjudicated clinical findings as reported by the WHI.[6,9,13–19] The analysis was made from the perspective of the National Health Service, only including direct costs. The evaluation was carried out on two independent patient groups (50 years of age) dependent on uterine status (intact uterus or hysterectomized). Women with an intact uterus were assigned to combined therapy, whereas hysterectomized women were assigned to estrogen alone. The age at which treatment was started was varied in sensitivity analysis.

Model

The cost-effectiveness model has previously been used to evaluate HRT in a US setting, and it has been extensively explained elsewhere.[10,11,20] The model was a Markov cohort simulation model that used tunnel techniques (TreeAge Pro 2005 user manual) to implement a memory of one previous event into the Markov cohort structure. For the current assessment, the model was adapted to a UK setting by populating it with UK-specific data. In the model, the patients were allowed to incur any disease event, stay in the same disease state or die in each cycle. The Markov model included the following disease events: stroke, venous thromboembolic event (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, angina and coronary insufficiency. The WHI trial defined CHD as death from CHD and non-fatal myocardial infarction (MI) (acute and silent MI), and was assumed to be valid for the three disease states used 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. The main output from the model was costs and QALYs, from which the ICER of different treatment alternatives was computed; in this case, HRT compared with no treatment. Some of the diseases had related costs and effects that lasted longer than one year.

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 to the model. For example, a remaining effect on fracture risk after stopping treatment was modelled as a linear decline in the effect for a given offset time.

Data

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

The effect of HRT

The effects of HRT on disease risks during therapy were taken from the WHI study[6,9,13–19] and the treatment duration was set to five years in the base case. Although some point estimates were of borderline significance or no significance, these estimates were used in the model to obtain a conservative scenario for the base case (Table 1). The non-significant effects, however, were set to zero in a sensitivity analysis. The original WHI publications were used for base case for a more conservative scenario of the effects of HRT.

A five-year offset time for fractures was assumed, consistent with recent analyses of osteoporotic treatments.[10,21] No other remaining effects were assumed on other disease outcomes[5,10] in the base case. However, a

Table 1 Relative risks (RR) of disease events and 95% confidence intervals (95% CI) based on adjudicated WHI data

Event	Estrogen		Estrogen plus progestin	
	RR	95% CI	RR	95% CI
Hip	0.65[18]	0.45–0.94	0.67[13]	0.47–0.96
Vertebral	0.64[18]	0.44–0.93	0.65[13]	0.46–0.92
Wrist	0.58[18]	0.47–0.72	0.71[13]	0.59–0.85
Breast cancer	0.80[19]	0.62–1.04	1.24[14]	1.01–1.54
Colorectal cancer	1.08[6]	0.75–1.55	0.61[15]	0.42–0.87
Stroke	1.33[9]	1.05–1.68	1.31[9]	1.03–1.68
CHD	0.95[9]	0.78–1.16	1.23[9]	0.99–1.53
VTE	1.32[16]	0.99–1.75	2.06[17]	1.57–2.70

CHD, coronary heart disease; VTE, venous thromboembolic event; WHI, Women's Health Initiative

recent WHI publication[22] indicated that there may be a remaining effect on cancers three years after stopping treatment of estrogen plus progestin. This effect was not significant when specified by cancer type. For breast cancer, the effect remained at the same level after three years as within trial (although not significant), whereas for colorectal cancer the effect had passed unity after three years. The results of the three-year WHI follow-up also indicated that there may be a fairly rapid offset time of the effect on other diseases. Therefore, two additional sensitivity analyses were conducted for women with an intact uterus. One where a three-year remaining effect on breast cancer was assumed (constant effect) while there was no offset time of other disease events, and one with a remaining effect on breast cancer while the other disease events in the model had a three-year offset time (declining effect).

Disease risks and mortality rates

The risks and mortality of disease event were derived from inpatient registers and published literature (listed in Table 2).[23–35]

Table 2 Sources of input data

Item	Value	Source
Disease risks (*per 1000*)		
Hip fracture	0.37–55.94	Singer *et al.*[23]
Vertebral fracture	0.95–20.93	Kanis *et al.*[24]
Wrist fracture	2.08–10.01	Singer *et al.*[23]
Breast cancer	2.36–4.2	Office for National Statistics[25]
Colorectal cancer	0.15–2.33	Office for National Statistics[25]
Stroke	0.54–15.08	Rothwell *et al.*[26]
AMI	0.17–2.36	Kannel *et al.*[27], Wilson *et al.*[28], Office for National Statistics[29], Sproston and Primatesta[30]
Angina	0.17–3.78	Kannel *et al.*[27], Wilson *et al.*[28], Office for National Statistics[29], Sproston and Primatesta[30]
Coronary insufficiency	0.042–0.66	Kannel *et al.*[27], Wilson *et al.*[28], Office for National Statistics[29], Sproston and Primatesta[30]
VTE	0.83–8.49	Silverstein *et al.*[31]
Mortality (*per 1000*)		
Adjusted normal	2.11–298.64	National statistics[32]
Hip fracture	13.16–480.95*	Odén *et al.*[33]
Vertebral fracture	14.57–413.67	Johnell *et al.*[34]
Breast cancer	89.42–438.44*	Inpatient and death register[35]
Colorectal cancer	93.98–756.10*	Inpatient and death register[35]
Stroke	123.82–833.4*	Inpatient and death register[35]
AMI	102–1000	Kannel *et al.*[27]
Angina	8.52–489.86	Kannel *et al.*[27]
Coronary insufficiency	11.4–527.7	Kannel *et al.*[27]
VTE	136.1–840.7*	Inpatient and death register[35]
Direct costs (*values for first year, £ 2006*)		
Hip fracture	5,157–12,978	van Staa *et al.*[52]
Vertebral fracture	477–581	van Staa *et al.*[52]
Wrist fracture	359–585	van Staa *et al.*[52]
Breast cancer	10,505	Hutton *et al.*[53]
Colorectal cancer	13,001	Ross *et al.*[54]
Stroke	7,262	Youman *et al.*[55]
AMI	4,332	Palmer *et al.*[56], NICE[57]
Angina	4,195	Daly *et al.*[58]
Coronary insufficiency	4,195	Daly *et al.*[58]
VTE	1,024–1,481	National Schedule of Reference Costs
Quality of life†		
General population	0.69–0.82	Kind *et al.*[42]
Hip fracture	0.8	Borgström *et al.*[43], Ström *et al.*[44], Jonsson *et al.*[45]
Vertebral fracture	0.65	Borgström *et al.*[43], Ström *et al.*[44], Jonsson *et al.*[45]
Wrist fracture	0.93	Borgström *et al.*[43], Ström *et al.*[44], Jonsson *et al.*[45]
Breast cancer	0.8	Lidgren *et al.*[46]
Colorectal cancer	0.9	N/A
Stroke	0.74	Tengs and Lin[47], Jorgensen *et al.*[48]
CHD	0.73	van Stel and Buskens[49], Hoeymans *et al.*[50]
VTE	0.9	N/A

*Values imputed from Swedish data, the source are for the Swedish data
†Data represent multipliers for each disease event for the first year after an event. For the general population the data represent actual utilities
N/A, not available (see text for assumptions made); AMI, acute myocardial infarction; CHD, coronary heart disease; VTE, venous thromboembolic event

It was assumed that the risk and mortality of a specific disease event was not affected by previously occurring events.

Mortality rates of the general population were adjusted to exclude the risk of dying from disease events already included in the model.[10,20] This was calculated as normal mortality multiplied by the share of all causes of death that were not explained by CHD, stroke, breast cancer or colorectal cancer.[32] However, the excess mortality after a vertebral or hip fracture cannot be entirely ascribed to the fracture event itself because of the high frequency of coexisting morbidity.[36] Results from previous studies of patients with hip or vertebral fractures have estimated that 17–42%[36–38] of all deaths could 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 causally associated with the fracture event. Wrist fracture was assumed not to be associated with any excess mortality.[34,39]

Mortality rates were missing for some disease events in the UK (Table 2). For this reason, our estimates were imputed from Swedish mortality rates by taking the age differentiated relative risk (RR) of dying after an event (i.e. event mortality divided by the mortality of the general population) multiplied by the UK normal mortality rates.[32] Mortality rates based on inpatient and death registers were estimated using logistic regression[40] (first-year mortality rates) and Weibull survival regression (subsequent years).[41]

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 was extrapolated from the decreasing trend found in the mortality function. In some instances, when many years have passed, the estimated mortality could be lower than that of the general population, 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 EQ-5D instrument.[42–50] An exception was the quality-of-life estimates for stroke, which were derived from a meta-analysis using different methods of estimation.[47] The quality-of-life estimates were used to derive multipliers for each disease (Table 1). The multipliers were then applied to utility estimates of the general population for UK.[42] This assumed that the quality-of-life effects of a given disease event were the same irrespective of country.

There is, however, a lack of quality-of-life data, especially with regard to non-skeletal events and some assumptions had to be 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[10,20] have assumed a utility loss of 0.1 for these outcomes. To be consistent with the previously used methodology, multipliers were used instead of a fixed reduction.

The estimation of the gain in quality of life from menopausal symptom relief with HRT was based on an empirical study in Sweden,[3] where quality of life was measured with the time trade-off method. Depending on the severity of symptoms, the quality of life lost from menopausal symptoms ranged from 0.18–0.42. In the base case, the mean quality-of-life loss from the study, i.e. 0.29, was used. The impact of different levels of quality-of-life reduction was extensively investigated in sensitivity analyses.

Costs

Only direct costs were included in the model and all costs were expressed in Euro prices of 2006. Where appropriate, the costs were inflated using national inflation rates. In the base case, a 3% discount rate was used for both costs and effects.

The annual intervention cost for women on combination therapy (with intact uterus) was estimated at £125 (1 mg estradiol and 0.5 mg norethisterone). This included drug costs and 1.5 general practitioner (GP) consultations.[51] The corresponding annual intervention cost for women on estrogen only therapy was estimated at £64 (1 mg estradiol), including drug costs and 1 GP consultation.[51]

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 may persist several years or even for the remaining lifetime of the patient. The range for the first-year costs and the sources for all cost estimates are listed in Table 2.[52–58] However, some calculations and assumptions are given below.

It was 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[10] and the US.[11] The long-term hip fracture 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.[59]

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

Results

A five-year treatment with HRT compared with no treatment was, at a life-time follow-up, associated with a loss in life years for women with an intact uterus in the UK. The decrease in life years was 0.06 (0.12 undiscounted) that corresponds to approximately 22 days. For hysterectomized women, on the other hand, there was a gain in life years of 0.01 (0.03 undiscounted), equivalent to 3.5

days of extra life. In all women, the results indicated a gain in QALYs due to HRT use of approximately 1.17 (1.21 undiscounted) for women with an intact uterus and 1.23 (1.33 undiscounted) for hysterectomized women.

The incremental costs were £677 for women with an intact uterus and £252 for hysterectomized, producing ICERs of £580 and £205 for the two patient groups, respectively. These values fall well below commonly used thresholds for cost-effectiveness in the UK[12] and therefore, these results indicate that it is very cost-effective to treat women with menopausal symptoms with HRT.

Sensitivity analysis indicated that the results were stable to changes in almost all input parameters, although small variations in the ICER were noted (Table 3). The exception was the disutility associated with menopausal symptoms. The effect of this disutility was demonstrated when it was set to zero, indicating that most of the gains of HRT were attained by symptom relief. A threshold analysis was therefore conducted to investigate what was the minimum increase in quality of life required for HRT to become a cost-effective alternative. Assuming a limit for cost-effectiveness of £30,000, the threshold for quality-of-life gain for women with intact uterus was 0.017, whereas for hysterectomized women, it was zero, i.e. it was cost-effective without any symptom alleviation (Figure 1).

Table 3 Cost (£) per quality-adjusted life years gained for 50-year old women in the UK

	Intact uterus	Hysterectomized
Base case	580	205
Sensitivity analysis		
Start age 55	600	207
Start age 60	591	202
No menopausal symptoms	HRT dominated*	16,680
Mild menopausal symptoms (0.18)	959	328
Severe menopausal symptoms (0.42)	395	142
Intervention cost ×1.5	827	325
No discounting	600	199
Discount rates 3% costs, 0% effects	561	190
Discount rates 5%	568	208
Treatment duration three years	617	215
No set time fractures	589	213
10 years set time fractures	572	198
Three-year remaining effect BC, no set time fractures†	615	NA
Three-year remaining effect BC, Three year set time other diseases†	648	NA
No effect of HRT on:		
CHD	525	216
Stroke	552	179
VTE	574	205
Colorectal cancer	586	204
Breast cancer	532	239
Fractures	603	225
BC, CC, CHD, VTE‡	NA	249

*'HRT dominated' means that HRT is associated with a higher cost and lower effects compared with no treatment, i.e. no treatment is the preferred alternative
†These effects have only been shown in women with intact uterus and the sensitivity analysis was therefore only performed on this group of women
‡The effects were not significant and in sensitivity analysis the treatment effect was set to zero
CHD, coronary heart disease; VTE, venous thromboembolic event; HRT, hormone replacement therapy; BC, breast cancer; CC, colorectal cancer

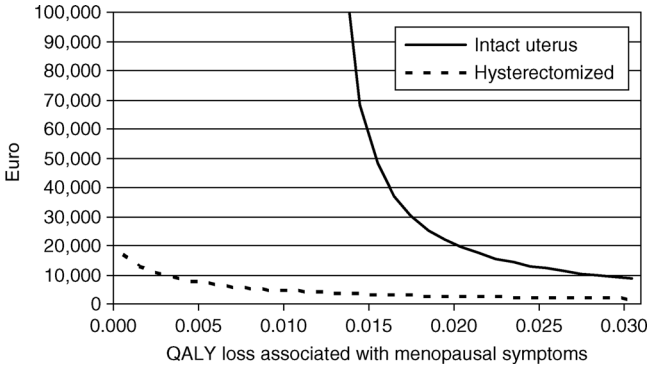

Figure 1 Incremental cost-effectiveness ratios at different levels of quality-adjusted life year (QALY) loss associated with menopausal symptoms

Discussion

The principal results of the present study indicate that it is cost-effective to treat women with menopausal symptoms with HRT in the UK. The cost per QALY gained was estimated at £580 and £205 dependent on uterine status, which is far below common willingness to pay thresholds. The results clearly indicate that the positive effects, mainly through symptom relief, outweighed the negative effects of HRT. Given that HRT increased the utility of a symptomatic menopausal woman by at least 0.017, HRT became cost-effective irrespective of uterine status. This threshold level was far below the mean gain in quality of life from HRT use, which has been estimated at 0.29. This indicates a large potential gain from HRT use for symptomatic women.

The model used in this present study was a previously validated model for the US[11] adapted to a UK setting. The modelled QALYs gained in the UK setting were in line with the results produced by the US model (Table 4).

Table 4 Comparison of UK, US and Swedish results (£ 2006)

	Incremental cost	QALYs gained	Cost/QALYs gained
Intact uterus			
UK	677	1.17	580
US	1,769	1.15	1,538
Sweden	1,123	1.19	944
Hysterectomized			
UK	252	1.23	205
US	282	1.21	233
Sweden	745	1.22	610

The analysis for Sweden included indirect costs and cost in added life years, both which are excluded in the other two countries
QALY, quality-adjusted life year

The costs differed somewhat, especially for women with an intact uterus where the US costs are almost three times the UK costs. As shown in sensitivity analyses (Table 3), the cost of intervention has an effect on the results which explains part of this difference between the countries. The difference can also be explained by smaller differences in the cost of care of different disease events. The QALYs gained in the UK model were also in line with previously published results for Sweden[10] (Table 4). The Swedish incremental costs were also higher than the UK costs, but some of this difference can be explained by the inclusion of indirect costs and cost in added life years in the Swedish estimates and a different modelling technique. Still, the ICERs remain below commonly used thresholds for cost-effectiveness for all three countries and uterine status.

Some of the data used in the model were based on assumptions that introduce uncertainty to the results. In particular, empirically based quality-of-life estimates for non-skeletal disease events were incomplete and there were disparities between the quality and amount of available data across the countries included in this analysis. There is also a discrepancy in literature of the remaining effect after stopping HRT. Previous publications[60,61] have indicated a long-offset time on fractures by HRT. On the other hand, a recent publication from WHI[22] indicated that there is possibly a declining effect (offset time) for many of the diseases in the current model, including fractures, within three years after stopping treatment. The WHI follow-up also indicated that there is a constant remaining effect on breast cancer for combined HRT. The results from the WHI were not significant, and there is hence a need for further investigation of the remaining effects after stopping HRT. However, sensitivity analyses around remaining effects indicated that it did not have major effect on the results.

There are also uncertainties about the applicability of the WHI data. First, it is not known whether the results from the WHI trial are valid for other populations, i.e. women outside the US and women who experience menopausal symptoms. Second, the WHI data were not adjusted for previous HRT use, which could have had a significant impact on the RR of disease events. For example, results from a subgroup assessment of the WHI showed that the risk of breast cancer for women on combination therapy increased for women who previously had used HRT (RR = 1.26) compared with those who had not previously used HRT (RR = 1.09).[14] Since this was the only data available that were adjusted for previous use, it was not included in the analysis. Notwithstanding, the treatment effects from the WHI trials are the best available today and for this reason were used for this analysis. Extensive sensitivity analysis was conducted where possible to investigate the impact of these shortcomings. The results indicated that our conclusions were stable to variations in input variables and that HRT was highly cost-effective for treatment of menopausal symptoms in the UK.

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Competing interest: All authors have conducted consultancy work for Wyeth. All authors have conducted health economic analyses in the field of HRT for Wyeth and health economic consultancy work in other therapeutic areas for Wyeth and many other pharmaceutical companies.

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References

1 SBU. *Behandling med östrogen – En evidensbaserad kunskapssammanställning*. Stockholm: Statens beredning för medicinsk utvärdering (SBU), 2002
2 Daly E, Gray A, Barlow D, McPherson K, Roche M, Vessey M. Measuring the impact of menopausal symptoms on quality of life. *Br Med J* 1993;**307**:836–40
3 Zethraeus N, Johannesson M, Henriksson P, Strand RT. The impact of hormone replacement therapy on quality of life and willingness to pay. *Br J Obstet Gynaecol* 1997;**104**:1191–5
4 Hulley S, Grady D, Bush T, *et al*. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. *JAMA* 1998;**280**:605–13
5 Beral V. Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet* 2003;**362**:419–27
6 Anderson GL, Limacher M, Assaf AR, *et al*. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 2004;**291**:1701–12
7 Rossouw JE, Anderson GL, Prentice RL, *et al*. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;**288**:321–33
8 International Menopause Society (IMS). HRT in early menopause: scientific evidence and common perceptions. www.imsocietyorg/pdf_files/comments_and_press_statements/ims_press_statement_13_05_08.pdf. (Downloaded 15 October 2008)
9 Rossouw JE, Prentice RL, Manson JE, *et al*. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA* 2007;**297**:1465–77
10 Zethraeus N, Borgstrom F, Jonsson B, Kanis J. Reassessment of the cost-effectiveness of hormone replacement therapy in Sweden: results based on the Women's Health Initiative randomized controlled trial. *Int J Technol Assess Health Care* 2005;**21**:433–41
11 Lekander I, Borgstrom F, Strom O, Zethraeus N, Kanis J. Cost-effectiveness of hormone therapy for menopausal symptoms in a US setting. *J Womens Health* (submitted 2008)
12 NICE. *The Guidelines Manual*. London: National Institute for Health and Clinical Excellence, 2007
13 Cauley JA, Robbins J, Chen Z, *et al*. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. *JAMA* 2003;**290**:1729–38
14 Chlebowski RT, Hendrix SL, Langer RD, *et al*. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. *JAMA* 2003;**289**:3243–53
15 Chlebowski RT, Wactawski-Wende J, Ritenbaugh C, *et al*. Estrogen plus progestin and colorectal cancer in postmenopausal women. *N Engl J Med* 2004;**350**:991–1004
16 Curb JD, Prentice RL, Bray PF, *et al*. Venous thrombosis and conjugated equine estrogen in women without a uterus. *Arch Intern Med* 2006;**166**:772–80
17 Cushman M, Kuller LH, Prentice R, *et al*. Estrogen plus progestin and risk of venous thrombosis. *JAMA* 2004;**292**:1573–80
18 Jackson RD, Wactawski-Wende J, LaCroix AZ, *et al*. Effects of conjugated equine estrogen on risk of fractures and BMD in postmenopausal women with hysterectomy: results from the women's health initiative randomized trial. *J Bone Miner Res* 2006;**21**:817–28
19 Stefanick ML, Anderson GL, Margolis KL, *et al*. Effects of conjugated equine estrogens on breast cancer and mammography screening in postmenopausal women with hysterectomy. *JAMA* 2006;**295**:1647–57
20 Zethraeus N, Borgström F, Jönsson B, Kanis J. *A Reassessment of the Cost-effectiveness of Hormone Replacement Therapy in Sweden – Results Based on the Women's Health Initiative Randomised Controlled*

Trial. Working Paper Series in Economics and Finance at the Stockholm School of Economics, 2004 (Working paper No. 571) http://swopec.hhs.se/hastef/papers/hastef0571.pdf/
21 Borgstrom F, Johnell O, Jonsson B, Zethraeus N, Sen SS. Cost effectiveness of alendronate for the treatment of male osteoporosis in Sweden. *Bone* 2004;**34**:1064–71
22 Heiss G, Wallace R, Anderson GL, *et al*. Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin. *JAMA* 2008;**299**:1036–45
23 Singer BR, McLauchlan GJ, Robinson CM, Christie J. Epidemiology of fractures in 15,000 adults: the influence of age and gender. *J Bone Joint Surg Br* 1998;**80**:243–8
24 Kanis JA, Johnell O, Oden A, *et al*. Long-term risk of osteoporotic fracture in Malmo. *Osteoporos Int* 2000;**11**:669–74
25 Cancer Statistics Registrations. *Registrations of cancer diagnosed in 1998, England*. London: Office for National Statistics, 2002 (Report No.: Series MB1 no29)
26 Rothwell PM, Coull AJ, Giles MF, *et al*. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). *Lancet* 2004;**363**:1925–33
27 Kannel W, Wolf P, Garrison R. *The Framingham Study: An Epidemiological Investigation of Cardivascular Disease*. Springfield: US Department of Commerce National Technical Information Service, 1987
28 Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation* 1998;**97**:1837–47
29 General Household survey, Office for National Statistics 'Focus on Health Data'. http://www.statistics.gov.uk/statbase/Product.asp?vlnk=12985 (6 December 2006)
30 Whitfield MD, Gillett M, Holmes M, Ogden E. Predicting the impact of population level risk reduction in cardiovascular disease and stroke an acute hospital admission rates over a 5-year period: a pilot study. *Public Health* 2006;**120**:1140–8
31 Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton III LJ. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. *Arch Intern Med* 1998;**158**:585–93
32 National Statistics Online. www.statistics.gov.uk (cited 12 December 2006)
33 Oden A, Dawson A, Dere W, Johnell O, Jonsson B, Kanis JA. Lifetime risk of hip fractures is underestimated. *Osteoporos Int* 1998;**8**:599–603
34 Johnell O, Kanis JA, Oden A, *et al*. Mortality after osteoporotic fractures. *Osteoporos Int* 2004;**15**:38–42
35 Inpatient and death register 1998–2001, data on file. Centre for Epidemiology at the National Board of Health and Welfare, Sweden. www.socialstyrelsen.se
36 Parker MJ, Anand JK. What is the true mortality of hip fractures? *Public Health* 1991;**105**:443–6
37 Kanis JA, Oden A, Johnell O, De Laet C, Jonsson B, Oglesby AK. The components of excess mortality after hip fracture. *Bone* 2003;**32**:468–73
38 Kanis JA, Oden A, Johnell O, De Laet C, Jonsson B. Excess mortality after hospitalisation for vertebral fracture. *Osteoporos Int* 2004;**15**:108–12
39 Center JR, Nguyen TV, Schneider D, Sambrook PN, Eisman JA. Mortality after all major types of osteoporotic fracture in men and women: an observational study. *Lancet* 1999;**353**:878–82
40 Gujarati DN. *Basic Econometrics*. Singapore: McGraw Hill, 1995.
41 Kiefer N. Economic duration data and hazard functions. *J Econ Lit* 1998;**26**:646–79
42 Kind P, Dolan P, Gudex C, Williams A. Variations in population health status: results from a United Kingdom national questionnaire survey. *Br Med J* 1998;**316**:736–41
43 Borgstrom F, Zethraeus N, Johnell O, *et al*. Costs and quality of life associated with osteoporosis-related fractures in Sweden. *Osteoporos Int* 2006;**17**:637–50
44 Strom O, Borgstrom F, Zethraeus N, *et al*. Long-term cost and effect on quality of life of osteoporosis-related fractures in Sweden. *Acta Orthop* 2007;**79**:269–80
45 Jonsson B, Christiansen C, Johnell O, Hedbrandt J, Karlsson G. Cost-effectiveness of fracture prevention in established osteoporosis. *Scand J Rheumatol Suppl* 1996;**103**:30–8
46 Lidgren M, Wilking N, Jonsson B, Rehnberg C. Health related quality of life in different states of breast cancer. *Qual Life Res* 2007;**16**:1073–81
47 Tengs TO, Lin TH. A meta-analysis of quality-of-life estimates for stroke. *Pharmacoeconomics* 2003;**21**:191–200
48 Jorgensen HS, Nakayama H, Raaschou HO, Vive-Larsen J, Stoier M, Olsen TS. Outcome and time course of recovery in stroke. Part II: Time course of recovery. The Copenhagen Stroke Study. *Arch Phys Med Rehabil* 1995;**76**:406–12
49 van Stel HF, Buskens E. Comparison of the SF-6D and the EQ-5D in patients with coronary heart disease. *Health Qual Life Outcomes* 2006;**4**:20
50 Hoeymans N, van Lindert H, Westert GP. The health status of the Dutch population as assessed by the EQ-6D. *Qual Life Res* 2005;**14**:655–63
51 SBU. *Behandling med östrogen*. Stockholm: Statens beredning för medicinsk utvärdering (SBU), 1996.
52 van Staa TP, Geusens P, Zhang B, Leufkens HG, Boonen A, Cooper C. Individual fracture risk and the cost-effectiveness of bisphosphonates in patients using oral glucocorticoids. *Rheumatology (Oxford)* 2007;**46**:460–6
53 Hutton J, Brown R, Borowitz M, Abrams K, Rothman M, Shakespeare A. A new decision model for cost-utility comparisons of chemotherapy in recurrent metastatic breast cancer. *Pharmacoeconomics* 1996;**9**(Suppl. 2):8–22
54 Ross P, Heron J, Cunningham D. Cost of treating advanced colorectal cancer: a retrospective comparison of treatment regimens. *Eur J Cancer* 1996;**32A**(Suppl. 5):S13–7
55 Youman P, Wilson K, Harraf F, Kalra L. The economic burden of stroke in the United Kingdom. *Pharmacoeconomics* 2003;**21**(Suppl. 1):43–50
56 Palmer S, Sculpher M, Philips Z, *et al*. Management of non-ST-elevation acute coronary syndromes: how cost-effective are glycoprotein IIb/IIIA antagonists in the UK National Health Service? *Int J Cardiol* 2005;**100**:229–40
57 NICE. *Hypertension. Management of Hypertension in Adults in Primary Care: Partial update* of NICE clinical guideline 18. NICE Clinical guideline 34. London: NICE, 2006
58 Daly E, Vessey MP, Barlow D, Gray A, McPherson K, Roche M. Hormone replacement therapy in a risk-benefit perspective. *Maturitas* 1996;**23**:247–59
59 Strom O, Borgstrom F, Sen SS, *et al*. Cost-effectiveness of alendronate in the treatment of postmenopausal women in 9 European countries – an economic evaluation based on the fracture intervention trial. *Osteoporos Int* 2007;**18**:1047–61
60 Bagger YZ, Tanko LB, Alexandersen P, *et al*. Two to three years of hormone replacement treatment in healthy women have long-term preventive effects on bone mass and osteoporotic fractures: the PERF study. *Bone* 2004;**34**:728–35
61 Kanis JA, Johnell O, Gullberg B, *et al*. Evidence for efficacy of drugs affecting bone metabolism in preventing hip fracture. *Br Med J* 1992;**305**:1124–8