Cost effectiveness of raloxifene in the treatment of osteoporosis in Sweden: an economic evaluation based on the MORE study

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The study examined the use of raloxifene (60 mg/day), a selective oestrogen receptor modulator, for the treatment of osteoporosis in postmenopausal women.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis and cost-utility analysis.

Study population
The study population comprised a cohort of postmenopausal women with osteoporosis. The characteristics of the study population were the same as those of the women included in the MORE study.

Setting
The setting was secondary care. The economic study was carried out in Sweden.

Dates to which data relate
The effectiveness data were derived from studies published from 1993 to 2004. The costs and resource use data were estimated from studies published between 1997 and 2004. The price year was 2001.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of completed studies and authors' assumptions.

Modelling
A published Markov model was used to simulate the clinical and economic outcomes associated with raloxifene treatment in a cohort of postmenopausal women. The model was slightly revised to include a health state for vertebral fracture patients in the second and following years after fracture. The model considered also the possibility of having breast cancer and CHD. Women moved across the various health states: vertebral fracture, hip fracture, wrist fracture, breast cancer, CHD, post-disease states (i.e. post-vertebral fracture, post-hip fracture, etc.) and dead. The cycle length was one year, and the time horizon of the model was lifetime. The model was validated using data from the MORE study.

Outcomes assessed in the review
The outcomes estimated from the literature were:
efficacy of treatment,
quality of life estimates,
the mortality rates,
the incidence of morphometric fractures,
the risk of (clinical) vertebral fractures in patients with or without prior vertebral fracture,
the risk of breast cancer, and
the risk of CHD.

A clinical vertebral fracture was defined as a fracture that comes to clinical attention. A morphometric fracture referred to both symptomatic and asymptomatic fractures and was defined as a significant change in vertebral shape.

Study designs and other criteria for inclusion in the review
It was unclear whether a systematic review of the literature was undertaken. The primary studies appear to have been identified selectively. Data on the efficacy of raloxifene in reducing vertebral fractures, breast cancer and CHD risk were taken from the MORE study. The MORE study was a multi-centre, randomised, double-blinded placebo-controlled trial involving 7,705 osteoporotic postmenopausal women. The incidence of morphometric and vertebral fractures, breast cancer and CHD were taken from Swedish sources. Quality of life data came from both Swedish sources and other studies. The age-specific mortality rates came from official statistics for Sweden. Limited information on the design and characteristics of the other studies was provided.

Sources searched to identify primary studies
Not stated.

Criteria used to ensure the validity of primary studies
Specific criteria to ensure the validity of the primary estimates were not reported. The validity of data obtained from the MORE study was enforced by the robust design of the clinical trial.

Methods used to judge relevance and validity, and for extracting data
Not stated.

Number of primary studies included
Approximately 19 primary studies provided clinical data.

Methods of combining primary studies
A narrative approach appears to have been used to combine the primary estimates.

Investigation of differences between primary studies
Not stated.

Results of the review
For patients without fractures taking the 60 mg/day dose, the reduction in risk of vertebral fractures (relative risk, RR) of raloxifene over placebo was 0.52 (95% confidence interval, CI: 0.35 - 0.78).
The RR for patients with prior vertebral fracture taking the 60 mg/day dose was 0.65 (95% CI: 0.52 - 0.81).

Raloxifene had no effect on the risk of nonvertebral fractures (RR 0.9, 95% CI: 0.8 - 1.1).

Raloxifene also reduced the risk of invasive breast cancer by 72% (95% CI: 54 - 83).

In the sub-group of patients at high risk of cardiovascular events, there was a 40% reduction in the risk of cardiovascular events (95% CI: 5 - 62).

For a patient having a clinical vertebral fracture, quality of life was 0.63 of that of healthy individuals of the same age the year after fracture. The population values for quality of life to which this multiplier was applied were 0.9 (for age 50 to 64 years), 0.79 (65 to 74 years), 0.63 (75 to 84 years) and 0.63 (> = 85 years).

Since 22.3% of all vertebral fractures came to clinical attention, the quality of life multiplier was 0.82 for the first year after a morphometric vertebral fracture and 0.97 for subsequent years.

The utility loss after CHD was 0.1 for all years after the disease event and for all ages. The utility loss associated with breast cancer was equal to the loss after CHD.

The RR of mortality was 2.5 for the year after clinical vertebral fractures, and 1.3 in subsequent years for all ages. These estimates were calculated on the hypothesis that only 30% of the observed excess mortality was causally related to the fracture itself. The RR of mortality was 1.5 the year after morphometric fractures, and 1 (no excess mortality) in subsequent years for all ages.

Patients without prior vertebral fractures had a 2-fold increase in risk (RR=2) of vertebral fracture compared with the average population risk, while patients with prior vertebral fractures had a 4-fold increase in vertebral fracture risk.

Other data were not reported.

**Methods used to derive estimates of effectiveness**

The authors made some assumptions that were used in the decision model.

**Estimates of effectiveness and key assumptions**

Patients were treated for 5 years, and it was assumed that the effect of raloxifene on vertebral fracture risk did not disappear immediately after stopping treatment, but declined linearly for 5 years after the intervention period. For breast cancer, no persistent effect after stopping treatment was assumed. Raloxifene was effective for CHD only during the treatment period. The loss of utility in the second and following years for a clinical vertebral fracture was 0.05, which gave a quality of life multiplier of 0.93. The utility loss of a sub-clinical fracture was one-third that of a clinically overt fracture.

**Measure of benefits used in the economic analysis**

The summary benefit measures were the life-years (LYs) gained and quality-adjusted life-years (QALYs) gained. These were estimated using a modelling approach over a lifetime time horizon. An annual rate of 3% was used to discount the long-term benefits. Details of the sources used for utility values and the method used to calculate QALYs were reported.

**Direct costs**

The main analysis was carried out from the health care perspective. It included all direct medical costs associated with osteoporosis (treatment of vertebral and morphometric fractures), CHD events (angina and myocardial infarction), breast cancer and raloxifene (drug and monitoring, including a physician visit and bone mineral density measurement). The costs associated with the added years of life were also taken into consideration. The costs of calcium and vitamin D supplements were not included because all patients, regardless of treatment, received such supplemental therapies. The
unit costs were not presented separately from the quantities of resources used. Both resource use and costs were estimated from published studies, thus the costs were presented as macro-categories. Some assumptions were also made. The drug costs came from official prices in Sweden. Discounting was relevant, as a lifetime time horizon was adopted in the model, and an annual rate of 3% was applied. The price year was 2001.

**Statistical analysis of costs**

The costs were treated deterministically in the base-case.

**Indirect Costs**

The indirect costs were included in the sensitivity analysis since a societal perspective was also adopted. Productivity losses for patients younger than 65 years of age were estimated from prior studies. No details of the approach used to derive such costs were provided.

**Currency**

Swedish kroner (SEK). These were converted into Euros (Euro) at the rate SEK 9.25 = Euro 1.

**Sensitivity analysis**

Several univariate sensitivity analyses were performed to examine the robustness of base-case results to variations in the model inputs. Such model inputs included the discount rate, breast cancer incidence, no effect of raloxifene after the treatment period, reduction in CHD risk, cost of vertebral fracture, and some mortality rates. The sensitivity analyses were described in detail and a justification for the choice of the alternative values was provided. In general, the alternative values and ranges were derived from the literature. Three sub-scenarios were considered. These corresponded to a societal perspective (with the inclusion of indirect costs and costs of added years of life), morphometric fractures (the morphometric definition was used), and prior vertebral fractures (with the higher risk of fracture).

**Estimated benefits used in the economic analysis**

In the base-case analysis, the estimated LYs gained with raloxifene over no treatment were 0.054 for 60-year-old women, 0.062 for 70-year-old women and 0.071 for 80-year-old women.

The estimated QALYs gained with raloxifene over no treatment were 0.061 for 60-year-old women, 0.067 for 70-year-old women and 0.065 for 80-year-old women.

**Cost results**

In the base-case analysis, the additional costs associated with raloxifene over no treatment were SEK 22,687 (Euro 2,453) for 60-year-old women, SEK 20,316 (Euro 2,196) for 70-year-old women and SEK 17,125 (Euro 1,851) for 80-year-old women.

**Synthesis of costs and benefits**

Incremental cost-effectiveness and cost-utility ratios were calculated to combine the costs and benefits of raloxifene over no treatment.

In the base-case analysis, the additional cost per LY gained with raloxifene over no treatment was SEK 420,130 (Euro 45,426) for 60-year-old women, SEK 327,677 (Euro 35,419) for 70-year-old women and SEK 241,197 (Euro 26,070) for 80-year-old women.

The additional cost per QALY gained with raloxifene over no treatment was SEK 371,918 (Euro 40,213) for 60-year-old women, SEK 303,224 (Euro 32,776) for 70-year-old women and SEK 263,462 (Euro 28,477) for 80-year-old women.
women.

The cost-effectiveness and cost-utility ratios were higher when the societal perspective was adopted, but similar estimates were obtained using the morphometric vertebral fracture definition. The improvements in cost-effectiveness derived from the higher incidence of morphometric fractures compared with clinical fractures were counterbalanced by the lower morbidity, mortality and costs of morphometric fractures.

The sensitivity analysis showed that the cost-effectiveness of raloxifene improved markedly with a 40% reduction in the risk of CHD among patients at high-risk of CHD. Variations in other model inputs led to slight changes in the base-case results.

Authors’ conclusions
Compared with no treatment, raloxifene was a cost-effective strategy for the treatment of postmenopausal women at increased risk of vertebral fracture in Sweden. Its cost-effectiveness ratio compared favourably with the thresholds commonly used in the literature.

CRD COMMENTARY - Selection of comparators
No intervention was selected as the comparator because the study intervention (i.e. raloxifene) was compared with placebo in the MORE study, which was the main source of clinical data for the current analysis. Other treatments available for postmenopausal women with osteoporosis were not included in the current study, as no head-to-head comparisons were available. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness data were estimated from published studies. It was not stated whether a systematic review of the literature had been undertaken to identify the primary studies, which appear to have been included selectively. The evidence on treatment efficacy came from the MORE study, which had a high internal validity due to the strong design (randomised, double-blinded and multi-centre) and the very large sample size. Data on mortality were derived from Swedish life tables, which represent a typical source of information for all-cause mortality. Limited information on the studies used to estimate other clinical inputs was provided. Further, the authors made some assumptions because of the lack of published evidence or the uncertainty in some data. The issue of variability in the data was addressed in the sensitivity analysis and in the sub-scenario analysis.

Validity of estimate of measure of benefit
The benefit measures used in the analysis were appropriate. QALYs capture the impact of the interventions on survival and quality of life, which are the most relevant dimensions of care for women with osteoporosis. Both survival and QALYs are comparable with the benefits of other health care interventions. Discounting was applied, as Swedish guidelines recommend, and the impact of alternative discount rates was assessed in the sensitivity analysis. Some information on the source of the utility weights and the approach used to calculate QALYs was provided.

Validity of estimate of costs
The perspective adopted in the study was explicitly stated, and the cost categories included in the analysis were consistent with such a perspective. The use of a broader perspective (i.e. society) was investigated in the sensitivity analysis. The cost analysis relied on cost estimates that had been published. Thus, no information on the unit costs and quantities of resources used was provided, with the exception of drug costs. In general, the costs were presented as macro-categories and a detailed breakdown of the cost items was not provided. This limits the possibility of replicating the analysis in other settings. The source of the data was reported for each group of costs. No statistical analyses of the costs were performed. However, some key cost estimates were varied in the sensitivity analysis. The price year was reported, which aids reflation exercises in other time periods.
Other issues
The authors stated that their study was the first economic evaluation of treatments for osteoporosis that had used a morphometric vertebral fracture definition. No comparisons with the results from other studies were made. In terms of the issue of the generalisability of the study results to other settings, the authors noted that caution is required when extrapolating the current findings to other contexts, but the results should hold in countries with similar epidemiological patterns, such as those in Scandinavia. The authors noted that patients in the MORE study, from which clinical parameters were extracted, received calcium and vitamin D supplements. This is not part of routine treatment patterns in Sweden. The authors pointed out that this "leads to a variance between the clinical trial population and patients in clinical practice". It was also stressed that a potential limitation of the analysis was the fact that side effects of raloxifene, such as venous thromboembolic events, were not modelled. However, the frequency of venous thromboembolic events was low, thus the impact on cost-effectiveness estimates was likely to have been negligible.

Implications of the study
The study results would appear to support the use of raloxifene for the treatment of postmenopausal osteoporosis. The authors stated that future studies should further investigate the effect of raloxifene on CHD.

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Bibliographic details

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Other publications of related interest


Indexing Status
Subject indexing assigned by NLM

MeSH
Adult; Age Factors; Aged; Aged, 80 and over; Breast Neoplasms /etiology /prevention & control; Computer Simulation; Cost-Benefit Analysis; Female; Humans; Middle Aged; Models, Economic; Osteoporosis /complications /drug therapy /economics; Quality-Adjusted Life Years; Raloxifene Hydrochloride /economics /therapeutic use; Randomized Controlled Trials as Topic; Selective Estrogen Receptor Modulators /economics /therapeutic use; Spinal Fractures /etiology /prevention & control; Sweden; Treatment Outcome