**Cost-effectiveness of osteoporosis screening and treatment with hormone replacement therapy raloxifene, or alendronate**


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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 a strategy of screening women for osteoporosis at age 65 years, and treatment for those who tested positive. The three alternative treatments considered were hormone replacement therapy (HRT), raloxifene and alendronate. All women were screened using dual-energy X-ray absorptiometry.

**Type of intervention**
Screening and treatment.

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

**Study population**
The study population comprised a hypothetical cohort of postmenopausal white women aged 65 years with intact uteri. Osteoporosis was defined as a femoral neck bone mineral density measurement of greater than 2.5 standard deviations below the mean for young healthy women.

**Setting**
The setting was secondary care. The economic study was carried out in the USA.

**Dates to which data relate**
The effectiveness data and some resource use data were derived from studies published between 1994 and 2002. The costs came from sources published between 1990 and 2002. The price year was 2002.

**Source of effectiveness data**
The effectiveness evidence was derived from a synthesis of published studies and authors’ opinions.

**Modelling**
A decision model was constructed to simulate lifetime osteoporosis-related costs and outcomes for postmenopausal white women aged 65 years with intact uteri. The model consisted of a treatment strategy followed by an osteoporosis progression module. Women could be screened or not screened for osteoporosis. In the case of a positive test, women could receive HRT, raloxifene or alendronate. For the osteoporosis progression component of the model, women with osteoporosis entered the module in the no-event state. They could then have a fracture, remain in the no-event state, or develop a non-fracture health effect. The non-fracture health effect state included coronary heart disease, stroke, breast cancer, colon cancer, and venous thromboembolism, which could result in mortality. The progression module was constructed as a discrete event simulation model, consisting of a Markov model containing 12 mutually exclusive states. These mutually exclusive states were no event, hip fracture, vertebral fracture, non-fracture health effect, post-hip
fracture, post-vertebral fracture, post-hip new vertebral fracture, post-hip new non-fracture health effect, post-hip post-
vertebral fracture, post-vertebral new hip fracture, post-vertebral new non-fracture health effect, and death. Women
with osteoporosis were followed in the model until they either reached an age of 90 years or died. Annual cycles were
considered.

Outcomes assessed in the review
The outcomes estimated from the literature were:

the annual incidence of fractures and non-fracture events in untreated women,

the prevalence of osteoporosis,

the relative risk (RR) of different treatment for fractures and non-fracture events, and

the loss in quality-adjusted life-years (QALYs).

Study designs and other criteria for inclusion in the review
It was unclear whether a systematic review of the literature was undertaken to identify the primary studies. The authors
stated that more details could be found in a technical report which was available on request. Some of the primary
studies were clinical trials. In particular, the RR for fractures with HRT was taken from the Women's Health Initiative
trial, while the RR for fractures with alendronate was obtained from a synthesis of data from 4 clinical trials. All-cause
mortality was estimated from US life tables. The QALY losses were derived from the Harvard School of Public
Health's online Cost Effectiveness Analysis Registry.

Sources searched to identify primary studies
Not reported.

Criteria used to ensure the validity of primary studies
Most of the evidence was derived from randomised clinical trials which are usually characterised by high internal
validity.

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

Number of primary studies included
Much of the clinical data were derived from 20 studies.

Methods of combining primary studies
A narrative approach appears to have been used to combine some primary estimates. However, some data were
obtained from a synthesis of data from clinical trials. The authors did not report methods of synthesis in this study, but
readers were referred to a technical report which was available on request.

Investigation of differences between primary studies
Not reported.

Results of the review
For untreated patients, the rate of hip fracture ranged from 0.32% (age 65) to 2.16% (age 89), the rate of vertebral fracture ranged from 1.10% (age 65) to 2.44% (age 89), the rate of coronary heart disease was 0.30%, the rate of stroke was 0.21%, the rate of venous thromboembolism was 0.15%, the rate of breast cancer was 0.31%, and the rate of colorectal cancer was 0.16%.

For untreated women, the annual mortality rates were 14% due to hip fracture, 0% due to vertebral fracture, 38% due to coronary heart disease, 25% due to stroke, 30% due to venous thromboembolism (30-day rate), 19.6% due to breast cancer (5-year rate), 38.3% due to colorectal cancer (5-year rate), and ranged from 1.22% (age 65) to 8.57% (age 89) for other causes.

The prevalence of osteoporosis in 65-year-old women was 19.6%.

The RR of hip fracture was 0.66 (+/- 0.5) with HRT and 0.4502 with alendronate.

The RR of vertebral fracture was 0.66 (+/- 0.5) with HRT, 0.595 (+/- 0.52) with raloxifene, and 0.5269 with alendronate.

The RR of coronary heart disease was 1.29 with HRT.

The RR of stroke was 1.41 with HRT.

The RR of venous thromboembolism was 2.11 with HRT and 3.0545 with raloxifene.

The RR of breast cancer was 1.26 with HRT and 0.2401 with raloxifene.

The RR of colorectal cancer was 0.63 with HRT.

The QALY losses were:

0.6 in the first year and 0.05 in later years for hip fracture,
0.2 in the first year and 0.05 in later years for vertebral fracture,
0.102 for coronary heart disease,
0.312 for stroke,
0.083 for venous thromboembolism,
0.6 for breast cancer, and
0.11 for colorectal cancer.

**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**
It was assumed that the patients were treated for 5 years. In addition, the treatment effects on fractures persisted for 2 years after the treatment was discontinued, declining linearly during this 2-year period.

Non-fracture health effects occurred at differential rates only while the women received treatment.

The RR was set at 1 for hip fracture with raloxifene, for coronary heart disease with raloxifene and alendronate, for stroke with raloxifene and alendronate, for venous thromboembolism and breast cancer with alendronate, and for colorectal cancer with both raloxifene and alendronate.
Measure of benefits used in the economic analysis
The summary benefit measures used were the number of life-years (LYs) saved and the number of QALYs saved. These were estimated using a modelling approach. The number of fractures avoided was also reported as a model output. The utility weights required to calculate the QALYs were derived from the literature, as reported above. The LYs and QALYs were discounted at an annual rate of 3%.

Direct costs
The analysis of the costs was conducted from the perspective of the health care system. It included only the direct medical costs associated with the screening for and treatment of osteoporosis, such as costs of fracture and non-fracture events (mainly hospital costs), physician visits, scans and drugs. The unit costs and the quantities of resources used were presented separately for some items only. Some costs were given as macro-categories. Resource use was mainly estimated using data derived from the literature. The costs came from multiple sources, such as published studies, average wholesale prices, Medicare rates, and the National Osteoporosis Foundation. Discounting was relevant, as the long-term costs were estimated, and an annual rate of 3% was applied. The price year was 2002.

Statistical analysis of costs
The costs were treated deterministically.

Indirect Costs
The indirect costs were not included in the economic evaluation.

Currency
US dollars ($).

Sensitivity analysis
Univariate sensitivity analyses were carried out to assess the robustness of cost-effectiveness ratios and cost-utility ratios to variations in several clinical and economic inputs. Such inputs included prevalence of osteoporosis, treatment-related RRs for fracture and non-fracture health effects, age at initiation of screening, duration of treatment, length of persistence of the treatment effect, fracture growth rates, discount rate, cost of fractures and non-fracture health effects, screening costs, drug therapy costs, and disease-related mortality rates. The ranges of values used appear to have been derived from the literature, although some may have been set by the authors.

Estimated benefits used in the economic analysis
With HRT, -88 LYs were gained, 13 hip fractures were avoided, 41 vertebral fractures were avoided, and -56 QALYs were gained.

With raloxifene, -45 LYs were gained, 0 hip fractures were avoided, 46 vertebral fractures were avoided, and 19 QALYs were gained.

With alendronate, 31 LYs were gained, 20 hip fractures were avoided, 52 vertebral fractures were avoided, and 86 QALYs were gained.

Cost results
The per-woman total cost of the ST strategy over NST was $521 with HRT, $848 with raloxifene, and $626 with alendronate.

All treatment strategies decreased the fracture costs, but these savings were smaller than the increased costs due to non-
fracture disease events (excluding raloxifene) and treatment.

**Synthesis of costs and benefits**
Incremental cost-effectiveness and cost-utility ratios were calculated in order to combine the costs and benefits.

The incremental cost per LY gained in comparison with NST was $204,441 with alendronate, while both HRT and raloxifene were dominated (they were more costly and less effective).

The incremental cost per QALY gained in comparison with NST was $447,559 with raloxifene and $72,877 with alendronate, while HRT was dominated.

The sensitivity analysis showed that the only scenario in which HRT would not be dominated was when there were no non-fracture health effects associated with the drug therapy (however, the resulting cost-effectiveness ratio was very high). Raloxifene had the lowest cost-effective ratio when treatment duration was 2 years, but this was still over $100,000 per QALY. The cost-utility ratio of alendronate was more stable to variations in the model inputs, and the treatment was more cost-effective when the discount rate was zero or when the treatment effect persisted for 5 years (incremental cost per QALY approximately $55,000).

**Authors' conclusions**
A screen-and-treat (ST) programme with alendronate may be a cost-effective treatment for osteoporosis in postmenopausal women if society is willing to pay around $70,000 to $75,000 per quality-adjusted life-year (QALY) gained by the programme. The other two strategies were not cost-effective and were dominated by the no-screen no-treat (NST) option in the majority of cases.

**CRD COMMENTARY - Selection of comparators**
The authors justified the choice of the treatments considered in the study. Calcitonin, a potential comparator, was excluded because it is less potent than other pharmacological treatments. The use of the NST strategy as the basic comparator was appropriate since it may reflect the actual treatment pattern in some contexts. You should decide whether these are valid comparators in your own setting.

**Validity of estimate of measure of effectiveness**
The effectiveness evidence came from a synthesis of studies, although it was not explicitly stated whether the primary studies were identified from a systematic review of the literature. Further, there was limited information on the characteristics of the primary studies, although the treatment effect was derived mostly from clinical trials. This should have increased the internal validity of the analysis. The issue of the comparability of the primary studies was not addressed. However, the authors noted that details of the sources of the clinical data and the methods used to synthesise these data were given in a technical appendix, which was available on request. Deterministic sensitivity analyses were carried out on key clinical data.

**Validity of estimate of measure of benefit**
The benefit measures used in the analysis were appropriate. QALYs capture the impact of the interventions on the most relevant dimensions of health (i.e. survival and quality of life). Further, both LYs and QALYs are comparable with the benefits of other health care interventions. Disease-specific measures were also reported. The utility weights were derived from a database, but no information was given on the instruments used to derive these values. Discounting was applied and the impact of changing the discount rate was investigated in the sensitivity analysis.

**Validity of estimate of costs**
The perspective adopted in the study was explicitly stated and the costs included were consistent with this viewpoint. The authors stated that the inclusion of non-medical direct costs and indirect costs would have favoured all ST
strategies. Both the unit costs and quantities of resources used were derived from published sources such as administrative databases and some previous cost studies. However, limited information on such studies was provided. The unit costs were not presented separately from the resource quantities for some categories of costs, which might limit the possibility of replicating the analysis in other settings. However, the costs of cancer care were often presented as yearly macro-estimates. The total costs were modelled. The authors reported the price year, which will facilitate reflation exercises in other time periods.

**Other issues**
The authors stated that their findings contrasted with those published in recent economic evaluations of treatments for osteoporosis. The different results might be explained by the fact that the model included non-fracture health effects, which reduce the benefits of HRT. The issue of the generalisability of the study results to other settings was not explicitly addressed, but some sensitivity analyses on key items were performed. The authors pointed out that the analysis was based on postmenopausal white women, thus caution will be required when extrapolating the results of the study to other ethnic groups. It was also noted that only hip and vertebral fractures were modelled, thus the potential benefits derived from the reduction of other fractures were not considered.

**Implications of the study**
The study results suggest that, among all available treatment options for osteoporosis in postmenopausal women, alendronate is the most cost-effective strategy. However, society's willingness-to-pay represents a key point in deciding on the implementation of such a programme.

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