Individual fracture risk and the cost-effectiveness of bisphosphonates in patients using oral glucocorticoids


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 bisphosphonates in the prevention of glucocorticoid (GC)-induced fractures compared with a population using oral GC (5- and 15-mg doses) and not receiving bisphosphonate treatment. No further details of the bisphosphonate treatment (dosage or frequency) were provided.

Type of intervention
Primary and secondary prevention.

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

Study population
The study population comprised patients aged 40 years or older who were prescribed an oral GC and who were registered in the UK General Practice Research Database (GPRD). Both men and women were included in the study. The results of fractures observed in this population were not presented in this study. The patients had various GC indications and clinical risk factors.

Setting
The setting was outpatient. The economic study was carried out in the UK.

Dates to which data relate
The effectiveness data were collected from an assessment report published by the National Institute for Clinical Excellence (NICE) in 2005 (see 'Other Publications of Related Interest' below for bibliographic details). The authors calculated the probabilities used in the study, using assumptions based on studies published between 1992 and 2002. The cost data and assumptions were obtained from the NICE report (2005). The price year was 2003/04.

Source of effectiveness data
The clinical data included the effectiveness of bisphosphonate treatment in reducing the risk of hip fractures, vertebral fractures and other non-vertebral fractures. The clinical risk factors used in the analysis included fracture and fall history, BMI, smoking history, and the presence of diseases and drugs associated with an increase risk of fracture. The probabilities of fracture and death were calculated from the cohort of oral GC users, specific for the patient's age, gender, daily and cumulative GC dose, GC indication and clinical risk factors.

Modelling
An individual patient-based pharmaco-economic model was developed using Monte-Carlo methods. The time horizon was 6 years. A GC user was randomly sampled and outcomes simulated; this was repeated 5,000 times within each
gender and 10-year age stratum, with replacement. The calculations of the individual mortality and fracture risks were explained in the study, along with a number of modelling assumptions which were fully justified. In brief, Cox proportional hazard models were used to calculate post-fracture excess mortality, while the survivor function of the Cox model was used to estimate excess mortality in the year following a fracture, for each age, gender and GC dose group (5 or 15 mg). The individual probabilities of fracture were estimated with Cox regression models that included all patients.

Sources searched to identify primary studies
The assumptions on the reduced risk of fractures were based on the NICE report (2005). The association of diseases and drugs with an increased risk of fracture was taken from a GPRD published study, the design of which was not reported. The clinical and demographic information about the study population was retrieved from the UK GPRD, which comprises the computerised records of general practices.

Methods used to judge relevance and validity, and for extracting data
The authors did not report how data used in the model were identified or selected for inclusion. The methods of reviewing the literature were not reported, thus it is unlikely that a systematic approach was taken.

Measure of benefits used in the economic analysis
The summary measure of benefit used in the cost-effectiveness analysis was the number of fractures avoided. This was derived from running the model. The measure of benefit used in the cost-utility analysis was the quality-adjusted-life-years (QALYs) gained. The utilities used were those of the general population retrieved through the EuroQol (EQ-5D) questionnaire (Kind et al. 1998, see ‘Other Publications of Related Interest’ below for bibliographic details). The utility of fractures was presented for the first and following years for hip fracture leading to nursing home, other hip fracture, clinically symptomatic vertebral fracture, radius/ulna and humerus. The benefits were discounted at a rate of 1.5%.

Direct costs
The direct costs included in the analysis were those of the health service. Only the direct costs incurred during the 6 years of the model were measured in the cost-effectiveness analysis. In the cost-utility analysis, the costs of fracture after the 6 years of the model were also included. Separate patient expenditure does not appear to have been included. The average costs presented were taken from the NICE report (2005). These comprised the annual costs of bisphosphonates, annual general practitioner visits, BMD measurement and fractures (hip fracture leading to a nursing home, other hip fracture, clinically symptomatic vertebral fracture, radius/ulna and humerus). The medication costs were based on the median cost of the three bisphosphonates available in the UK market for the treatment and/or prevention of GC-induced osteoporosis. The resources and the unit costs were not reported separately, but the probability of a hip fracture leading to nursing home was presented for 10-year age strata. The price year was 2003/04. The costs were discounted at an annual rate of 6%.

Statistical analysis of costs
No statistical analysis of the costs was conducted, as the objective of the study was to produce cost-effectiveness and cost-utility measures.

Indirect Costs
No productivity losses were considered.

Currency
UK pounds sterling ().
Parameter uncertainty was investigated by means of seven one-way sensitivity analyses. The analyses performed were as follows:

- use of general population mortality rates;
- no discounting of the costs and benefits;
- fracture reduction due to bisphosphonates of 10, 20, 30, 40 and 50%;
- doubling the direct cost of fracture;
- reducing the proportion of vertebral fractures that are clinically symptomatic to 20%;
- 5-year offset of the bisphosphonate effect; and
- the use of median costs instead of mean costs.

The impact of the aforementioned changes in the parameters was assessed through the variation in the cost-effectiveness estimates. The authors also performed sub-group analyses to study the variability in cost-effectiveness estimates across GC indications and for low (≤20) and high (>26) BMI.

**Estimated benefits used in the economic analysis**

The estimated benefits, QALYs and fractures avoided, were not presented disaggregated from the cost-effectiveness estimates.

**Cost results**

The cost results were not presented disaggregated from the cost-effectiveness estimates.

**Synthesis of costs and benefits**

The costs and benefits were combined by estimating the cost per QALY gained and the cost per fracture avoided from the perspective of the health system. These results were estimated incremental to no bisphosphonate treatment.

The authors reported that the costs per QALY (in thousands) were 23 (95% confidence interval CI: 14 to 38) with 5-mg GC use and 15 (95% CI: 11 to 20) with 15-mg GC use for all women.

For men, these figures were 41 (95% CI: 30 to 56) with 5-mg GC use and 30 (95% CI: 21 to 43) with 15-mg GC use.

The costs per QALY mostly decreased with age in women, while it was stable or increased with age in men. This increase in men was related to the fact that, despite experiencing more fractures, older men have a much shorter life expectancy than older women. The costs per QALY gained were shown to be inversely related to life expectancy.

With cost per fracture avoided as the outcome, increasing age was associated with lower costs in both men and women. The cost per fracture avoided did not vary with life expectancy. It was also shown that baseline fracture was inversely correlated with the cost per fracture avoided.

The results of the sub-group analysis showed that patients with rheumatoid arthritis had the best cost-effectiveness, given their higher baseline fracture risk and better life expectancy. A lower BMI was related to better cost-effectiveness estimates.

The results from the sensitivity analysis showed that, with a lesser effect of bisphosphonates on fracture risk, both the costs per fracture avoided and the costs per QALY increased. The authors noted that, when using general population mortality, the cost per QALY gained improved, especially in men using 15-mg GC, but this did not change the results for cost per fracture. There were no differences in the mean and median costs of a fracture prevented.
The authors commented that changes in discounting and in the proportion of clinically symptomatic fractures did not have major effects on the results of the study.

**Authors’ conclusions**

The cost-effectiveness of bisphosphonates varied substantially. Bisphosphonates were cost-effective in patients with higher fracture risks, such as elderly patients with a life expectancy over 5 years and younger patients with a fracture history, low BMI, rheumatoid arthritis or using high GC doses.

**CRD COMMENTARY - Selection of comparators**

Although no explicit justification was provided for the comparator used (no bisphosphonate treatment), it would appear to represent current practice in the study setting. However, it was mentioned that other interventions have been evaluated for the treatment of GC-induced osteoporosis but that vertebral fracture reductions have only been observed for bisphosphonates. You should decide if the comparator represents current practice in your own setting.

**Validity of estimate of measure of effectiveness**

The effectiveness estimates were taken from a single report for which no other information was given, making it difficult to comment on the quality of the effectiveness estimates. The other parameters were derived from a database, authors' assumptions and published studies. Although the authors provided some justifications for their selection of the estimates, they did not report any search methods or inclusion criteria. It is therefore possible that the data from the available studies were used selectively.

**Validity of estimate of measure of benefit**

Two measures of benefit (i.e. fractures avoided and QALYs gained) were used. Neither of these measures was reported disaggregated from the costs. This does not enable the reader to reproduce the results. Both measures seem to be appropriate, with QALYs allowing for comparisons with other technologies and fully capturing health outcomes. The authors provided an extensive discussion comparing the two measures of benefit used and how they affect the results. The estimation of health benefits was derived using a complex mathematical model. The utility values were reported accurately and the estimation of QALYs was explained. However, as the authors acknowledged (as a limitation of the study), there were no utility values for GC users and general population values were used.

**Validity of estimate of costs**

Though not explicitly stated, the perspective of a health system seems to have been adopted. It would appear that the categories of costs included were in accordance with this perspective. Although some costs appear to have been omitted from the analysis, their omission is unlikely to have affected the authors' conclusions. The costs were discounted, which was appropriate given the time horizon of the study. The price year was given and resource use was determined by the developed model. The cost data were not reported in detail, which may have implications for the generalisability of the study beyond the study setting.

**Other issues**

The authors compared their findings and methodology with those from other studies, presenting reasons for the superiority of their approach. The main distinguishing characteristic of this study was that it was based on an individualised pharmaco-economic model in which fracture and mortality probabilities were estimated for each individual separately, based on their age, gender and clinical characteristics. The authors discussed the issue of generalisability and stated that their findings might not be generalisable to populations with very different risks. The authors do not appear to have presented their results selectively, although they did not report all the results of the analyses that they performed. The study population was reflected in the authors’ conclusions.

A number of limitations were reported. For example, it was noted that not all possible interactions between the risk factors and risk factor combinations were evaluated. Also, there was no information on all risk factors for fracture, which would improve the accuracy of prediction for an individual patient. The assessment of direct costs only, and the
fact that non-compliance was not considered, were also pointed out as limitations of the study. As the authors commented, this study used a complex mathematical model which may pose serious difficulties when trying to reproduce the results.

**Implications of the study**
The implications of the study are that GC dose, indication, baseline fracture risk, life expectancy and outcome measure have a large impact on the cost-effectiveness of bisphosphonates. The intervention can be considered cost-effective in patients with higher fracture risk, such as elderly patients (with a life expectancy over 5 years) and younger patients with a fracture history, low BMI, rheumatoid arthritis or using high GC doses. The authors did not make any recommendations for policy or practice. No further research was explicitly identified, although the discussion highlighted some areas where limitations are present, implying the need for greater information.

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**Other publications of related interest**
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**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Adult; Age Factors; Aged; Aged, 80 and over; Bone Density Conservation Agents /economics /therapeutic use; Cost-Benefit Analysis; Diphosphonates /economics /therapeutic use; Dose-Response Relationship, Drug; Drug Costs /statistics & numerical data; Fractures, Bone /chemically induced /economics /prevention & control; Glucocorticoids /administration & dosage /adverse effects; Great Britain; Health Care Costs /statistics & numerical data; Humans; Middle Aged; Models, Econometric; Osteoporosis /chemically induced /drug therapy /economics; Quality-Adjusted Life Years; Sensitivity and Specificity

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