Rheumatology 2007;46:460–466
Advance Access publication 9 August 2006
doi:10.1093/rheumatology/kel249

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

T. P. van Staa[1,2], P. Geusens[3,4], B. Zhang[5], H. G. M. Leufkens[1], A. Boonen[3] and C. Cooper[2]

***Objectives*. There are few data on the cost-effectiveness of bisphosphonates with oral glucocorticoids (GCs). An individual patient-based pharmaco-economic model was developed.**

***Methods*. Data were obtained from a cohort of oral GC users aged 40+ ($n = 190\,000$) in the UK General Practice Research Database. Individualized fracture and mortality risks were calculated specific for age, sex, daily and cumulative GC dose, indication and other clinical risk factors. UK costs of medication and direct costs of fracture were obtained from National Institute for Clinical Excellence and used to estimate costs per quality-adjusted life-year (QALY) gained and fracture prevented for bisphosphonates in patients treated for 5 yrs with GCs.**

***Results*. With the use of 5 mg GCs daily, the cost per one QALY gained with bisphosphonates was 41k UK pounds (95% confidence intervals 22–72k) in women aged <60 [men £40k (29–54k)], £17k (13–24k) in women aged 60–79 [men £43k (31–60k)], £5k (3–6k) in women aged 80+ [men £35k (25–46k)]. With 15 mg GC, these figures were £17k (14–21k), £13k (10–16k) and £15k (9–26k) in women and £22k (17–26k), £34 (23–53k) and £33k (27–42k) in men, respectively. When stratifying by overall fracture risk and life expectancy at the start of GC therapy, cost per QALY increased with decreasing life expectancy. Patients with rheumatoid arthritis had comparatively better cost-effectiveness, given higher fracture risk and better life expectancy.**

***Conclusions*. The cost-effectiveness of bisphosphonates varied substantially. Bisphosphonates can be considered cost-effective in patients with higher fracture risks, such as elderly patients (with a life expectancy over 5 yrs), and younger patients with a fracture history, low body mass index, rheumatoid arthritis or using high GC doses.**

KEY WORDS: Glucocorticoids, Corticosteroids, Osteoporosis, Fracture, Iatrogenic disease, Cost-effectiveness.

Introduction

Osteoporosis and fracture are recognized side-effects of oral glucocorticoid (GC) therapy. Many cross-sectional studies have found that patients using oral GCs have reduced bone mineral density (BMD) and longitudinal studies have reported a rapid onset of this BMD loss [1]. In the only two randomized trials available, the loss of lumbar spine BMD at 3–5 months was statistically significantly greater in patients using an average of 7.5 mg prednisolone per day compared with randomly selected controls [2, 3]. Several epidemiological studies reported increased risks of fractures, including vertebral and hip, in patients using oral GCs [4–6].

Various drug therapies, such as vitamin D, calcitonin, fluoride and bisphosphonates, have been evaluated for the management of GC-induced osteoporosis. Vertebral fracture reductions have been observed only for bisphosphonates [7]. There are few data on the cost-effectiveness of bisphosphonate treatment in patients using oral GCs. To date, two pharmaco-economic analyses of the cost-effectiveness of bone protection in patients using oral GCs have been published [8, 9]. These studies modelled general data from literature and estimated BMD changes, with fracture rates indirectly derived from BMD. The calculation of fracture risk from BMD used data from studies of non-users of GCs. However, BMD changes during GC therapy may predict only to a moderate extent the increases in fracture risk. A prospective study reported that fracture risk at a given BMD was higher in GC users than non-users [10]. And a recent meta-analysis of prospective cohort studies found that GC exposure confers an increased risk of fracture that is of substantial importance beyond that which can be explained by BMD [11]. Another study reported that the increases in fracture risk with GC therapy were much larger than expected on the basis of the BMD changes [1].

The objective of this study was to assess the cost-effectiveness of bisphosphonate treatment in the prevention of GC-induced fractures. An individual patient-based pharmaco-economic model was developed using data from a large cohort of oral GC users in actual clinical practice. Fracture and mortality rates were estimated specifically for age, sex, GC dose and clinical risk factors. An incremental cost-effectiveness analysis was conducted comparing the costs and benefits with and without bisphosphonate treatment.

Material and methods

Study population

The study population included all patients aged 40 yrs or older who were prescribed an oral GC and who were registered in the

[1]Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands, [2]MRC Epidemiology Resource Centre, University of Southampton, Southampton, UK, [3]Department of Rheumatology, University Hospital, Maastricht, The Netherlands, [4]University Hasselt, Campus Diepenbeek, Belgium and [5]Statistician consultant, USA.

Submitted 9 March 2006; revised version accepted 1 June 2006.

Correspondence to: Prof. Cyrus Cooper, MRC Epidemiology Resource Centre, Southampton General Hospital, Southampton SO16 6YD, UK. E-mail: cc@mrc.soton.ac.uk

UK General Practice Research Database (GPRD). The GPRD comprises the computerized medical records of general practitioners (GPs). GPs play a key role in the UK health care system, as they are responsible for primary health care and specialist referrals. Patients are semi-permanently affiliated to a practice that centralizes the medical information from the GPs, specialist referrals and hospitalizations [12]. Details of the overall fracture results in the oral GC users are available elsewhere [6].

Model and transition probabilities

Using data from this large cohort of oral GC users, an individual patient-based pharmaco-economic model was developed. The model considered seven outcomes, comprising hip (or femur or pelvis) fracture, clinically symptomatic vertebral fracture, clinically asymptomatic vertebral fracture, radius/ulna (or clavicle, scapula, rib and sternum) fracture, humerus (or tibia, fibula) fracture and death. Patients could suffer each fracture type twice.

The individual probabilities of fracture or death were calculated from this cohort of oral GC users. These probabilities were specific for the patient's age, sex, daily and cumulative GC dose, GC indication and clinical risk factors. The clinical risk factors used in the analysis included fracture and fall history, body mass index (BMI), smoking history, and presence of diseases and drugs that have been associated in a previous GPRD study with an increased risk of fracture [13]. The methods for calculating the individual probabilities of fracture and death have been described elsewhere [14]. Briefly, the follow-up of oral GC users was divided into periods of current and past GC use. Daily and prior cumulative dose were assessed at the start of each current exposure period. Cox proportional hazards models were used to estimate the long-term risks of fractures. Various methods were used to test the fitting of the Cox models, including visual evaluation of the proportional hazards assumption and a comparison of the observed and predicted fracture probabilities. The individual probabilities of fracture were estimated with Cox regression models that included all patients. The individual probabilities of mortality were estimated separately for each sex and 10-yr age stratum, given strong interaction between mortality risk and age and sex.

The model included both clinically symptomatic and asymptomatic vertebral fractures. The risks of vertebral fractures were based on those observed in our study population. But the observed risks were increased because vertebral fractures are under diagnosed in UK general clinical practice and systematic morphometry was not routinely done by GPs. The rate of (morphometric) vertebral fractures, as reported in the European Prospective Osteoporosis Study (EPOS) was about nine times higher than those in GPRD [15]. We multiplied the GPRD vertebral risks by half of this ratio, a more conservative approach, in line with estimates from a recent pharmaco-economic analysis [16]. One-third of these fractures was considered to be clinically symptomatic and the remaining clinically asymptomatic (morphometric) [17]. In our analysis, it was assumed that clinically asymptomatic fractures did increase the risk of other types of fractures, but that they were not associated with any costs, loss of quality-of-life, or excess mortality.

In order to account for post-fracture excess mortality, cases with each fracture type were randomly matched to four controls using GCs but without a fracture. The analysis was restricted to current GC users and the cases were matched by age, sex, calendar time and GC indication. Cases and controls were then compared for mortality in the following year using Cox proportional hazards models. These analyses were adjusted for the clinical risk factors, GCs indication and GCs dose. Interaction terms between fracture status and age, sex and GCs dose were also included, if statistically significant. The excess mortality in the year following a hip, clinically symptomatic vertebral, wrist or humerus fractures was then estimated for each age, sex and GC dose group, based on the survivor function of the Cox model.

Using the individual mortality and fracture risks, the outcomes were simulated (using Monte-Carlo methods) over a 6-yr period, comparing presence and absence of bisphosphonate treatment (5 yrs of GC use followed by 1-yr off GC use). It was assumed that bisphosphonates reduced the risk of hip fractures by 38%, vertebral fractures by 44% and other non-vertebral fractures by 19% [18]. It was assumed that there was a linear offset of the protective effect of bisphosphonates over 1 yr after stopping GCs. Out of the total study population, one oral GC user was randomly sampled and the characteristics at start of GC exposure were used to calculate the individual fracture and mortality rates. Over the course of the model, the individual rates were adjusted, at each 3-month period, for increasing age and cumulative GC dose and, in case of fracture occurrence in the model, for fracture history. This process of randomly sampling a GC user and simulating the outcomes over a 6-yr period was reiterated 5000 times within each sex and 10-yr age stratum (with replacement). Within each age and sex cohort of 5000 people, the total costs over the 6-yr period and number of fractures were estimated. The incremental cost-effectiveness ratio for the cost to avoid one fracture was then calculated by dividing the difference in total costs between the two strategies (bisphosphonate treatment or not) by the differences in number of fractures. The cost-effectiveness in the overall study population was determined by weighting the age- and sex-specific estimates by the proportion of patients in each stratum.

The random variability of the cost-effectiveness ratios was determined as follows. The fracture and mortality transition probabilities were randomly selected from a normal distribution based on the mean and S.D. of the parameter. Non-parametric bootstrapping techniques were then used to estimate the 95% confidence intervals (CIs), repeating the analysis 5000 times using data from 20 cohorts. The 95% CI was based on the 2.5 and 97.5% percentile of the distribution of the bootstrapping results [19].

Utility

We could not identify a good source of data on the quality-of-life in patients using oral GCs and the corresponding loss of quality-of-life due to a fracture in this population. The underlying disease may reduce quality-of-life, while GC therapy may improve it. For this reason, quality-of-life information was obtained from a study of the general population that used the EuroQol (EQ-5D) questionnaire [20]. The gain of quality-adjusted life-years (QALYs) was estimated as follows. For cases with a hip, clinically symptomatic vertebral, wrist or humerus fracture, the life expectancy with and without fracture-related excess mortality in the 1 yr after the fracture was calculated and quality-of-life utility was assigned [18]. The number of QALYs gained by avoiding fractures was then estimated by comparing the two strategies (bisphosphonate treatment or not).

Costs and assumptions

The cost data and other assumptions used in the model are listed in Table 1 [18]. In the analysis of costs per fracture avoided, only direct costs incurred during the 6 yrs of the model were measured. In the analysis of QALYs, the costs of fracture after the 6 yrs of the model were also included. 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 (alendronate, cyclical etidronate and risedronate). Costs were discounted annually by 6% and benefits by 1.5% in line with the National Institute of Clinical Excellence (NICE) guidelines.

TABLE 1. Cost data and assumptions used in the model

Overall costs[a]						
Annual costs bisphosphonates		£284				
Annual GP visits	aged <75 yrs (1/3 of patients)	£18				
	aged ≥75 yrs	–				
BMD measurement	aged 65 yrs	£34				
(baseline)	aged ≥ 65 yrs	–				
Annual discounting percentages						
Costs		6%				
Benefits		1.5%				
Direct costs of fractures[a]		Age 40–69		Age 70–79		Age 80+
		Year1	Year 2+	Year 1	Year 2+	Year1	Year 2+
Hip fracture leading to nursing home		£31 299	£23 562	£32 606	£24 240	£34 654	£25 357
Other hip fracture		£5157	–	£6487	–	£8538	–
Clinically symptomatic vertebral fracture		£477	£222	£539	£222	£581	£222
Radius/ulna		£359	–	£359	–	£585	–
Humerus		£1024	–	£1024	–	£1024	–
Health utility of fractures [multiplier for quality of life (QoL)][a]		Year 1	Year 2+				
Hip fracture leading to nursing home		0.4	0.4				
Other hip fracture		0.83	0.925				
Clinically symptomatic vertebral fracture		0.83	0.93				
Radius/ulna		0.981	1				
Humerus		0.794	0.973				
Move to a nursing home following hip fracture[a]		Age 40–59		Age 60–79		Age 80–89	Age 90+
Hip fracture leading to nursing home		0%		4%		12%	17%

[a]Data from the assessment report on the clinical effectiveness and cost-effectiveness of prevention and treatment of osteoporosis, as prepared by the NICE; data based on women only [18]. Costs were applicable to 2003/2004.

Sensitivity analyses

Six one-way sensitivity analyses were performed: (i) use of general population mortality rates, (ii) no discounting of costs and benefits, (iii) fracture reduction due to bisphosphonates of 10, 20, 30, 40 and 50%, (iv) doubling the direct costs of fractures, (v) reducing the proportion of vertebral fractures that are clinically symptomatic to 20% and (vi) 5 yr offset of the bisphosphonate effect.

Results

Study population

The study population consisted of 191 752 patients who were aged ≥40 yrs and prescribed oral GCs. There were 2481 patients with a hip/femur/pelvis fracture, 1269 with a clinical vertebral, 3419 with a radius/ulna/clavicle/scapula/rib/sternum, and 2090 with a humerus/tibia/fibula fracture.

The overall mortality was high among current users of GCs compared with past users (41 338 patients died during follow-up). Mortality was strongly related to daily GC dose. Compared with past users, the relative rate (RR) was 2.67 in current users of <10 mg GC daily aged 40–59 and 10.16 with a dose of 10–20 mg (for the age of 80+, the RRs were 1.32 and 2.62, respectively).

Cost-effectiveness

The costs per QALY gained were £23k (95% CI 14–38k) with 5 mg GC use and £15k (95% CI 11–20k) with 15 mg GC use for all women combined. For men, these costs were 41k (95% CI 30–56k) and 30k (95% CI 21–43k), respectively. The costs per QALY gained mostly decreased with age in women, while it was stable or increased with age in men (Fig. 1a). With cost per fracture avoided as the outcome, increasing age was associated with lower costs in both men and women (Fig. 1b). Although older men experienced more fractures, their life expectancy was much shorter.

As shown in Table 2, the cost per QALY gained was inversely related to life expectancy. Those with shorter life expectancy had higher cost per QALY gained. In contrast, the cost per fracture avoided did not vary with life expectancy. Baseline fracture risk was inversely correlated with the cost per fracture avoided. Patients with a baseline life expectancy of <5 yrs generally had high costs per QALY gained.

Subgroup analyses

There was a strong variability in cost-effectiveness across GC indications (Table 3). Patients with rheumatoid arthritis had comparatively the best cost-effectiveness, given their higher baseline fracture risk and better life expectancy. Also, patients with low BMI (<20) had better cost-effectiveness compared with patients with high BMI (≥26). With the use of 5 mg GCs, the cost per QALY gained was 16k in women aged <60 with low BMI (men 25k) compared with 34k in women with high BMI (men 43k). With use of 15 mg GCs, the costs were 12k in women aged <60 yrs with low BMI (men 16k) compared with 17k in women with high BMI (men 25k). For patients aged ≥60 yrs, the costs were 7k with low BMI in women (men 29k) compared with 18k in women with high BMI using 5 mg GCs (men 44k). With use of 15 mg GCs, these figures were 6k (32k) and 14k (32k), respectively.

Sensitivity analyses

Table 4 shows the results of various sensitivity analyses. With a lesser effect of bisphosphonates on fracture risk, both cost per fracture avoided and per QALY gained increased. Conversely, the cost per QALY gained improved with GC users experiencing the mortality of the general population, especially in men and those using 15 mg GCs. But results on cost per fracture avoided did not change materially using general population mortality. It was also found that the *median* costs of (i.e. the middle value in the repeated simulations) were considerably lower

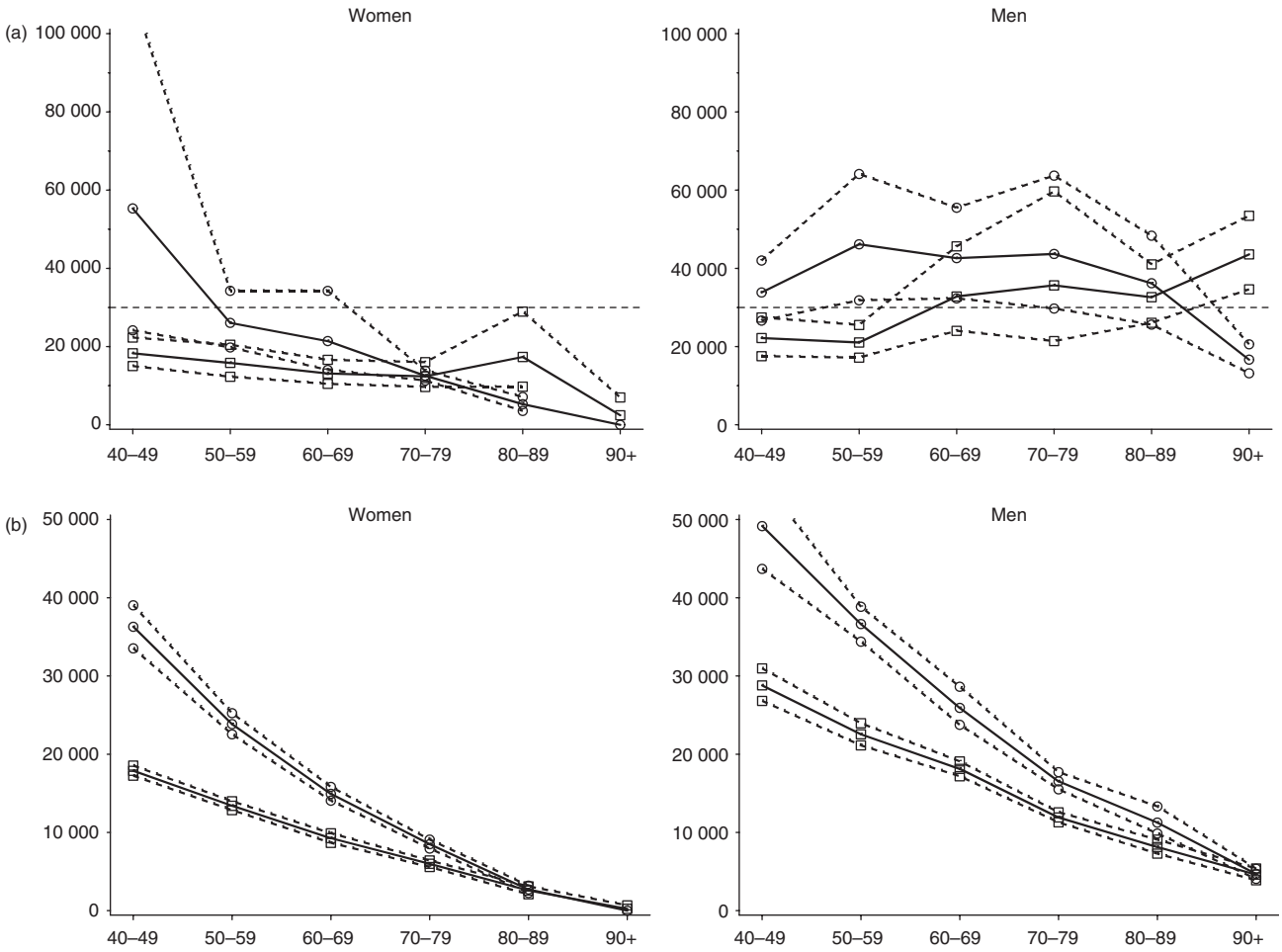

FIG. 1. Cost (£) per QALY gained (Fig. 1a) and fracture avoided (Fig. 1b) stratified by age in men and women (○ = use of 5 mg GCs for 5 yrs, □ = use of 15 mg GCs for 5 yrs). The dotted lines represent the 95% CIs. The line at £30k represents the NICE threshold for incremental cost-effectiveness.

than the mean costs, especially in groups of patients with shorter life expectancy. There were no differences in mean and median costs of fracture prevented. Changes in discounting, the proportion of clinically symptomatic fractures did not have major effects on the results of the study.

Discussion

The costs for preventing fractures with bisphosphonates were found to be strongly related to GC dose and the patient's age, sex and baseline fracture risk. But the results on the costs of QALYs with bisphosphonates were less straightforward, due to competing effects on QALYs of life expectancy and fracture risk. In some of the elderly GC users, bisphosphonates would not be considered cost-effective on the basis of QALYs, while it would be considered highly cost-effective on the basis of fractures avoided.

This analysis was based on an individualized pharmaco-economic model: fracture and mortality probabilities were estimated for each individual separately, based on their age, sex and clinical characteristics. The typical approach in pharmaco-economics is to utilize rates that are based on averages in populations. For example, the recent NICE report on post-menopausal osteoporosis used data that were derived from general population fracture and mortality rates (with an adjustment for BMD) [18]. In our study population, mortality was considerably higher than the general population mortality and also strongly related to patient characteristics. Furthermore, we found that cost-effectiveness varied substantively with GC indications and patient characteristics. For example, there was a 3-fold difference in overall cost per QALY gained with different life expectancy that would be missed in an economic analysis based on population averages. It is questionable whether treatment should be denied to an individual patient with an above-average risk, because treatment is not cost-effective in the 'average' patient. Conversely, treatment should not be given to some patients with below-average fracture risk. There are also methodological reasons for preferring an individualized pharmaco-economic model. We found that patients with the higher baseline fracture risks had on an average much lower life expectancy. An analysis that does not take into account this interaction would underestimate the cost per QALY gained, as patients who suffer fractures may have lower life expectancy than the average patient.

Some of our results on the costs per QALYs gained are not directly intuitive (e.g. it dramatically *increased* with age in elderly men using 15 mg GCs). As QALYs are based on both quality- and quantity-of-life, the costs per QALY are strongly related to life expectancy. Thus, it will be less cost-effective (in QALY terms) to treat men, even if fracture risks were comparable with women, because of their lower life expectancy. The underlying ethical assumption of QALYs is that older and sicker patients have less 'capacity to benefit' from interventions than those who are

TABLE 2. Cost per QALY gained and fracture avoided stratified by baseline fracture risk and baseline life-expectancy[a]

			5 mg		15 mg	
			Cost per fracture avoided	Cost per QALY gained	Cost per fracture avoided	Cost per QALY gained
Women	Life-expectancy	High	18k	15k	10k	10k
		Medium	14k	15k	9k	15k
		Low	16k	24k	10k	40k
	Fracture risk[b]	Very low	21k	22k	12k	16k
		Low	17k	21k	10k	15k
		Medium	13k	14k	8k	13k
		High	7k	10k	4k	6k
Men	Life-expectancy	High	30k	33k	18k	21k
		Medium	28k	41k	16k	28k
		Low	31k	63k	21k	105k
	Fracture risk[b]	Very low	36k	50k	21k	36k
		Low	31k	48k	18k	29k
		Medium	25k	46k	15k	58k
		High	15k	40k	9k	42k

[a]Data based on patients aged <90 yrs, due to small number of patients within some of the strata.
[b]Based on the baseline hip fracture risk score [14] derived from the clinical risk factors (not age and sex): lowest (score ≤0), second lowest (1–4), second highest (5–9), highest (10+).

TABLE 3. Cost per QALY gained stratified by GC indication[a]

	5 mg		15 mg	
Indication	Age <60	Age 60+	Age <60	Age 60+
Women				
Overall	41k	14k	17k	13k
Respiratory disease	23k	14k	15k	14k
Rheumatoid arthritis	12k	5k	6k	5k
Non-infectious enteritis and colitis	14k	7k	9k	6k
Polymyalgia rheumatica	18k	9k	10k	8k
Polyarteritis	16k	9k	10k	7k
Other[b]	22k	10k	13k	9k
Rest	51k	27k	50k	38k
Men				
Overall	40k	42k	22k	34k
Respiratory disease	45k	40k	21k	29k
Rheumatoid arthritis	25k	17k	11k	12k
Non-infectious enteritis and colitis	28k	20k	14k	23k
Polymyalgia rheumatica	28k	27k	18k	17k
Polyarteritis	27k	22k	14k	16k
Other[b]	37k	44k	16k	24k
Rest	81k	71k	50k	124k

[a]Data based on patients aged <90 yrs, due to small number of patients with some of the indications in the very old.
[b]Including other connective tissue disorders, dermatitis, other inflammatory skin disorders, urticaria, facial nerve disorders and other peripheral nervous system disorders.

younger and healthier [21]. The use of QALYs in prioritizing interventions, morally giving lower weight to elderly and sicker patients, is not uniformly accepted [22]. There are also practical limitations in the use of QALYs, as they require long-term prediction of quality- and quantity-of-life (from the onset of fracture until death). There are no data on QALYs in GC users; in post-menopausal osteoporosis, the data mostly concern information collected only over a short period of time [18]. The data on QALYs are typically derived from other studies, while the costs per fracture avoided can be estimated directly from representative populations, as shown in this study. Also, the costs per QALY gained may provide more unstable estimates than the costs per fracture prevented, as the statistical variability is larger as it is based on a longer time period. In this study, the median estimate for costs per QALY gained was considerably lower than the mean, due to some large values, while they did not differ for the costs for fracture prevented. Therefore, the costs per fracture avoided may be a more attractive measure of cost-effectiveness, as it only requires data collected during the time-window of the model. This measure does not allow direct comparisons with other diseases (e.g. the costs to prevent one myocardial infarction). But this may be done by weighting the short-term consequences (quality-of-life and mortality) of the different diseases. This would negate the need to measure lifetime data and to assume moral superiority of health and youthfulness over aging and illness.

The costs per fracture avoided are directly related to the number-needed-to-treat (NNT). NNT provides information about treatment benefit by incorporating both the baseline risk without preventative treatment and the risk reduction with treatment [23]. But NNTs are typically derived from clinical studies or systematic reviews. The populations included in clinical trials are often not representative of patients in actual clinical practice. A more attractive approach for estimating NNTs, as used in this study, could be to combine the overall risks observed in a representative population [14] with the RRs observed in clinical studies.

Guidelines have been developed to establish intervention thresholds in GC users. The recent guidelines of the American College of Rheumatology advocate intervention in all patients starting GC therapy at ≥5 mg/day, and in those patients on long-term GC therapy with a BMD below a T score of –1 [24]. The UK advocates intervention in all patients aged ≥65 yrs and in younger patients with a fracture history or T score below –1.5 [7]. The results of this study suggest that bisphosphonate treatment in elderly GC users could be generally considered cost-effective, especially in those with a life expectancy over 5 yrs. Similarly, bisphosphonates are cost-effective in younger patients who have a history or develop a clinical fracture during GC therapy. In this study, we did not have data on BMD. But there is now increasing evidence that GC therapy influences fracture not just by reducing BMD but also by a mechanism independent of BMD [1, 11, 25]. In this study, cost-effectiveness improved in patients with higher fracture risk and this will also apply to patients with reduced BMD, given their increased risk of fracture.

There are various limitations of this study. Our findings are based on a complex mathematical model. We evaluated the key underlying assumptions utilized and its overall predictive

TABLE 4. Sensitivity analyses for cost per QALY gained and fracture avoided in total population

	5 mg GCs				15 mg GCs			
	Cost per fracture avoided		Cost per QALY gained		Cost per fracture avoided		Cost per QALY gained	
Sensitivity analysis	Women	Men	Women	Men	Women	Men	Women	Men
Overall (mean)	17k	27k	23k	41k	10k	18k	15k	30k
Overall (median)	17k	26k	16k	30k	9k	18k	12k	23k
General population mortality	15k	27k	15k	28k	8k	14k	10k	18k
Zero discounting of costs and benefits	18k	35k	15k	40k	11k	19k	15k	27k
Fracture reduction by bisphosphonates								
10%	92k	166k	78k	110k	49k	105k	53k	76k
20%	28k	55k	38k	58k	18k	37k	35k	71k
30%	18k	32k	22k	47k	12k	21k	22k	47k
40%	13k	25k	15k	38k	8k	16k	11k	31k
50%	10k	18k	10k	24k	6k	12k	9k	19k
Direct costs per fracture doubled	15k	27k	15k	39k	9k	17k	10k	33k
20% of vertebral fractures clinically symptomatic	16k	28k	20k	51k	10k	17k	20k	39k
Offset of bisphosphonate effect over 5 yrs	13k	25k	16k	44k	9k	17k	16k	26k

capacity performed well. However, we did not evaluate all possible interactions between the risk factors and for certain risk factor combinations; the model may therefore have over- or under-estimated risks. But the fracture risk model was validated in another population and performed well [14]. Another limitation was that we did not have information on all risk factors for fracture (such as BMD, exercise or diet), which would improve the accuracy of prediction for an individual patient. Like any pharmaco-economic analysis, findings on cost-effectiveness may not be generalizable to populations with very different risks. The estimates used in this study can only be considered as approximate. Also, there are limited data on the efficacy of bisphosphonates in GC users on non-vertebral fractures [7]. But the effects of bisphosphonates on hip and vertebral fractures in post-menopausal osteoporosis have been well-studied and the assumption is generally made that anti-fracture efficacy is similar in GC users, although this has not been rigorously tested [7]. Our model also only assessed direct costs [18], and did not take into account any effects on costs or quality-of-life of any side effects of bisphosphonates, as we did not have a good source of information on these. The effects of non-compliance were also not considered for similar reasons.

In conclusion, the cost-effectiveness of bisphosphonates in patients using GC varied substantially across GCs dose, indication, baseline fracture risk, life expectancy and on the outcome measure (fracture avoided or QALYs gained). Bisphosphonates can be considered cost-effective in patients with higher fracture risks, such as elderly patients (with a life expectancy over 5 yrs) and younger patients with a fracture history, low BMI, rheumatoid arthritis or using high GC doses.

Conflict of interest statement. The study received no funding. T.P.S. was previously employed by Procter & Gamble Pharmaceuticals, Egham, UK and acquired company stocks during his employment. The manuscript was approved only by the authors.

References

1. van Staa TP, Leufkens HGM, Cooper C. The epidemiology of corticosteroid-induced osteoporosis: a meta-analysis. Osteoporos Int 2002;13:777–87.
2. Laan RFJM, van Riel PLCM, van de Putte LBA, van Erning LJTO, van't Hof MA, Lemmens JAM. Low-dose prednisone induses rapid reversible axial bone loss in patients with rheumatoid arthritis. Ann Intern Med 1993;119:963–8.
3. McKenzie R, Reynolds JC, O'Fallon A *et al*. Decreased bone mineral density during low dose glucocorticoid administration in a randomised-placebo controlled trial. J Rheumatol 2000; 27:2222–5.
4. Cooper C, Coupland C, Mitchell M. Rheumatoid arthritis, corticosteroid therapy and hip fracture. Ann Rheum Dis 1995; 54:49–52.
5. Naganathan V, Jones G, Nash P, Nicholson G, Eisman J, Sambrook PN. Vertebral fracture risk with long-term corticosteroid therapy. Arch Intern Med 2000;160:2917–22.
6. van Staa TP, Leufkens HGM, Abenhaim L, Zhang B, Cooper C. Use of oral corticosteroids and risk of fractures. J Bone Miner Res 2000;15:993–1000.
7. Royal College of Physicians. Glucocorticoid-induced osteoporosis: guidelines for prevention and treatment. London: Royal College of Physicians, 2002.
8. Buckley LM, Hillner BE. A cost effectiveness analysis of calcium and vitamin D supplementation, etidronate, and alendronate in the prevention of vertebral fractures in women treated with glucocorticoids. Rheumatol 2003;30:132–8.
9. Solomon DH, Kuntz KM. Should postmenopausal women with rheumatoid arthritis who are starting corticosteroid treatment be screened for osteoporosis? A cost-effectiveness analysis. Arthritis Rheum 2000;43:1967–75.
10. van Staa TP, Laan RF, Barton I, Cohen S, Reid DM, Cooper C. Predictors and bone density threshold for vertebral fracture in patients using oral glucocorticoids. Arth Rheum 2003;48:3224–9.
11. Kanis JA, Johansson H, Oden A *et al*. Meta-analysis of prior corticosteroid use and fracture risk. J Bone Miner Res 2004; 19:893–9.
12. Walley T, Mantgani A. The UK General Practice Research Database. Lancet 1997;350:1097–9.
13. van Staa TP, Leufkens HGM, Cooper C. Utility of medical and drug history in fracture risk prediction among men and women. Bone 2002;31:508–14.
14. van Staa TP, Geusens P, Pols HAP, de Laet C, Leufkens HGM, Cooper C. A simple score for estimating the long-term risk of fracture in patients using oral glucocorticoids. QJM 2005;98:191–8.
15. Felsenberg D, Silman AJ, Lunt M *et al*. Incidence of vertebral fracture in Europe: results from the European prospective Osteoporosis Study (EPOS). J Bone Miner Res 2002;17:716–24.
16. Kanis JA, Brazier J, Calvert N, Lloyd-Jones M, Stevenson M. Treatment of established osteoporosis. Health Technology Assessment 2002; Vol. 6: No. 29. Available at: http://www.ncchta.org/execsumm/summ629.htm

17. Cooper C, Atkinson EJ, O'Fallon M, Melton LJIII. Incidence of clinically diagnosed vertebral fractures: a population-based study in Rochester, Minnesota, 1985–1989. J Bone Miner Res 1992;7:221–7.
18. Stevenson M, Lloyd M, de Nigris E, Brewer N, Oakley J. Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary and secondary prevention of osteoporotic fragility fractures in postmenopausal women. National Institute for Clinical Excellence, September 2005.
19. Glick HA, Briggs AH, Polsky D. Quantifying stochastic uncertainty and presenting results of cost-effectiveness analyses. Expert Rev Pharmacoeconomics Outcomes Res 2001;1:25–36.
20. 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.
21. La Puma J, Lawlor EF. Quality-adjusted life years: ethical implications for physicians and policymakers. JAMA 1990; 263:2917–21.
22. Harris J. Unprincipled QALYs: a response to Cubbon. J Med Ethics 1991;17:185–8.
23. Osiri M, Suarez-Almazor ME, Wells GA, Robinson V, Tugwell P. Number needed to treat (NNT): implication in rheumatology clinical practice. Ann Rheum Dis 2003;62:316–21.
24. American College of Rheumatology Ad Hoc Committee on Glucocorticoid-Induced Osteoporosis. Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. Arthritis Rheum 2001;44:1496–503.
25. Manolagas SC. Corticosteroids and fractures: a close encounter of the third cell kind. J Bone Miner Res 2000;15:1001–5.