

Cost-effectiveness of inhaled steroids in asthma: Impact of effect on bone mineral density

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Background: The effects of inhaled corticosteroid (ICS) preparations on bone health have been debated. Multiple analyses have been published examining the question, with mixed results.

Objectives: We examined how assumptions about the effect of ICS on bone mineral density (BMD) influence the cost-effectiveness of ICS in asthma.

Methods: We developed a mathematical simulation model to estimate clinical outcomes and costs for a cohort with mild/moderate asthma. The analysis conformed to reference case recommendations of the US Panel on Cost-Effectiveness in Health and Medicine. Sensitivity analysis evaluated the stability of our results to uncertainty in treatment duration, age at treatment, and ICS dose.

Results: Assuming a dose of 200 µg twice per day of ICS, a literature-based average effect of ICS on BMD and a 10-year time horizon, we observed a minimal increase in the costs attributed to hip fracture and incremental cost effectiveness ratio of \$26,000 per quality-adjusted life-year and \$14.00 per symptom-free day gained. Over an extended time horizon (lifetime), the incremental cost effectiveness ratio increased to \$42,000/quality-adjusted life-year. Only under a scenario of high-dose ICS, a lifetime horizon, and a large effect of ICS on BMD did the potential impact of ICS on BMD dramatically affect the economic attractiveness of therapy.

Conclusion: To minimize any potential impact, use of the lowest effective dose of ICS and measures to target and intervene in high-risk individuals are warranted. However, ICS therapy in mild/moderate asthma compares favorably with commonly accepted interventions over a wide range of assumptions

regarding this treatment and its effects on BMD. (*J Allergy Clin Immunol* 2006;117:359-66.)

Key words: Asthma, inhaled corticosteroids, cost-effectiveness, drug toxicity, bone density, osteoporosis, hip fracture, treatment outcome, Markov models

National guidelines recommend inhaled corticosteroids (ICSs) as first-line therapy in persistent asthma.¹ Yet widespread nonadherence on the part of physicians and patients to these guidelines persists^{2,3} and may be caused, in part, by concerns about the safety of ICS. The effects of oral corticosteroids on bone metabolism are well documented, and all ICS preparations are known to be absorbed to some extent into the systemic circulation from the lungs.⁴ Furthermore, previous analysis has demonstrated that the clinical and economic attractiveness of ICS therapy is sensitive to assumptions about ICS toxicity.⁵ Therefore, the tradeoff between the known benefits of ICS therapy and potential side effects of accelerated osteoporosis and fractures may play a role in patients' and physicians' nonadherence to guideline recommendations.

However, the link between ICS use and potential changes in bone mineral density (BMD) has not been established with certainty, with studies yielding conflicting results.⁶⁻¹⁹ Therefore, the aim of the current study was to assemble the existing evidence and provide guidance about the appropriateness of ICS therapy in persistent disease. By using a literature-based estimate of the range of potential effects of ICS therapy on BMD in combination with the proposed link between BMD and subsequent fracture rate, we examined the impact of these effects on the cost-effectiveness of the use of inhaled corticosteroids in mild-to-moderate asthma. Preliminary results of this analysis have been previously presented in abstract form.²⁰

METHODS

Analytic overview: The Asthma Policy Model

The Asthma Policy Model is a Markov, state-transition simulation of the natural history of asthma. The details of the model development are described in detail in a separate publication.⁵ See this article's detailed summary of model development in the [Online Repository](http://www.jacionline.org) at www.jacionline.org.

Target population

We evaluated (1) quick relievers (eg, short-acting β-agonists) on an as-needed basis and (2) a quick reliever plus ICS therapy for a

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Abbreviations used

BMD:	Bone mineral density
HRQOL:	Health-related quality of life
ICER:	Incremental cost-effectiveness ratio
ICS:	Inhaled corticosteroid
OR:	Odds ratio
QALM:	Quality-adjusted life-month
QALY:	Quality-adjusted life-year

baseline cohort of women, age 35 years, with mild-to-moderate persistent asthma. We chose to model women because data on the relationship between BMD and fracture risk are best defined among female populations. In addition, after age 35 years, the overall incidence of fractures in women climbs steeply and becomes twice that in men.²¹

Input data

Effect of BMD on fracture risk. The decline in BMD has been estimated from large population-based studies of white women and found to be a function of age. Femoral neck and trochanteric hip fracture rates were estimated by using the equations developed by Melton et al.²² The total hip fracture rate was calculated as the sum of femoral neck and trochanteric fracture rates. For this analysis, the overall incidence of all fractures was calculated by using the percentage of hip fractures relative to all fractures.²³

Effect of ICS on BMD. Systematic review of published literature yielded 6 randomized controlled trials and 3 longitudinal studies that allowed calculation of the effect of ICS therapy on BMD, standardized to a unit dose per year of steroid.^{10,15,16,24,25} For the base-case analysis, we assumed an ICS dose of 200 µg twice per day (400 µg once per day) and a weighted average of the published estimates of the potential effect of ICS use on BMD ($-0.00028 \text{ g/cm}^2/100 \text{ µg/y}$). Moreover, we assumed equivalency across all ICS preparations.

Health-related quality of life. The US Panel on Cost-effectiveness in Health and Medicine recommends that community preferences for health states be used, whenever feasible, to value morbidity consequences.²⁶ Preference weights were collected in a companion study.²⁷ We obtained health-related quality of life (HRQOL) weights for hip fracture and for nursing home placement after hip fracture from the literature and assumed a time effect of hip fracture on the quality of life weight.²⁸

Costs. Costs were estimated from published studies,⁵ including nursing home costs of \$3082/month and acute hospitalization costs associated with hip fracture of \$13,499 per event and other fracture of \$921/event.²⁹ We adjusted all costs estimates to 2003 US dollars by using the medical care component of the Consumer Price Index.³⁰

Sensitivity analysis

In previous analysis, the cost-effectiveness of ICS was sensitive to assumptions about efficacy of ICS therapy and estimates for HRQOL. In addition, the cost-effectiveness ratio was moderately sensitive to assumptions about costs of ICS drugs and duration of therapy but relatively insensitive to assumptions about costs of acute event rates.⁵ In the current sensitivity analysis, we did not repeat these sensitivity analyses but focused on the impact of variation in parameters directly associated with the effect of ICS on BMD. Because some studies suggest that the effect of ICS on BMD may not be linear,³¹ we explored the effect of 2 different nonlinear models of the effect of ICS on BMD; the models assumed that the effect of ICS on BMD decreased exponentially over a 10-year and 20-year period.

RESULTS

Cost-effectiveness of ICS incorporating the effects of ICS on BMD

In the absence of ICS therapy, patients receiving quick relievers alone will live for an average of 7.32 QALYs over a 10-year period. Discounted and unadjusted for HRQOL effects, this equates to 8.58 years of life, with virtually all deaths attributable to nonasthma-related causes (Table I). The model predicts a population average of 36.9% symptom-days, 4.6 acute episodes per person, and \$6400 in per-person, discounted, total direct costs over the 10-year period.

The addition of ICS increases discounted, quality-adjusted life to 7.58 QALYs. In addition, the proportion of days with symptoms (symptom days) are reduced to 21.8%, and the average patient has only 3.1 acute events. However, improved asthma morbidity occurs at an increased cost of \$13,000/year, which is primarily secondary to the cost of the medication (ICS). For our base-case analysis, if we assume a population with a starting age of 35 years receiving 200 µg of ICS twice per day (400 µg once per day) and a literature-based weighted average of the effect of ICS on BMD ($-0.00028 \text{ g/cm}^2/100 \text{ µg/y}$), we observed a minimal increase in the costs attributed to fractures (including hip) and its associated morbidity (\$76.00). Viewed in terms of an incremental cost-effectiveness ratio (ICER), we estimate an incremental cost of \$26,000 per QALY gained and \$14.00 per additional symptom-free day over a 10-year horizon of ICS compared with quick relievers alone.

Not surprisingly, the results are less favorable when one considers an older target population. The deleterious effects of ICS on bone health may become important among an elderly population who use ICS therapy for prolonged periods. The impact on the ICER is dependent on the dose of ICS, the duration of therapy, and the assumptions regarding the impact of ICS on BMD (Table II). When we extended the time horizon to the lifetime of the cohort, the ICER ratio increased by 60% (\$42,000/QALY). When we assumed the use of high-dose ICS (1000 µg/d) over the lifetime of an individual and incorporated the high estimate of the effect of ICS on published BMD values among an asthma population ($-0.00058 \text{ g/cm}^2/100 \text{ µg/y}$), the use of ICS is dominated by the alternative strategy (the use of quick relievers alone). Only when we consider this worst case scenario can the use of quick relievers alone be considered a better health value when decisions are made about the distribution of limited health care resources.

Sensitivity analysis

We modeled the effect of ICS on BMD as a continuous linear effect over time; sensitivity analyses examined 4 values of duration of therapy: (1) 10 years, (2) 20 years, (3) 30 years, and (4) a lifetime effect. As illustrated in Fig 1, A, the incidence of hip fracture begins to increase significantly when the time horizon is extended to 30 years or beyond, even among populations not using ICS preparations. With the institution of ICS, although the

TABLE I. Base-case analysis (400 µg/d, weighted average of ICS effects on BMD): cohort of 10,000 women starting at age 35 years over various time horizons

	10 y		30 y		Lifetime	
	no ICS	ICS	no ICS	ICS	no ICS	ICS
Fracture-related morbidity per 1000 persons						
Hip fracture	0.3	0.4	8.7	11.6	192	240.6
Other fracture	6.2	6.8	135.8	180.1	1059	1033
Asthma-related mortality	0.004	0.003	0.013	0.009	0.013	0.021
Hip fracture mortality	0.06	0.07	1.7	2.3	38.4	48.1
Other fracture mortality	0.2	0.2	4.9	6.5	38.1	48
Asthma-related outcomes						
% Symptom days	36.9	21.8	36.8	21.8	36.5	21.5
Average n ED visits	0.8	0.6	2.6	1.71	4.0	2.6
Average n hospitalizations*	0.2	0.1	0.7	0.44	1.0	0.7
Average n urgent care visits	3.8	2.6	11.7	7.81	18.4	11.9
Average months of life (discounted)	102.7	102.9	229.7	229.9	285.5	284.7
Discounted QALM	87.8	90.9	195.4	201.8	239.4	245.6
Discounted symptom days	1136	672	2537	1500	3124	1836
Costs, discounted						
Acute asthma care cost (\$)	1140	769	2689	1786	3404	2331
Chronic asthma cost, without drug (\$)	5184	5187	11,574	11,573	14,252	14,158
Total fracture-related costs (\$)	71.5	76	1427	1829	12,609	16,477
Drug cost (\$)	0	6955	0	15,517	0	18,985
Total cost (\$)	6396	12,988	15,689	30,705	30,265	51,950
Cost-effectiveness ratios						
Cost per QALY gained (\$/QALY)	—	26,040	—	27,948	—	41,952
Cost per SFD gained (\$/SFD)	—	14.2	—	14.5	—	16.8

ED, Emergency department; SFD, symptom-free day.

*The number of ED visits listed includes visits that did and did not result in hospital admission.

proportion of health care costs associated with acute asthma-related events decreases, the proportion of health care costs associated with hip fracture and its morbidity increase (Fig 1, B). However, the effect of ICS on BMD and the resultant increase in ICER are meaningful only when patients reach an age >65 years and are attenuated when one does not assume a continuous linear effect of ICS on BMD. In sensitivity analyses, assumptions regarding the dose and effect of ICS on BMD had the most impact on the ICER, whereas the baseline level of bone health in the population had only a small influence on the ICER of ICS use in asthma (Fig 2).

Validation of model: direct effect of ICS on hip fracture

We examined the association between ICS and hip fracture indirectly by combining the possible association of ICS on BMD with the relationship between BMD and hip fracture rates. To validate our model-based approach, we compared our results with those published by Hubbard et al⁸ on the direct relationship between ICS use and hip fracture rates. Hubbard et al⁸ reported a case-control study among an elderly population; the mean age of the cases was 79.⁸ When adjusting for use of oral corticosteroids, Hubbard et al⁸ observed an increased risk of hip fracture associated with ICS use (odds ratio [OR], 1.19; CI, 1.10–1.28). When we examined the effect of ICS on a population whose starting age was similar (75 years) and treatment for 3 years, we observed only a minimal increase in the

odds for hip fracture associated with ICS use (OR, 1.01). However, Hubbard et al⁸ reported that the median duration of prescribing data available for the population was only 2.7 years; it is likely that individuals used ICS for longer than the ~3-year period available in the database. Therefore, we repeated our analysis (400 µg ICS/d, weighted average estimate of ICS on BMD) and assumed a longer duration of therapy. We observed the odds of hip fracture increased to an OR of 1.06 and an OR of 1.15 for 10 years (starting therapy at age 65 years) and 20 years (starting therapy at age 55 years) of therapy, respectively; estimates were similar to those reported by Hubbard et al⁸ (Table III).

DISCUSSION

Our results suggest that ICS therapy in women with mild-to-moderate asthma compares favorably with other uses of health care resources. As an example, Medicare has recently approved lung volume reduction surgery on the basis of the results of the National Emphysema Treatment Trial. Results of that trial showed the cost for lung volume reduction surgery, even when restricted to the subpopulation with the greatest benefit, those with upper-lobe–predominant disease, was \$98,000 per QALY gained over a 2-year period.³² Similarly, the cost of treatment with bisphosphonates for women age 50 years with a high risk of hip fracture is estimated to be \$130,000/

TABLE II. Incremental cost-effectiveness ratio (\$/QALY) varied across assumptions of ICS dose and effect on monthly rate of decline in BMD

Duration of ICS therapy	No effect 200 µg/d	Weighted average 200 µg/d	High estimate* 200 µg/d	No effect 400 µg/d	Weighted average 400 µg/d	High estimate* 400 µg/d	No effect 1000 µg/d	Weighted average 1000 µg/d	High estimate* 1000 µg/d
10 y	\$15,000	\$15,000	\$15,100	\$26,000	\$26,000	\$26,100	\$61,000	\$61,200	\$61,500
20 y	\$15,000	\$15,100	\$15,300	\$26,000	\$26,300	\$26,900	\$60,800	\$62,900	\$66,500
30 y	\$15,000	\$15,700	\$16,800	\$26,000	\$28,000	\$31,000	\$60,900	\$72,100	\$99,700
Lifetime	\$15,000	\$21,300	\$32,000	\$26,000	\$42,000	\$84,000	\$61,300	\$191,700	Dominated†

*Maximal value obtained from studies among subjects with asthma (-0.00058 g/cm²/y/100 µg).

†Dominated strategies: strategies that are more expensive and deliver fewer benefits than some other approach or combinations of approaches.

QALY. Alternatively, screening exercise electrocardiography in 60-year-old asymptomatic but high-risk subjects, eg, men with diabetes, hypertension, and smoking, has been estimated to cost \$41,600/QALY.³³ However, we found that the use of high-dose ICS over extended periods can influence the overall costs and health of a population with asthma, a result that highlights the importance of using the lowest possible dose of ICS needed to achieve asthma control. This is further supported by the dose-response curve for ICS efficacy among those with mild-to-moderate persistent asthma. Evidence suggests that the dose-response curve plateaus, with the majority of the benefit achieved at low doses (eg, fluticasone propionate 200 µg/d).^{4,34,35}

Although the impact of ICS on BMD is still controversial, evidence of the impact of oral corticosteroids on bone metabolism and the hypothalamic-pituitary-adrenal axis has generated continued concern about the use of ICSs.^{36,37} Although the use of ICS minimizes the systemic effects, all inhaled preparations have documented systemic absorption,^{4,38} and ICS preparations may have deleterious effects when used at high doses over long periods.³⁹ In addition, individuals may differ in their responses to both the therapeutic and to toxic effects, even at more moderate doses.^{40,41} In a randomized trial of inhaled steroid preparations, 6 subjects (4 %) met the criteria for early study withdrawal by demonstrating a rate of bone loss at the lumbar spine of $\geq 5\%$, suggesting that some individuals may be more susceptible than others to the systemic effects of ICS.⁴²

Our model-based analysis allows evaluation of the range of parameters considered to influence the potential association between ICS use and bone health. As an illustration, we compared the results of our modeling exercise with the results of 2 published case-control studies on the relationship between ICS use and rates of hip fracture. Suissa et al⁷ published a case-control analysis within a population-based cohort who received at least 1 respiratory medication and was followed for at least 4 years. Similar to our estimates, they observed no significant effect of short-term ICS use on hip fracture risk when they adjusted for age, sex, and use of other medications, including oral corticosteroids. In contrast, Hubbard et al⁸ reported an association between ICS use and hip fracture rate in a similar case-control analysis. However,

if we made less favorable assumptions in estimating the effect of ICS on BMD and the duration of therapy, we demonstrated a risk of fracture similar to that published by Hubbard et al.⁸ ICS has been a pivotal therapy for asthma for over 2 decades. It is reasonable to assume that the elderly population included in the study by Hubbard et al⁸ may have been using ICS for longer than the 2.7 years suggested by the mean duration of dispensing data available for analysis.

We found that the potential detrimental effect of long-term ICS use on bone health is sensitive to assumptions about the baseline BMD and age of the target population. A decrease of 10% in the baseline BMD of the population increased the cost-effectiveness ratio for the use of ICS over a prolonged period. In addition, because the risk of hip fracture is associated with age,^{43,44} targeting patients with asthma at high risk of fracture for screening and initiation of prophylaxis may be warranted for individuals requiring long-term ICS therapy.

Our findings should be interpreted with some caution because they hinge on several uncertainties, most notably the efficacy of ICS therapy and its impact on bone health. Data on the effects of ICS on bone health are limited, with few placebo-controlled prospective trials having examined the impact of ICS on BMD and few comparing low-dose and high-dose ICS. Within the available literature, cross-sectional and retrospective studies are confounded by previous oral steroid use, variability of baseline BMD, and duration of therapy. Although we have conducted sensitivity analyses to explore the potential impact of variations in our assumptions, we acknowledge that our findings in this regard are speculative. They provide thresholds for the average decrements in BMD that have been documented with ICS use in a population.

Model-based analyses such as ours make it possible to synthesize data from multiple sources and offer a practical framework for managing uncertainty via sensitivity and what-if analysis.^{45,46} They also help to set priorities for further data acquisition⁴⁷ when the data available from traditional forms of investigation are inconclusive. Model-based analyses also permit the analyst to extrapolate beyond time horizons, geographic settings, and target populations.^{48,49}

A second limitation is that we did not assess the independent impact of oral corticosteroid bursts used in

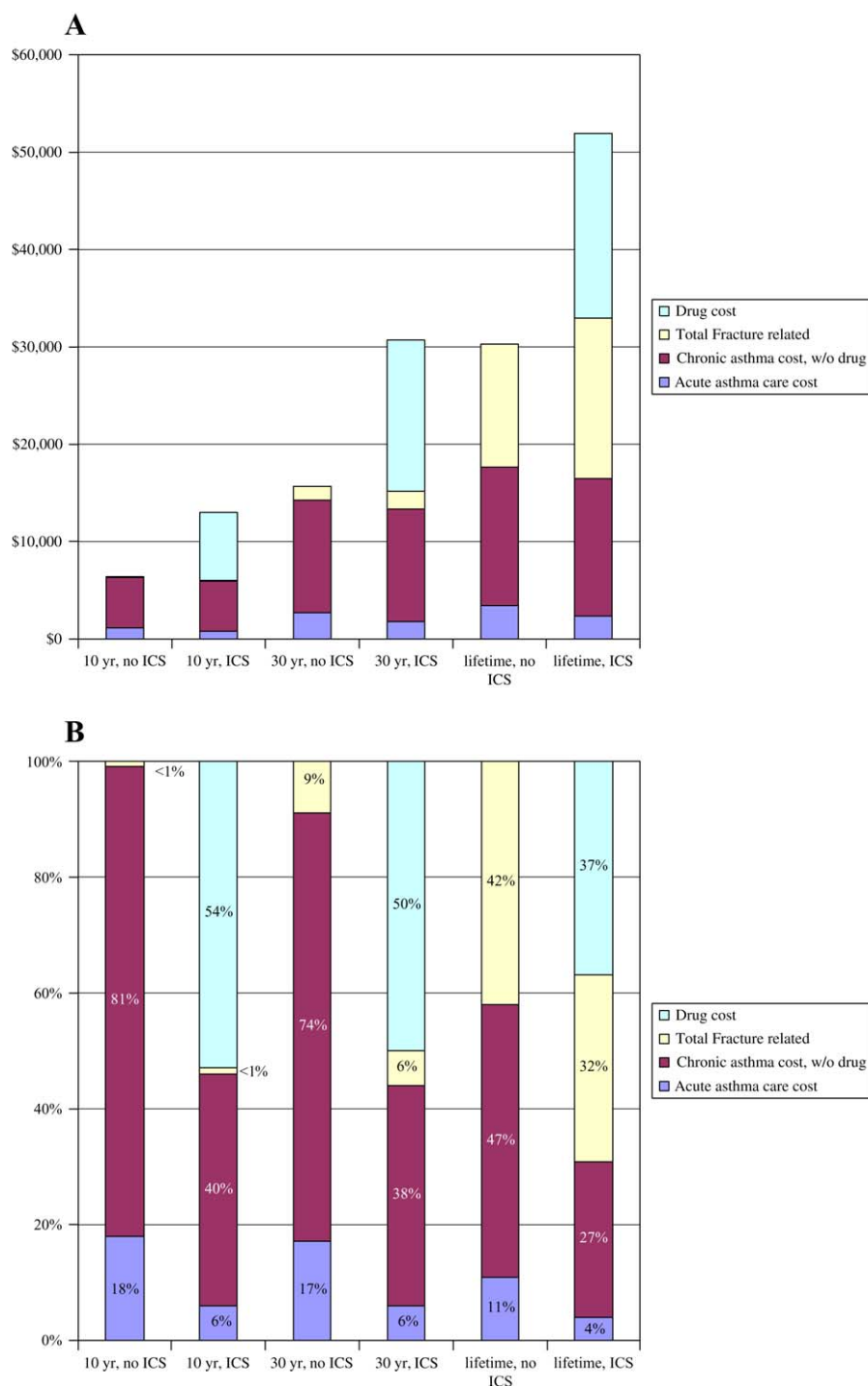


FIG 1. Cost components as a function of time. **A**, Actual costs (2003 US dollars) divided into cost components (fracture-related costs, chronic asthma-related costs [excluding drugs], acute event costs, and drug costs). **B**, Cost as a percentage of total costs. Example: for a lifetime horizon and no ICS, fracture-related costs were 42% of total costs, compared with 32% with ICS therapy.

the treatment of asthma exacerbations. ICS use is associated with a decreased risk of exacerbations, and therefore is associated with a decrease in the use of oral corticosteroid bursts. The inclusion of the impact of oral steroid use on bone health could alter the ICER in favor of ICS use. In

addition, our model examines the association between ICS and hip fracture indirectly by combining the effect of ICS on BMD with the relationship between BMD and hip fracture rates. BMD may capture only part of the impact of steroids on fracture risk. However, when we compare our

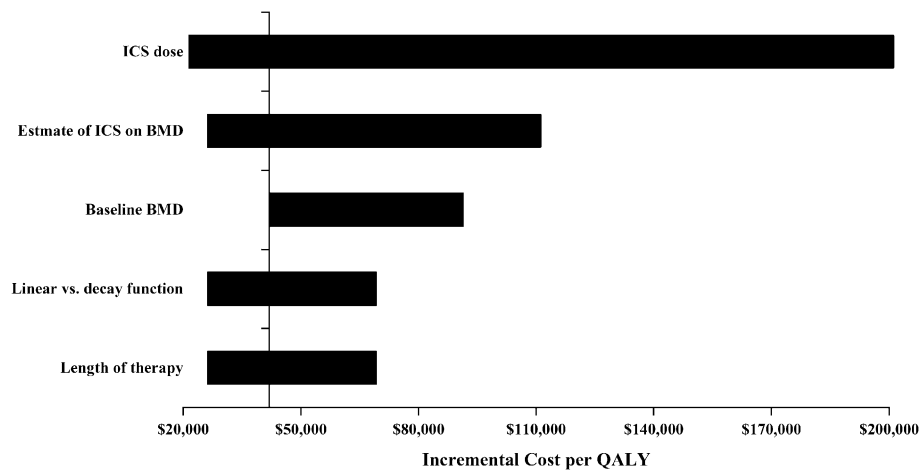


FIG 2. Incremental cost-effectiveness. The results of a series of 1-way sensitivity analyses are summarized in a tornado diagram. Each *horizontal bar* represents a given model parameter. The *vertical axis* sits at the base-case (400 μ g/d, weighted average of effect of ICS on BMD for a lifetime time horizon) incremental cost-effectiveness estimate (\$42,000/QALY). The length and position of a given horizontal bar denote the range of cost-effectiveness outcomes produced by varying that specific parameter over its plausible range.

TABLE III. Hip fracture incidence rate: impact of ICS therapy (base case = 400 μ g/d, weighted average of effect of ICS on BMD)

Starting age	Duration of ICS treatment	Risk of fracture in ICS treatment group	Risk of fracture in no-treatment group	OR
35	Lifetime	0.241	0.192	1.33
45	30 y	0.050	0.040	1.26
55	20 y	0.045	0.040	1.15
65	10 y	0.035	0.033	1.06
75	3 y	0.023	0.023	1.01

results with published analyses, which evaluated the direct effect of ICS use on fracture risk controlled for oral steroid use, our model-based estimates are consistent with these published results. We assembled cost data from a variety of sources, reflecting different patient populations and specific size, quality, and design limitations. As acknowledged previously in the initial development of our model, we estimated our HRQOL weights from relatively few studies. We used FEV₁ percent predicted as the primary severity marker, and other factors may independently predict use and HRQOL. Finally, we have limited our analysis to women. Yet the overall incidence of fractures in women climbs steeply and becomes twice that in men.²² Also, the available data on the relationship between BMD and fracture risk are best defined among female populations.

CONCLUSION

Although the economic attractiveness of ICS therapy is dependent on assumptions regarding the impact of ICS on BMD and resultant fracture rate, ICS therapy in mild/

moderate asthma compares favorably with commonly accepted interventions over a wide range of assumptions regarding this treatment. Because of the potential impact of high doses of ICS over prolonged periods, risk can be minimized by using the lowest effective dose and by identifying high-risk individuals for appropriate intervention.

GLOSSARY^{26,45,50}

Markov model (Markov, state transition simulation).

A simulation that models chronic disease, such as asthma, as a series of health states. The natural history of a disease is modeled as a series of transitions between health states over time.

Quality-adjusted life-years (QALYs). A health outcome measure that combines quality of life, as determined by some valuation process (eg, time tradeoff), and length of life. One year in perfect health equals 1 QALY or 12 quality-adjusted life-months (QALMs). One year in a health state that is rated by the patient as 40% of perfect health equals 0.4 QALY (or 4.8 QALMs).

Cost-effectiveness ratio. The added cost of attaining a unit of health effect. The numerator represents the cost difference between the health care intervention and its alternative, whereas the denominator is the difference in health effect (ie, clinical or quality of life outcome), measured in natural units, between the intervention and its alternative. In this study, cost-effectiveness ratios are reported in cost per QALY and cost per symptom-free day.

Time tradeoff. A quality of life (utility) measure derived by asking patients a series of questions; the responses result in an expression of the value of time spent in the current health state in terms of time spent in perfect health.

Direct cost. The value of all goods, services, and other resources that are consumed in the provision of an intervention or in dealing with the side effects or other current and future consequences linked to it.

Indirect costs (also known as *productivity costs*). The value of lost time or reduced productivity resulting from morbidity or premature mortality because of a medical condition or treatment as well as the value of informal care-giving costs.

Discount rate (annual). The rate used to convert both future costs and future health effects to their current values.

Dominated strategies. Strategies that were more expensive and delivered fewer benefits than some other approach or combinations of approaches.

Sensitivity analysis. A series of repeated analyses in which input data are systematically varied across a range of values. This can assess how variation in important input variables and assumptions affects the cost-effectiveness ratio.

Base case. The baseline analysis to which alternative scenarios are compared when performing the sensitivity analysis.

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