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A real-life cost-effectiveness evaluation of budesonide/formoterol maintenance and reliever therapy in asthma

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Summary
Objective: To evaluate direct asthma-related costs in Swedish primary care in a real-life setting.
Design: 12-month open-label study.
Setting: Swedish primary care in a real-life setting.
Participants: 1776 patients with persistent asthma.
Interventions: Patients with persistent asthma were randomised to one of three treatments: a free adjustable combination of budesonide (100–400 μg/inhalation) and formoterol (4.5 or 9 μg/inhalation) via separate inhalers plus terbutaline as needed; budesonide/formoterol (160/4.5 μg or 80/4.5 μg, two inhalations twice daily) plus terbutaline as needed; budesonide/formoterol (160/4.5 μg or 80/4.5 μg, one inhalation twice daily or two inhalations once daily), for maintenance plus additional inhalations as needed. Doses depended on previous inhaled corticosteroid dose. Patients attended the clinic at 0, 1.5, and 12 months. Telephone interviews were conducted at 4, 6, 8, and 10 months.
Main outcome measures: The primary endpoint was direct asthma-related healthcare costs.
Results: Statistically significant reductions in annual direct costs per patient were observed with budesonide/formoterol maintenance and reliever therapy compared with the free adjustable combination of budesonide and formoterol (−13%, $P<0.001$) and fixed-dose budesonide/formoterol plus terbutaline (−20%, $P<0.001$). Time to first severe exacerbation did not differ

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significantly across treatment groups, with a mean reduction of 28% versus the free adjustable combination of budesonide and formoterol ($P=0.076$). Patients receiving budesonide/formoterol maintenance and reliever therapy used a significantly lower daily dose of budesonide compared with the conventional ($P<0.001$).

Conclusions: This study reports direct cost savings with budesonide/formoterol maintenance and reliever therapy compared with conventional treatment regimens with at least equivalent efficacy.

Introduction

Global asthma treatment guidelines recommend an inhaled corticosteroid (ICS) for the treatment of persistent asthma with a short-acting β_2-agonist (SABA) as needed for symptom relief. For patients not well controlled by this treatment, addition of a long-acting β_2-agonist (LABA) is recommended.[1]

Budesonide/formoterol (Symbicort®) as both maintenance and reliever therapy (Symbicort SMART®) promotes the use of ICS in proportion to disease severity, with low doses used during periods of asthma control and higher doses used in response to breakthrough symptoms. This ensures treatment of the underlying inflammation of asthma with every inhalation. This treatment concept is simple for patients to use[2] and is one treatment option recommended in the latest Global Initiative for Asthma guidelines for use in patients not controlled on ICS alone.[1] Budesonide/formoterol maintenance and reliever therapy has been investigated in a number of large-scale clinical trials[3–9] and is approved for use in adult patients (≥18 years) in the European Union.

Concerns have been raised regarding the impact of the reliever therapy on total treatment cost in routine asthma care since budesonide/formoterol costs more per inhalation than SABA as reliever medication.[10] Furthermore, treatment with budesonide and formoterol in separate inhalers may facilitate down-titration of the individual components, resulting in lower total drug use and lower costs compared with budesonide/formoterol as both maintenance and reliever.

Health economic evaluations using efficacy studies as the primary data source have suggested that budesonide/formoterol maintenance and reliever therapy is cost-effective compared with other treatment options recommended in current guidelines.[10–13] Studies primarily designed to address clinical efficacy might, however, be associated with a number of disadvantages when deriving conclusions related to health economics.[14] Although other studies have assessed the efficacy of asthma therapies in a real-life setting,[15,16] none, to our knowledge, has used costs as the primary endpoint in a study of real-life practice. Thus, the aim of this 12-month Swedish study was to evaluate the direct asthma-related costs incurred in a real-life setting in primary care, with budesonide/formoterol maintenance and reliever therapy compared with two conventional asthma treatment regimens: free adjustable or fixed combinations of ICS and LABA plus SABA as needed. Secondary objectives were to compare indirect costs and investigate patient- and physician-reported outcomes, efficacy, and safety in the treatment groups.

Materials and methods

The Symbicort and Health Economics in a Real Life Evaluation (SHARE) study was a 12-month, randomised, open-label, parallel-group study (study code NCT00259766). The primary endpoint was direct asthma-related costs and the study was designed to minimise the impact of the study procedure on the behaviour of both physicians and patients, on patient treatment, and on treatment cost.

Study design

The study evaluated three treatment alternatives.

(1) A free combination of budesonide (Pulmicort®; AstraZeneca, Sweden) Turbuhaler® (100–400 μg/inhalation) and formoterol (Oxis®; AstraZeneca, Sweden) Turbuhaler (4.5 or 9 μg/inhalation) plus terbutaline (Bricanyl®; AstraZeneca, Sweden) as needed (0.25 or 0.5 mg/inhalation) at an appropriate dose according to asthma severity as judged by the investigator. Budesonide and formoterol doses could be adjusted up or down within the approved dose range throughout the study at the discretion of the investigator. However, in contrast to formoterol, budesonide was not permitted to be completely withdrawn.

(2) Budesonide/formoterol 160/4.5 μg or 80/4.5 μg (Symbicort®; AstraZeneca, Sweden), depending on previous ICS therapy, two inhalations twice daily plus terbutaline as needed (0.25 or 0.5 mg/inhalation).

(3) Budesonide/formoterol 160/4.5 μg or 80/4.5 μg (Symbicort®), depending on previous ICS dose, one inhalation twice daily or two inhalations once daily for maintenance plus additional inhalations as needed (Symbicort SMART®; AstraZeneca, Sweden).

Budesonide/formoterol maintenance and reliever therapy was investigated with both a twice-daily regimen and a once-daily regimen to evaluate if either was superior with respect to efficacy or patient compliance. However, the main analysis, as defined by the study protocol, compared the three treatment regimens using merged data from the two budesonide/formoterol maintenance and reliever treatment groups.

This study was conducted according to the Declaration of Helsinki and Good Clinical Practice guidelines at 222 primary care centres and paediatric out-patient clinics (195 and 27, respectively) in Sweden. The study protocol, patient information, and consent forms were approved by an ethics committee. All patients gave written informed consent. The first patient was enrolled on 5 April 2004 and the last patient completed the study on 12 May 2007.

Patients had three scheduled clinic visits at 0, 1.5, and 12 months after randomisation. Furthermore, telephone interviews were conducted by a trained independent interviewer at 4, 6, 8, and 10 months (±14 days). This pre-empted the need for patient diaries and maximised adherence to a real-life environment. Patients randomised to receive any treatment including budesonide/formoterol were stratified according to baseline ICS dose. Those previously treated with ICS 400–500 μg/day were allocated to treatment with the budesonide/formoterol Turbuhaler (80/4.5 μg delivered dose) and those previously treated with ICS >500 μg/day were allocated to the budesonide/formoterol Turbuhaler (160/4.5 μg delivered dose). Even though all medications were prescribed by the investigator for 1 year, the patient had to visit the pharmacy repeatedly to collect the required drugs as in usual clinical practice. In order to avoid any risk of additional medication costs related to the study, both patients and county councils were compensated after the patient completed the study. In Sweden, county councils are responsible for funding medical treatment as well as paying drug costs, but do not carry the burden of sick-leave costs.

Patient characteristics

Male and female outpatients aged ≥12 years with a diagnosis of asthma as defined by the American Thoracic Society[17] and using a constant daily dose of ICS (≥400 μg) for ≥30 days prior to randomisation were eligible for inclusion. Patients were also required to have persistent asthma and to be receiving daily maintenance treatment with a free combination of an ICS and a LABA, or to be symptomatic despite regular use of an ICS alone. Study exclusion criteria included treatment with a fixed combination of budesonide/formoterol or salmeterol/fluticasone in the year preceding randomisation. Patients using oral corticosteroids within the 30 days prior to randomisation, those with a smoking history of >10 pack-years, and individuals with any disease or disorder which may be affected by study medication were also excluded from the study.

Randomisation and blinding

The randomisation scheme was computer generated at AstraZeneca Research and Development, Alderley Park, UK. At each centre patients were randomised strictly sequentially as they became eligible. Coded envelopes with individual treatment codes stating the treatment allocation for each randomised patient were provided. Any patient requiring >10 inhalations of as-needed medication on any 1 day was instructed to contact the investigator.

Patient- and physician-reported outcomes

At visit 1, patients were provided with a copy of a five-item asthma control questionnaire (ACQ),[18,19] and at each subsequent contact were asked for their responses by the investigator or the telephone interviewer. At each contact patients were also asked to complete a questionnaire regarding their asthma symptoms, ranging from 'no symptoms' to 'very severe symptoms'. At visits 1 and 3 patients were requested to rate their asthma status according to a four-point scale, ranging from 'not at all controlled' to 'very well controlled'. A physician-reported 'treatment change' was defined as a change in the prescribed study medication outside the study protocol and lasting for more than 30 days.

Clinical effectiveness and safety

The measure to determine clinical effectiveness in the cost-effectiveness analysis was the number of patients suffering at least one exacerbation during 1 year. An exacerbation was defined as deterioration in asthma resulting in a hospitalisation/emergency room visit or the use of oral corticosteroids due to asthma. Any patient experiencing more than three exacerbations was considered for a change in maintenance medication.

Since the primary objective of the study was to capture real-life costs and effects, collection and reporting of adverse events was limited to serious adverse events (SAEs) and discontinuations due to an adverse event (DAEs). Previously, several studies have reported that budesonide, formoterol, and budesonide/formoterol maintenance and reliever therapy are well tolerated in patients with moderate to severe asthma.[3–9]

Cost-effectiveness analysis

The cost-effectiveness analysis was performed from a county council perspective, taking into account only direct costs as the primary endpoint and using number of patients suffering at least one exacerbation as the effectiveness measure. The study was not powered to capture differences in asthma-related sick leave.

Healthcare resource utilisation

Direct resource use consisted of prescribed study medication collected from the pharmacy, use of other asthma medication, number of contacts (telephone or visit) with a nurse or physician due to asthma or treatment for asthma, and number of asthma-related hospitalisations/emergency room visits. Patients were required to record all information related to the use of additional asthma medication, sick leave related to asthma, or asthma-related use of healthcare resources. Patients were asked about any use of oral steroids at each visit and were further asked at each telephone interview about any hospitalisations/emergency room visits since last contact. At each contact after visit 1, patients were also asked about their use of asthma medication during the previous 24 h. The investigator was responsible for ascertaining all medications and resources used during hospitalisations/emergency room visits.

Patients were instructed to retain all used, unused, and current drug medication containers both for study drug collected from the pharmacy and for any additional asthma medication. These were handed to the investigator at visit 3. In addition, patients were instructed to record any use of additional asthma medication or healthcare resources. Investigators were also instructed to ask patients at visits 2 and 3 regarding the use of any additional asthma medication. Patients experiencing a 'treatment change', as defined previously, were followed for the entire study period as long as they remained willing to participate. Scheduled study visits were omitted from the resource use analysis as these were likely to have been protocol driven and thus not representative of normal clinical practice. Indirect asthma-related resource loss comprised number of days absent from work for employed patients or caregivers (<65 years) that were due to the patient's asthma.

Unit costs

Costs were quantified in Swedish Kronor (SEK). Healthcare costs were calculated as the quantity of each resource used multiplied by the corresponding unit cost in SEK derived in 2006 (Table 1). In Sweden, current regulations require that pharmacies provide the lowest-priced substitutable drug, according to the list of substitutable medicinal products defined by the Medical Products Agency, with the pricing system allowing prices to change every month. As parallel importation of medicines occurs widely in Sweden, it was decided to use the prices actually paid for medicines in order to reflect the actual costs incurred by the county councils and patients. Hence, the unit costs used for medication reflect the actual prices paid during 2006, including patients' co-payment. The unit costs were calculated by dividing the total costs for the present drugs, provided by the pharmacies during 2006, with the total number of provided doses during the same period. Indirect resource loss was measured as days of sick leave and was estimated using the national average daily wage, including social benefits. A part-time worker was assumed to work 60% of full time.

Statistical and economic analysis

The sample size calculation was based on the primary outcome variable. With a two-sided test, a significance level of 5%, and a power of 80%, a sample size of 394 patients per treatment group was determined based on the need to find a difference of 500 SEK (~€50) per patient. This difference was considered by the study advisory board to be a relevant difference in cost between treatments for the Swedish healthcare system. Analyses were based on the full analysis set. All randomised patients who received at least one dose of prescribed study medication and who generated at least one data point after randomisation were included in the full analysis set.

The group mean approach was used, in which means were calculated as the sum of all resource use (and cost) in the group divided by the total observation time for the group (in days) and scaled to 1 year. Significance tests and confidence intervals were calculated using the bootstrap method, a re-sampling procedure.[20] The costs were calculated from resource usage by applying defined unit prices, which were defined prior to the clinical trial database being locked for analysis. As the study did not assess outcomes or costs after 12 months, discounting was not applied. The secondary variables were analysed by analysis of covariance with treatment and centre as factors and baseline value as covariate. The efficacy variables (number of patients with an asthma exacerbation and number of treatment failures) were analysed using a Cochrane–Mantel–Haenzel test. Sensitivity analysis was conducted for each included cost parameter by adjusting the base case unit price.

Results

Patient characteristics

A total of 1776 patients with persistent asthma were enrolled and randomised, as shown in the CONSORT

Table 1 Unit costs (SEK, year 2006 values)

Type of cost	Unit	Cost, SEK
Absence from work, assisting person, full-time worker	Day	2126[22,23a]
Absence from work, full-time worker	Day	2126[22,23a]
Absence from work, part-time worker	Day	1276[22,23b]
Telephone contact with physician	Contact	313[24]
Telephone contact with nurse	Contact	128[24c]
Primary care physician	Visit	820[25d]
Nurse	Visit	335[25]
Unplanned/emergency visit	Visit	820[24e]
Hospitalisation (general care unit), low specialised care	Bed day (inpatient)	6097[25]
Budesonide/formoterol 80/4.5 μg	Dose	4.40[26,27f]
Budesonide/formoterol 160/4.5 μg	Dose	4.67[26,27f]
Budesonide/formoterol 320/9 μg	Dose	9.68[26,27f]
Formoterol 4.5 μg	Dose	3.52[26,27f]
Formoterol 9 μg	Dose	4.23[26,27f]
Terbutaline 0.25 mg	Dose	0.76[26,27f]
Terbutaline 0.5 mg	Dose	0.74[26,27f]
Budesonide 100 μg	Dose	1.28[26,27f]
Budesonide 200 μg	Dose	1.88[26,27f]
Budesonide 400 μg	Dose	3.39[26,27f]

[a] A full-time worker is assumed to work 8 h per day.
[b] A part-time worker is assumed to work 60% of full time.
[c] Assuming the same ratio as of visits.
[d] Ratio of visit to other healthcare contact/visit to physician = 0.41.
[e] Assuming the same cost as a physician visit.
[f] Based on actual sales (including parallel import). $1.00 = SEK 5.895; €1.00 = SEK 9.304 xe.com, 23 May 2008).

diagram in Fig. 1. The treatment groups were well balanced with respect to demographics, clinical status, baseline ICS use (mean 641 μg/day), and previous LABA prescriptions (Table 2). Results for both dosing regimens of budesonide/formoterol maintenance and reliever treatment were combined, according to the study protocol. No significant differences in any measured baseline parameters were detected in a subgroup analysis between the once-daily and twice-daily dosing regimens.

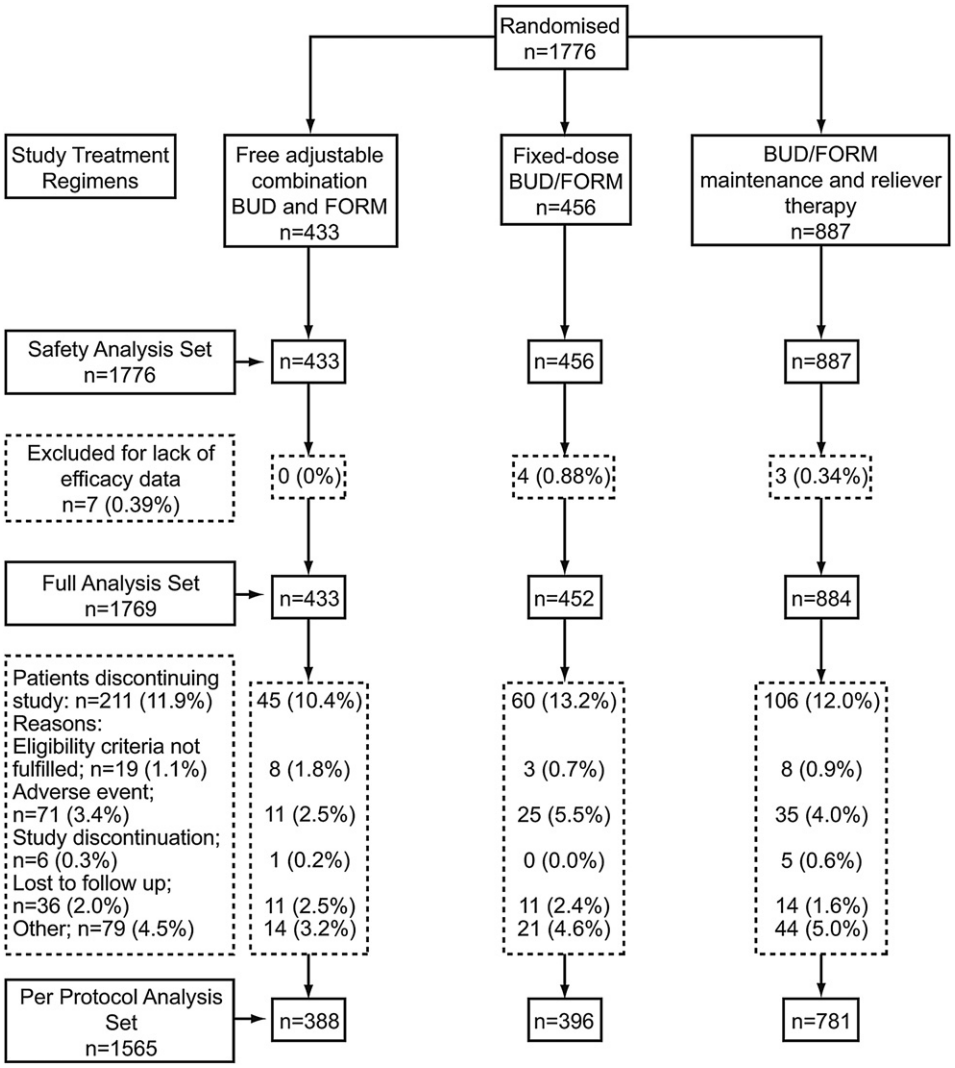

Figure 1 Study design and patient flow. Figures in parentheses are percent of patients randomised. Study discontinuation criteria indicate patients who developed study-specific discontinuation criteria. **Analysis sets.** *Safety Analysis Set:* All patients randomised irrespective of whether they did or did not receive study treatment. *Full Analysis Set:* All randomised patients who received at least one dose of study medication and generated at least one data point after randomisation. **Study protocols**. *Free adjustable combination of budesonide and formoterol:* Budesonide (100—400 μg/inhalation) and formoterol (4.5 or 9 μg/inhalation) in separate inhalers (usual care in Sweden) (at an appropriate dose according to asthma severity, as judged by the investigator) plus terbutaline as needed. *Fixed-dose budesonide/formoterol:* Patients on 400—500 μg ICS/day at randomisation: Budesonide/formoterol 80/4.5 μg, two inhalations twice daily plus terbutaline as needed. Patients on > 500 μg ICS/day at randomisation: Budesonide/formoterol 160/4.5 μg, two inhalations twice daily plus terbutaline as needed. *Budesonide/formoterol maintenance and reliever therapy:* Includes treatment with budesonide/formoterol one inhalation twice daily plus as needed and budesonide/formoterol two inhalations once daily plus as needed. Patients receiving 400—500 μg ICS/day at randomisation received budesonide/formoterol 80/4.5 μg, one inhalation twice daily plus as needed or budesonide/formoterol 80/4.5 μg, two inhalations once daily plus as needed. Patients receiving > 500 μg ICS/day at randomisation received budesonide/formoterol 160/4.5 μg, one inhalation twice daily plus as needed or budesonide/formoterol 160/4.5 μg, two inhalations once daily plus as needed. No significant differences were observed between results for the two budesonide/formoterol maintenance and reliever therapy arms and both protocols were equally effective. Furthermore, both once and twice daily dosing regimens with budesonide/formoterol maintenance and reliever therapy are approved treatments in Sweden. The data for the two budesonide/formoterol maintenance and reliever therapy arms were therefore combined for analysis.

Table 2 Patient demographics and characteristics

	Free adjustable combination of budesonide and formoterol	Fixed-dose budesonide/ formoterol	Budesonide/ formoterol maintenance and reliever therapy
No. of patients			
Randomised	433	456	887
Full analysis set	433	452	884
Per protocol set	388	396	781
No. of adolescents (12–19 years)	66	65	127
Sex, % women	59	56	60
Mean age, years	43	45	43
Employment, *n* (%)[a]			
Full-time	182 (42)	191 (42)	373 (42)
Part-time	61 (14)	47 (10)	118 (13)
Non-employed[b]	190 (43)	214 (47)	393 (45)
Peak expiratory flow, l/min	465	461	462
Forced expiratory volume in 1 second, % predicted normal post-bronchodilator	96	97	95
Long-acting β_2-agonist use, %	51	52	52
Inhaled corticosteroid, μg/day			
400–500/>500, at inclusion, %	50/50	51/49	51/49
Daily dose[c] (SD) at inclusion	640 (285)	650 (315)	636 (293)
Daily dose[d] during treatment (according to phone interviews)	550	368	291

[a] Based on full analysis set.
[b] Non-employed includes: student, house-person, retired/long-term sick leave, and unemployed.
[c] Metered dose.
[d] Delivered dose.

Healthcare resource utilisation and cost analysis

Few patients utilised non-medication healthcare resources and no significant differences were observed in non-medication resource use between the treatment groups (Table 3). A total of 23% of patients visited their physician during the study (excluding study visits) and 4% visited their nurse. In addition, 15% and 6% of patients had telephone contact with the physician or nurse, respectively. A total of 15% of patients had an unscheduled emergency room visit and only <0.5% were hospitalised due to asthma.

Annual direct costs per patient were significantly lower with budesonide/formoterol maintenance and reliever therapy compared with either the free adjustable combination of budesonide and formoterol plus SABA as needed (−795 SEK, $P < 0.001$) or the fixed-dose budesonide/formoterol plus SABA as needed (−1335 SEK, $P < 0.001$) (Fig. 2). Furthermore, analysis of direct-cost components showed that >85% of direct costs were attributable to asthma medication in all treatment groups. The remaining direct costs were predominantly comprised of asthma-related physician visits and unscheduled emergency room visits (Table 4).

Sensitivity analysis was conducted for each included cost parameter by adjusting the base case unit price. An increase of 18% of the price for budesonide/formoterol would offset the difference in total direct costs. Similarly, a decrease in the price of budesonide by 28% or a decrease of the formoterol price by 38% would offset the direct cost difference. Changing any other unit price had a negligible impact on the total direct costs.

The difference in total cost, including both direct and indirect costs, did not reach statistical significance in any comparison between treatment groups. However, the study was not powered to capture any difference in asthma-related sick leave and only a few patients were cost drivers and contributed to the major part of the indirect costs.

Exacerbations

No significant differences in the time to first exacerbation were observed between the three treatment groups (Fig. 3). A positive trend in favour of budesonide/formoterol maintenance and reliever therapy compared with the free adjustable combination of budesonide and formoterol plus SABA as needed was observed (28% risk reduction; $P = 0.076$). No statistically significant difference was found between budesonide/formoterol maintenance and reliever therapy and the fixed-dose budesonide/formoterol group (23% risk reduction; $P = 0.17$). The rate of severe exacerbations was similar in the three treatment groups (Table 5). The percentage of hospitalisations/emergency room visits and use of oral steroids were similar in the three treatment groups.

Table 3 Resource use per patient per year by treatment group

	Free adjustable combination of budesonide and formoterol, $n = 433$	Fixed-dose budesonide/formoterol, $n = 452$	Budesonide/formoterol maintenance and reliever therapy, $n = 884$
Hospitalisation, days	0.010	0.000	0.007
Unplanned/emergency visits	0.295	0.346	0.448
Visit to primary care physician	0.811	0.466	0.511
Visit to primary care nurse	0.102	0.058	0.084
Telephone contact with physician	0.334	0.464	0.284
Telephone contact with nurse	0.120	0.146	0.152
Absence from work, days (patient)	1.874	1.266	2.317
Absence from work, days (assistant)	0.113	0.080	0.028
Number of inhalers			
Budesonide/formoterol 80/4.5 μg	0	4.576	3.648
Budesonide/formoterol 160/4.5 μg	0.005	5.115	4.158
Budesonide/formoterol 320/9 μg	0	0.017	0.007
Budesonide 400 μg	2.487	0.008	0.004
Budesonide 200 μg	2.98	0.025	0.009
Budesonide 100 μg	0.026	0	0
Formoterol 9 μg	3.765	0.016	0
Formoterol 4.5 μg	5.038	0.008	0.01
Terbutaline 0.5 mg	1.118	1.052	0.003
Terbutaline 0.25 mg	0.724	0.715	0

Use of ICS and reliever medication

Patients receiving budesonide/formoterol maintenance and reliever therapy used a significantly lower daily dose of budesonide compared with either the free adjustable combination of budesonide and formoterol plus SABA as needed or with fixed-dose budesonide/formoterol plus SABA as needed ($P < 0.001$); 291 μg/day (delivered dose), 550 μg/day (estimated delivered dose), and 368 μg/day (delivered dose), respectively (reported average use based on the telephone interviews).

Patients used approximately 0.7 rescue inhalations in the 24 h prior to each contact in all treatment groups. There was no difference in reported reliever medication use between treatment groups and no change in the pattern of reliever medication use was observed over the study period.

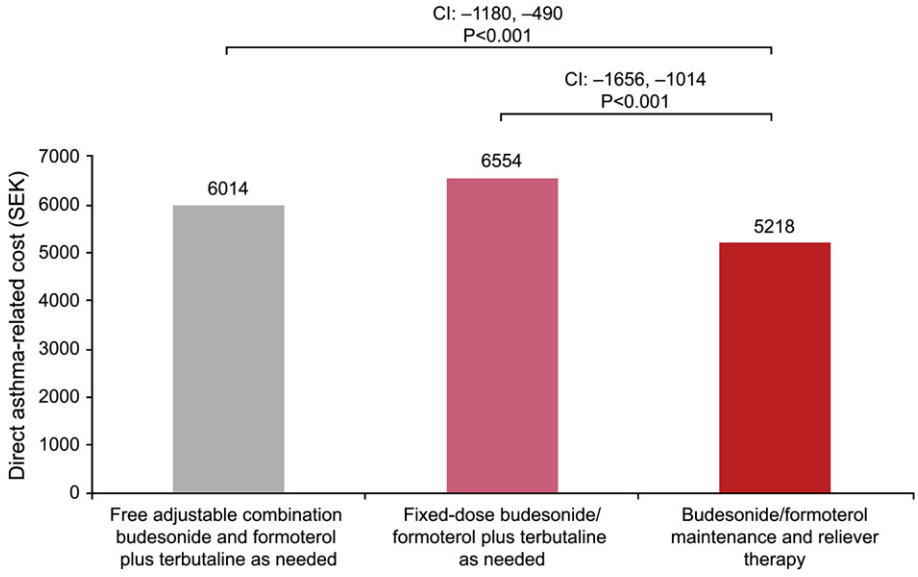

Figure 2 Direct asthma-related costs. $1.00 = SEK 5.895; €1.00 = SEK 9.304 xe.com, 23 May 2008).

Table 4 Costs per patient per year

	Free adjustable combination of budesonide and formoterol, $n = 404$	Fixed-dose budesonide/formoterol, $n = 412$	Budesonide/formoterol maintenance and reliever therapy, $n = 821$	Budesonide/formoterol maintenance and reliever therapy versus free adjustable combination of budesonide and formoterol		Budesonide/formoterol maintenance and reliever therapy versus fixed-dose budesonide/formoterol	
	Cost (SEK)	Cost (SEK)	Cost (SEK)	Difference	*P*-value	Difference	*P*-value
Total asthma medication	5282	5848	4474	−807	<0.001	−1374	<0.001
Hospitalisation	47	0	69	22	0.726	69	<0.001
Unplanned/emergency visits	255	280	230	−25	0.592	−50	0.326
Visit to primary care physician	307	301	312	5	0.904	12	0.777
Visit to primary care nurse	16	21	31	15	0.097	10	0.412
Telephone contact with physician	90	90	88	−2	0.899	−3	0.885
Telephone contact with nurse	17	14	15	−2	0.583	1	0.819
Direct non-medication costs	732	706	744	12	0.915	38	0.712
Total direct costs	6014	6554	5218	−796	<0.001	−1336	<0.001
Indirect costs	2241	2066	3173	932	0.209	1107	0.094
Total costs	8255	8620	8391	137	0.855	−228	0.776

$1.00 = SEK 5.895; €1.00 = SEK 9.304 xe.com, 23 May 2008).

Patient- and physician-reported outcomes

Across all treatment groups, 55% and 24% of patients self-rated their asthma status as being quite well-controlled or very well-controlled at baseline, respectively. All treatment groups experienced an improvement in asthma status and asthma control questionnaire scores over the course of the study with a similar change from baseline observed in all treatment groups and no statistically significant differences between treatments.

Cost-effectiveness analysis

Budesonide/formoterol maintenance and reliever therapy was associated with the lowest direct costs (Table 6), and demonstrated the lowest number of patients suffering an exacerbation, compared with the other two treatment groups. The direct cost differences for budesonide/formoterol maintenance and reliever therapy compared with the free adjustable combination of budesonide and formoterol plus SABA and fixed-dose budesonide/formoterol plus SABA were −13% and −20%, respectively (both $P < 0.001$). Calculation of the incremental cost-effectiveness ratio was not relevant as budesonide/formoterol maintenance and reliever therapy showed at least as good efficacy at lower cost, hence being a cost-saving treatment option (Table 6).

Treatment change outside of protocol

More patients treated with budesonide/formoterol maintenance and reliever therapy ($P = 0.004$) and fixed-dose budesonide/formoterol ($P = 0.014$) were subjected to changes in asthma medication outside the study protocol for more than 30 days compared with those receiving the free adjustable combination of budesonide and formoterol (5%, 5%, and 2% of patients, respectively). Some patients (approximately 2%) on budesonide/formoterol changed back to previous care and received terbutaline as rescue medication. There was no difference between treatment groups in change of medication related to asthma exacerbations.

Safety and withdrawals

All study treatments were well tolerated. The number and type of SAEs and DAEs were low (66 SAEs and 71 DAEs in total) and similar between the treatment groups and no clinically important differences were observed.

Discussion

This pragmatic study demonstrates that budesonide/formoterol maintenance and reliever therapy is at least as effective as conventional treatment options for asthma at a significantly lower cost and lower overall corticosteroid load.

One of the benefits of this study was its reflection on real-life practice without the rigorous selection and monitoring procedures typical of clinical trials. It is well known

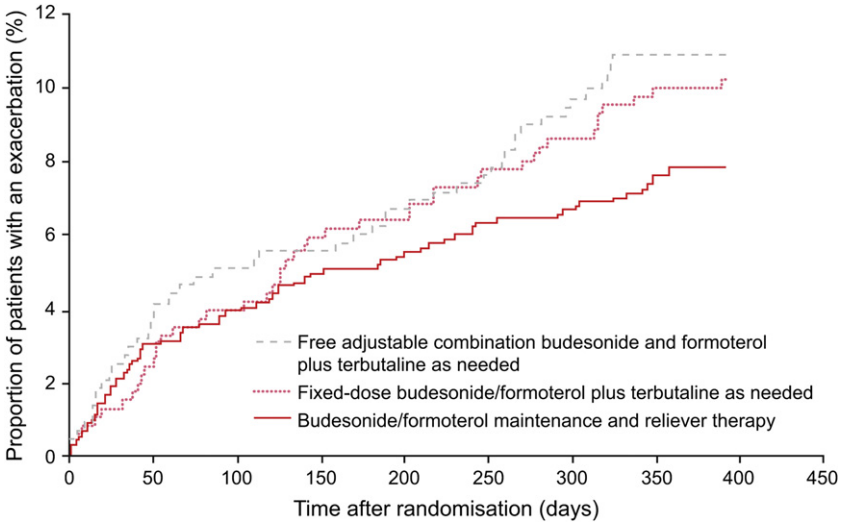

Figure 3 Time to first asthma exacerbation.

that the enforced conditions in a randomised clinical trial are unlikely to reflect the much less well-controlled clinical practice setting and that any observed benefits may not necessarily be equivalent in real life.[15,16] Previously it has been suggested that realistic estimates of cost–benefit relationships can only be obtained under conditions approaching real life.[15] Over the 12-month study period, patients were only requested to attend the clinic on three occasions and the majority of information was collected by telephone interviews. Furthermore, patient instructions were similar to ordinary instructions associated with a prescription for asthma medication.

Recent studies of budesonide/formoterol maintenance and reliever therapy have reported a significant reduction in severe exacerbations together with preserved daily asthma control at a lower overall steroid load compared with salmeterol/fluticasone[7,9] or budesonide/formoterol,[7] both plus SABA as needed. The present study showed a similar reduction in exacerbations as in previous studies, however not statistically significant, with preserved overall daily asthma control at a significantly lower daily dose of budesonide. This study was powered based on the primary outcome variable of direct asthma-related costs and thus a considerably lower number of patients were randomised than in previous studies designed to investigate the effectiveness of budesonide/formoterol maintenance and reliever therapy.

This study supports the notion that budesonide/formoterol maintenance and reliever therapy in one inhaler is at least as effective as conventional treatment using separate inhalers for ICS and LABA, and, moreover, can lead to a significant reduction in costs. The observed cost differences can be considered reliable; estimates of the cost savings available to a healthcare provider since direct costs were the primary endpoint and the sensitivity analysis showed stability for reasonable changes in unit price. Furthermore, this study shows that down-titration of budesonide and formoterol to the lowest effective dose of each monocomponent is seldom practiced in real life.

Health economic analyses of previous clinical trials using budesonide/formoterol maintenance and reliever therapy indicate that this treatment approach is efficacious and cost-effective,[11–13] despite concerns that the use of budesonide/formoterol as reliever might increase costs in

Table 5 Exacerbation burden

	Treatment groups			Treatment comparison of risk and rate (95% CI); *P*-value	
	Free adjustable combination of budesonide and formoterol, $n = 433$	Fixed-dose budesonide/formoterol, $n = 452$	Budesonide/formoterol maintenance and reliever therapy, $n = 884$	Budesonide/formoterol maintenance and reliever therapy vs. free adjustable combination of budesonide and formoterol	Budesonide/formoterol maintenance and reliever therapy vs. fixed-dose budesonide/formoterol
Patients with at least 1 exacerbation, *n* (%)	46 (10.6)	45 (10.0)	68 (7.7)	−28% (−51, 5); $P = 0.07$	−23% (−47, 12); $P = 0.17$
No. of exacerbations per 100 patients per year	13.9	15.2	12.4	−11% (−34, 20); $P = 0.75$	−19% (−39, 9); $P = 0.57$

Table 6 Cost-effectiveness analyses

	Free adjustable combination of budesonide and formoterol	Fixed-dose budesonide/ formoterol	Budesonide/ formoterol maintenance and reliever therapy
Patients with at least 1 exacerbation, %	10.6	10.0	7.7
Direct costs (SEK)	6014	6554	5218
Total costs (SEK)	8255	8620	8391
Direct cost change			
Budesonide/formoterol maintenance and reliever therapy versus free adjustable combination of budesonide and formoterol			−795*
Budesonide/formoterol maintenance and reliever therapy versus fixed-dose budesonide/ formoterol			−1335*
Incremental cost-effectiveness ratio			
Budesonide/formoterol maintenance and reliever therapy versus free adjustable combination of budesonide and formoterol			Cost saving
Budesonide/formoterol maintenance and reliever therapy versus fixed-dose budesonide/ formoterol			Cost saving

$1.00 = SEK 5.895; €1.00 = SEK 9.304 xe.com, 23 May 2008). *$P < 0.001$.

comparison to a generic SABA.[10] In these studies budesonide/formoterol maintenance and reliever therapy emerged as dominant (greater efficacy at a lower cost) compared with dose titration of salmeterol/fluticasone plus SABA,[11] fixed-dose salmeterol/fluticasone plus SABA,[12] and fixed-dose budesonide/formoterol plus SABA.[12] The cost savings reported with budesonide/formoterol maintenance and reliever therapy appear to be due to reduced exacerbations and a lower overall dose of maintenance medication, the benefits of which outweigh the difference in reliever cost.[10] The present study demonstrates that budesonide/formoterol as reliever therapy does not increase costs compared with SABA as reliever medication.

Although the real-life trial design has several advantages, it also has a number of inherent limitations. The open-label format may raise concerns regarding the introduction of bias. However, given the procedures used in this study this should not be a major issue. For example, patients were randomised in strict sequential order using numbered, sealed randomisation envelopes containing the allocated treatment regimen. Information was collected at telephone interviews and not by standard patient diaries or any electronic device. This may have affected the data accuracy, but it is unlikely to have introduced any systematic bias leading to differences between treatment groups.

Assessment of medication use on the basis of inhalers returned to the investigator at visit 3, rather than on the basis of pharmacy purchase records, may suggest that patients cannot be relied upon to return all their inhalers. However, careful questioning ensured that this risk was effectively minimised. Another potential limitation arises from the decision not to track costs incurred in treating adverse events not related to asthma. In theory, such costs can form a significant proportion of all direct costs. However, in this study the incidence of adverse events was minimal, and similar between treatment groups, and the cost of treating them could therefore be safely disregarded. Lastly, the emphasis on a real-life environment for this study precluded the use of patient diaries, meaning no record of symptom-free days was maintained. However, it is likely that changes in the number of symptom-free days have a minimal impact on direct costs as exacerbations account for roughly half the total cost of asthma care.[21] Furthermore, patients who suffer frequent exacerbations comprise approximately 20% of all patients but incur up to 80% of the direct costs of asthma.[21]

In summary, this study demonstrates, in a real-life setting, that budesonide/formoterol maintenance and reliever therapy is a cost-saving treatment option with at least equivalent efficacy at a lower corticosteroid load compared with conventional asthma treatment.

Conflict of interest statement

Björn Ställberg has been paid for lectures and for consulting by AstraZeneca, GlaxoSmithKline, Merck Sharp & Dohme, and Schering Plough. B.S. owns a small number of shares in AstraZeneca, with a total value less than 3000 USD. Per Olsson has been paid for lectures and for consulting by AstraZeneca and Schering Plough. He does not hold any stocks or shares in any pharmaceutical company. Bengt-Eric Skoogh has been paid for lectures and for contributing to advisory boards, and has received institutional grants from AstraZeneca, Boehringer Ingelheim, Merck Sharp & Dohme, and GlaxoSmithKline. He does not hold any stocks or shares in any pharmaceutical company. Göran Wennergren has been paid for lectures by AstraZeneca, Merck Sharp & Dohme, and GlaxoSmithKline. He does not hold any stocks or shares in any pharmaceutical company. Claes-Göran Löfdahl has been paid for lectures and for contributing to advisory boards, and has received institutional grants from AstraZeneca, Boehringer Ingelheim, Merck Sharp & Dohme, Novartis, and GlaxoSmithKline. He does not hold any stocks or shares in any pharmaceutical company. Tommy Ekström

and Fredrik Neij are employed by AstraZeneca, Södertälje, Sweden.

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