Adv Ther (2009) 26(9):872-885.
DOI 10.1007/s12325-009-0063-0

ORIGINAL RESEARCH

An Economic Evaluation of Budesonide/Formoterol for Maintenance and Reliever Treatment in Asthma in General Practice

Lucas M. A. Goossens · Roland A. Riemersma · Dirkje S. Postma · Thys van der Molen · Maureen P. M. H. Rutten-van Mölken

Received: May 14, 2009 / Published online: September 19, 2009 / Printed: October 5, 2009

ABSTRACT

Introduction: In budesonide/formoterol (Symbicort® Turbuhaler®, AstraZeneca, Lund, Sweden) maintenance and reliever therapy (SMART), patients with asthma take a daily maintenance dose of budesonide/formoterol, with the option of taking additional doses for symptom relief instead of a short-acting β_2-agonist (SABA). This study assesses the cost-effectiveness of SMART compared with usual care in patients with mild-to-moderate persistent asthma treated by general practitioners in the Netherlands from a societal perspective. ***Methods:*** The study was linked to a randomized, active-controlled, open-label, multicenter, 12-month clinical trial, with a prospective collection of resource use. One hundred and two patients ≥18 years with mild-to-moderate persistent asthma and daily inhaled corticosteroids (ICS) prior to the trial were included. SMART was given as two inhalations of budesonide/formoterol (100/6 µg) once daily, plus additional doses as needed. The control group was treated according to guidelines, which prescribe medium daily doses of ICS plus an SABA if needed. A long-acting β_2-agonist (LABA) is added if necessary. Effectiveness was measured as the proportion of asthma-control days, Asthma Control Questionnaire (ACQ) scores, the net proportion of patients with relevant ACQ improvement, and the proportion of well-controlled patients. Costs included asthma medication, physician contacts, and absence from work. ***Results:*** Mean total costs for SMART were €134.81 lower (95% CI: –€439.48; €44.85). Production losses were €94.10 (95% CI: –€300.60; €0.29) lower for SMART (€10.77 vs. €104.87). No significant differences in health outcomes were seen, with 3.81 fewer asthma-control days per patient-year for SMART (95% CI: –36.8; 30.8), a 0.049 better ACQ score (95% CI: –0.21; 0.29), a 5.8% larger net proportion of improved

Lucas M. A. Goossens (✉) · Maureen P. M. H. Rutten-van Mölken
Institute for Medical Technology Assessment, Erasmus University Medical Center, P.O. Box 1738, 3000 DR Rotterdam, The Netherlands.
Email: goossens@bmg.eur.nl

Roland A. Riemersma · Thys van der Molen
Department of General Practice, University Medical Center Groningen, Groningen, The Netherlands

Dirkje S. Postma
Department of Pulmonary Diseases, University Medical Center Groningen, Groningen, The Netherlands

patients (95% CI: –15.6%; 27.3%), and a 2.1% (95% CI: –25.5; 20.8%) smaller increase in the proportion of well-controlled patients. ***Conclusions:*** Treating primary care patients with mild-to-moderate persistent asthma with SMART instead of ICS plus bronchodilators does not affect health outcomes and does not increase costs; therefore, is likely to be an alternative for guideline-directed treatment, from a health and economic perspective.

Keywords: asthma; budesonide/formoterol; cost-effectiveness; inhaled corticosteroid; Symbicort

INTRODUCTION

When asthma control is not achieved with a medium daily dose of inhaled corticosteroids (ICS) alone (equivalent to 400-800 µg budesonide), current international treatment guidelines for asthma recommend a maintenance therapy with a combination of ICS and inhaled long-acting β_2-agonists (LABA).[1] These can be delivered in separate inhalers or simultaneously in a combination inhaler. Two combination inhalers are currently available, delivering either budesonide and formoterol (Symbicort® Turbuhaler®, AstraZeneca, Lund, Sweden) or fluticasone propionate and salmeterol (Seretide®, GlaxoSmithKline, Philadelphia, PA). Both combination inhalers are as effective as giving each drug alone,[2,3] but they simplify the treatment and potentially improve adherence to maintenance therapy.[4]

Currently, patients using a combination inhaler are also being prescribed a short-acting β_2-agonist (SABA), such as salbutamol, on an as-needed basis for rapid symptom relief. However, this practice has been challenged by recent clinical trials that have studied the concept of treating asthma using Symbicort Maintenance And Reliever Treatment (SMART), without the use of an additional SABA.[5-9] SMART implies that patients are given a relatively low dose of Symbicort with the possibility to take more inhalations to provide both rapid symptom relief and an increase in anti-inflammatory treatment at the early stages of symptom worsening. Trials have shown that SMART provided better protection against severe exacerbations than higher doses of ICS or maintenance combination therapy.[5-9] They also provided evidence that improved asthma control was reached at relatively low doses of ICS.

Several economic evaluations of SMART have been published, but most of those were done in relatively severely ill patients and/or secondary care settings.[10-13] Compared with Seretide plus an SABA as needed, SMART leads to fewer exacerbations at equal or lower costs.[10,12,13] Compared with Symbicort plus an SABA as needed, SMART either lead to the same health effects at lower costs[11] or better health at equal or lower costs.[12] For less severe patients, the picture is less clear. Only one study has been performed in a primary care setting in patients with mild-to-moderate persistent asthma.[14] In Sweden, Ställberg et al.[14] compared SMART with Symbicort plus terbutaline as needed, and with a free combination of budesonide and formoterol plus terbutaline as needed. Healthcare costs were found to be lowest for SMART, whereas exacerbations and quality of life were similar across treatment groups.[14] However, compared with the free combination, the costs for SMART were higher when the costs due to absence from work were included.

Therefore, SMART has the potential to reduce the healthcare costs of asthma. Whether it does so in less severe patients and in a different setting remains unknown. It is well known that the health economic impact of a therapy depends heavily on national and local

treatment patterns, healthcare delivery structures, funding and reimbursement systems, absolute and relative differences in unit costs of resource use, and drug prices. This was also reflected by the cost-effectiveness (CE) study of Johansson et al.,[10] who found that compared with physician-titrated salmeterol/fluticasone plus an SABA for relief, SMART was dominant (ie, generated superior effects at lower costs) in Germany, whereas it did not significantly affect costs in Italy, France, and the UK.

Earlier studies have compared SMART with one or more fairly strictly described alternatives. In practice, however, patients are treated in many different ways. Furthermore, most of the previous studies used exacerbations as a measure of health effects.

The present paper aims to investigate the potential savings and health effects if SMART were the standard treatment of patients in primary care who need ICS. The focus of this economic evaluation is on asthma-related quality of life. In the Symbicort Single Inhaler Therapy for Asthma in General Practice (SiTA) study, SMART was compared with usual care for patients with mild-to-moderate persistent asthma treated by general practitioners (GPs) in the Netherlands. Usual care is based on and driven by "Nederlands Huisartsen Genootschap" (NHG) guidelines (treatment guidelines issued by the Dutch College of General Practitioners).[15] The clinical results of the SiTA study have recently been reported more extensively in a separate paper (Riemersma RA, et al. Submitted for publication). The study found that SMART resulted in similar effects in terms of the provocative dose causing a 20% fall in forced expiratory in 1 second (PD_{20} FEV_1), lung function, symptoms, and asthma control, and a better effect in terms of peak expiratory flow (PEF) than guideline-directed usual care at half the dose of ICS. In addition, SMART was found to be easier to use.

METHODS

Patients

The study included patients ≥18 years of age with a GP's diagnosis of mild-to-moderate persistent asthma according to the NHG guidelines (PD_{20} histamine ≤4.5 mg) and a prebronchodilator FEV_1 ≥60% of predicted normal values. These tests were performed to confirm the diagnosis. To be included, patients were required to have used ICS daily during the 3 months prior to the start of the run-in period. In addition, patients should not have used more than 10 inhalations of as-needed medication on any day during the run-in, should not have had an asthma exacerbation during the run-in, and should use constant daily dosages of ICS ≤800 µg budesonide/beclomethasone or ≤500 µg fluticasone if used in combination with an LABA, or ≤1600 µg budesonide/beclomethasone or ≤1000 µg fluticasone if used without an LABA.

The study was powered to detect a difference of 1 in the log of the outcome variable PD_{20} histamine with a two-sided alternative hypothesis and a significance level of 5% with 80% power, which resulted in a required sample size of 50 per treatment group (Riemersma RA, et al. submitted).

Interventions

The clinical trial to which this economic evaluation is linked was designed as a 1-year, randomized, active-controlled, open-label, multicenter trial. SMART was given as two inhalations of budesonide/formoterol 100/6 µg (Symbicort) delivered using a metered-dose inhaler once daily in the evening, plus additional doses as needed (100/6 µg per inhalation refers to the metered dose, which is equivalent to 80/4.5 µg per delivered dose). The control group (usual care) was treated according to guidelines, which prescribe

low or medium daily doses of ICS (≤800 µg budesonide/beclomethasone or ≤500 µg fluticasone) plus an SABA if needed. An LABA was added if the patient's asthma was not controlled using this medication.

Study Design

After the 1-month run-in period, clinic visits were scheduled at randomization as well as at 1 month and 12 months after the start of treatment. In addition, telephone interviews were scheduled after 3 months and 6 months of treatment. At each clinic visit, lung function was measured and the Asthma Control Questionnaire (ACQ)[16,17] and the Satisfaction with inhaled Asthma Treatment Questionnaire (SATQ)[18] were completed. The latter measurement was not used in this economic evaluation.

Effects

The first health outcome measure was the change in the proportion of asthma-control days (ACD; calculated as the difference in the proportion of ACD from the run-in period to the last month prior to the end of treatment). An ACD is defined as a daytime and night-time symptom score of 0 and no awakenings during the night. The second outcome measure was the mean change in ACQ score (five-item symptoms only version, ACQ-5) between the start of study treatment and at the end of the trial. This ACQ consists of five questions for the patient on asthma symptoms and limitation of daily activities.[16] The total score, on a scale of 0 (totally controlled) to 6 (completely uncontrolled), is the average of the scores on each question.[17]

The third outcome measure was the net proportion of patients with a clinically relevant improvement in the ACQ score (ie, the proportion of patients with ≥0.5 improvement in ACQ score[19] minus the proportion of patients with ≥0.5 deterioration in ACQ score). The fourth measure was the change in the proportion of patients with well-controlled asthma according to the ACQ (score of ≤0.75),[20] calculated as the difference in these proportions between run-in and end of treatment.

Costs

The economic evaluation was performed from a societal perspective, which means that all medical and nonmedical costs of illness and treatment are taken into account, irrespective of who bears them. Specifically, production losses due to sick leave from work were included.

At all clinic visits and telephone interviews the use of the following types of asthma-related healthcare services was recorded: number of hospitalizations and hospitalization days (distinguished into intensive care unit and regular ward); clinic visits to specialists, GPs, and other healthcare providers; home visits by physicians and other healthcare providers; telephone contact with physicians and other healthcare providers.

Maintenance medication, as-needed use of medication, and asthma-related inability to perform usual daily activities were recorded in patient diaries. Patients with full-time paid jobs were assumed to lose 8 hours of work for each day they were on sick leave; 4 hours were counted for patients with part-time jobs.

Following the Dutch manual for calculating costs in economic evaluations,[18] production losses were calculated as 80% of salaries to account for working time elasticity of production, which indicates that 1% of additional time yields only 0.8% of additional production. Salaries were estimated as the weighted average of age- and gender-specific gross salaries in the Netherlands, with the age and gender

distribution of the study population as weights. Gross salaries and standard costs for healthcare use were retrieved from the Dutch costing manual.[21] Medication prices were retrieved from an online databank compiled by the Dutch Health Care Insurance Board (CVZ).[22] In accordance with the choice of a societal perspective, medication costs excluded VAT, but included mark-ups to cover pharmacy expenses.

Unit costs were taken from or indexed to 2007 and are listed in Table 1.

Table 1. Unit costs for the major types of resource utilization (2007 values).

Resource	Costs
Symbicort per dose	€0.41
Flixotide 250 mg per dose	€0.38
Prednisolone 30 mg per dose	€0.42
Pulmicort 200 per dose	€0.16
Pulmicort 400 per dose	€0.32
Salbutamol 200 per dose	€0.12
Seretide 50/250 per dose	€0.88
Specialist visit	€56.49
GP consult	€21.46
GP phone call	€10.73
Productivity costs per hour	€29.94

GP=general practitioner.

Statistical Analysis

The analysis was performed according to the intention-to-treat principle. All randomized patients who started study treatment and completed at least one post-randomization resource utilization questionnaire or one post-randomization outcome measurement were included in the analysis. To account for the costs and health outcomes that were missing after patients prematurely dropped out from the trial, the last observation of the health outcomes was carried forward and the costs were linearly extrapolated.

Ordinary least squares regression was used to analyze the change in proportion of ACDs and the change in ACQ scores. The regression models included treatment group and either the proportion of ACDs or the ACQ score during the run-in period. Differences in proportions were tested using Pearson's chi-square test.

Because of the non-normal distribution of variables, parametric techniques could not be used to test the differences between the groups besides proportions or to construct confidence intervals. Therefore, we performed nonparametric bootstrap analyses on healthcare utilization, costs, and health outcomes. Using this technique the sampling distribution of variables can be estimated from the original data, by taking a large number of samples with replacement. For each bootstrap sample the differences between treatment groups in healthcare contacts, costs, and health effects were calculated. By applying the bias-correction and acceleration (BCa) method, these simulated results were used to estimate 95% confidence intervals.[23-25] Twenty thousand bootstraps were performed, a number that guaranteed stability of the results.

Differences between the two treatments in the use of the various types of healthcare services were tested separately and as an aggregate measure of resource use, ie, the total number of healthcare contacts, which included all types of contacts with all types of healthcare providers, because of the potential substitution effects between the various healthcare services (eg, if there were more GP visits, there might have been fewer telephone calls to the GP).

The uncertainty regarding the difference in costs and effects was analyzed simultaneously by plotting the bootstrap replications of both cost differences and differences in health outcomes on a CE plane.[26] These dots form the 95% confidence region around the CE ratio. In order to report what proportion of the total

costs in both treatment groups was due to exacerbations, the costs per exacerbation were also calculated. If the costs were higher in one treatment group while the effects were better, an incremental CE ratio was computed: the costs per unit of health gain. This was done irrespective of whether the differences in costs and effects between treatment groups were statistically significant.[27]

Sensitivity Analysis

In addition to the bootstrap analysis described in the previous section, one-way sensitivity analysis was performed on the method of calculating productivity loss by also including the (8-hour) inactivity days of patients without paid employment. Further sensitivity analysis was performed on the method of calculating the proportion of patients with improvement in the ACQ score (calculating the proportion with a ≥0.5 unit improvement instead of the net proportion). Finally, different cut-off points were used to define well-controlled asthma based on the ACQ (1.0 and 1.5 instead of 0.75).

RESULTS

Patients

One hundred and two patients with asthma were randomized: 54 in the SMART group and 48 in the group with guideline-directed usual care (Figure 1). Three patients (5.6%) from the SMART group and four patients (8.3%) from the usual care group did not complete the study to the final visit, but they were included in the intention-to-treat analysis. On average, patients in the SMART group were somewhat older, more likely to be male, and to use a high dose of LABA, during the run-in of the trial (Table 2). Combination inhalers Symbicort and Seretide, containing a corticosteroid, as well as an LABA, were used by 21 patients (44%) in the usual-care group, and ICS without an LABA as maintenance therapy by 27 patients (56%).

Healthcare Use and Absence from Work

In the SMART group, six patients (11.1%) had an asthma-related contact with a physician during the trial period, compared with 13 (27.1%) in the usual-care group (Table 3). The difference, –16%, was statistically significant (P=0.039). A higher proportion of patients in the usual-care group used antibiotics (P=0.014) and prednisone/prednisolone (P=0.099). SMART patients inhaled significantly smaller doses of corticosteroids (P<0.00005). The percentage of patients reporting inability to perform usual daily activities was lower in the SMART group than in the usual-care group (P=0.071).

Patients in the SMART group had a total number of 10 asthma-related contacts with healthcare providers, or 0.19 (SD±0.62) per patient-year. For the usual-care group the total number was 20, or 0.41 per patient-year (SD±0.90), a difference of –0.22 per patient-year (95% CI: –0.56; 0.05). No hospital admissions and emergency room visits were observed.

Costs

Table 4 lists the mean costs per patient-year. The mean total costs were €426.37 in the SMART group, compared with €561.17 in the usual-care group, a mean difference of €134.81 (95% CI: €439.48; 44.85). In 90% of the bootstrap replications SMART resulted in cost savings. The mean medication costs in the SMART group were €36.11 lower (–€161.11; €70.82) than in the usual-care group. Productivity costs were €94.10 lower (95% CI –€300.60; €0.29).

Figure 1. Study flow chart.

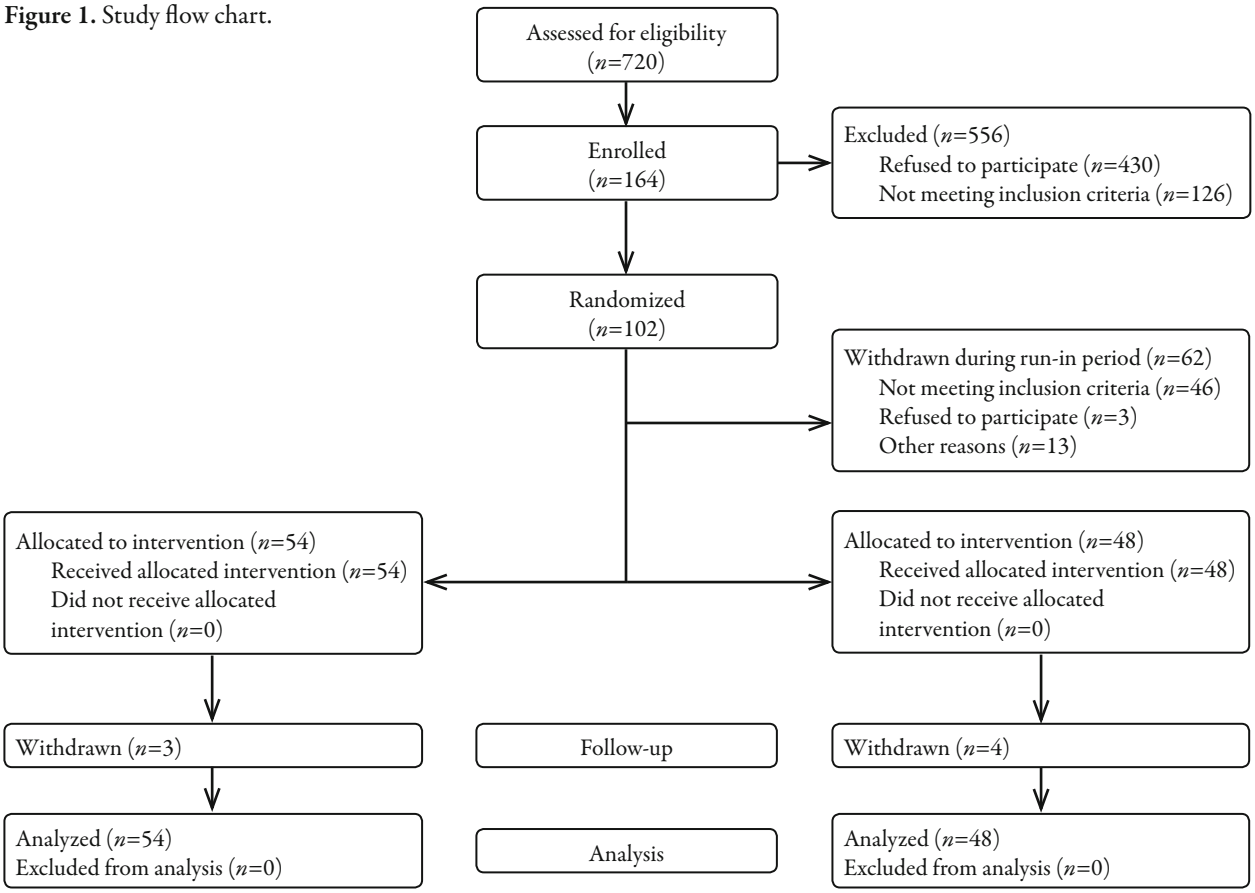


Table 2. Baseline characteristics.

	SMART (*n*=54)	Usual care (*n*=48)
Age, years (±SD)	44.7 (±13.2)	40.6 (±12.0)
Female, %	59	65
Prebronchodilator FEV_1%pred (±SD)	96.9 (±17.2)	101.6 (±17.4)
Moderate persistent asthma (PD_{20} histamine at start ≤1 mg), %	68.5	70.8
Long-acting β_2-agonist at start, %	53.7	60.4
Mean dose of inhaled corticosteroids at start, μg (±SD)	566 (±304)	506 (±226)
High-dose inhaled corticosteroids at start*, %	51.6	45.8
Currently smoking, %	9.3	18.8
Body mass index (±SD)	26.8 (±4.7)	27.7 (±4.5)
Full-time paid work, %	40.7	45.8
Part-time paid work, %	25.9	14.6
Asthma-control days during run-in, % (±SD)	68.0 (±34.5)	54.4 (±38.7)
ACQ at start (±SD)	0.80 (±0.77)	0.93 (±0.71)
Proportion well-controlled at start (ACQ ≤0.75), %	53.7	39.6

*≥800 μg budesonide/beclamethasone or ≥500 μg fluticasone.

ACQ=Asthma Control Questionnaire; BMI=body mass index; FEV_1%pred=forced expiratory volume in 1 second percent predicted; PD_{20}=provocative dose causing a 20% fall in FEV_1; SMART=Symbicort Maintenance And Reliever Therapy.

Table 3. Healthcare utilization and productivity losses.

	SMART (*n*=54)	Usual care (*n*=48)	Difference	95% CI of difference
Proportion of patients with resource use				
GP visits	5.6	22.9	–17.5	–30.9; 4.4
Telephone calls to GP	3.7	2.1	1.6	–5.6; 7.6
Specialist visits	3.7	2.1	1.6	–5.6; 7.6
Any physician contacts	11.1	27.1	–16.0	–31.5; 0.10
Antibiotics use	3.7	18.8	–15.05	–28.0; 3.5
Use of Symbicort	100	29.2	70.8	57.1; 83.3
Use of Seretide	0	14.6	–14.6	–26.0; –5.9
Use of inhaled corticosteroids	1.9	56.3	–54.4	–68.6; –40.0
Use of β_2-agonist	1.9	52.1	–50.2	–65.2; –35.8
Prednisone/prednisolone use	3.7	12.5	–8.8	–20.3; 1.1
Absence from paid work	5.6	8.3	–2.8	–13.4; 6.7
Inability to do usual activities	5.6	16.7	–11.1	–23.8; 0.0
Resource use and productivity losses, mean per patient-year				
GP visits	0.10	0.37	–0.270	–0.59; –0.012
Telephone calls to GP	0.05	0.02	0.0338	–0.041; 0.14
Specialist visits	0.04	0.02	–0.0149	–0.056; 0.074
Total contacts	0.19	0.41	–0.221	–0.56; 0.054
Daily dose of inhaled corticosteroids* (±SD)	336 μg (±157)	800 μg (±473)	–464	–608 μg; –330 μg
Antibiotics, days	0.11	0.73	–0.62	–1.28; –0.059
Prednisone/prednisolone, days	0.65	1.03	–0.38	–1.55; –0.96
Days lost, paid work	0.05	0.44	–0.39	–1.23; 0.0042
Days lost, all activities	0.09	0.90	–0.81	–1.88; 0.18

Values are percentages unless otherwise indicated.
*In beclamethasone diproprionate equivalents (800 μg budesonide = 500 μg fluticasone = 1000 μg beclamethasone).
GP=general practitioner; SMART=Symbicort Maintenance And Reliever Therapy.

The cost difference was heavily influenced by one patient in the usual-care group, who had 15 days of sick leave and visited her GP five times. Without this patient, the average total costs in the usual-care group would have been €457.41, and the difference with the SMART group would decrease to €31.04 (95% CI: –€160.47; €78.48). In that case, the difference in mean productivity costs would then be €21.68 and the probability that SMART results in cost savings would be 72%.

Costs Related to Exacerbations

A total of 11 exacerbations were recorded: four in the SMART group (or 0.0823 per patient-year) and seven in the usual-care group (or 0.1440 per patient-year). The difference, –0.0617, was not statistically significant (95% CI: –0.218; 0.131). Overall, costs of asthma exacerbations were €73.88 lower per patient in the SMART group compared with the usual-care group (95%CI: –€219.22; –€5.24, Table 4). Without the outlying patient, €23.93 (95%CI: –€63.25; €3.92) of

Table 4. Costs of medication, healthcare utilization, and production losses, mean per patient-year.

	SMART (*n*=54)	Usual care (*n*=48)	Difference	95% CI*
Symbicort	€408.65	119.90	n/a	n/a
Seretide	0.00	108.95	n/a	n/a
β_2-agonists	0.41	48.37	n/a	n/a
Inhaled corticosteroids	1.24	115.49	n/a	n/a
Oral corticosteroids	0.27	0.76	n/a	n/a
Antibiotics	0.25	1.95	n/a	n/a
Total medication costs†	410.85	446.97	−36.11	−161.11; 70.82
GP visits	2.14	7.93	−5.79	−12.73; 0.30
Phone calls	0.58	0.22	0.36	−0.44; 1.48
Specialist visits	2.02	1.18	0.84	−3.12; 4.20
Total physician costs	4.75	9.33	−4.59	−12.02; 2.32
Paid work lost	10.77	104.87	−94.10	−300.60; 0.29
Total costs	426.37	561.17	−134.81	−439.48; 44.85
Costs related to exacerbations, mean per patient-year				
Medication costs	0.42	1.95	−1.53	−3.47; −0.08
Physician costs	1.77	5.30	−3.53	−9.39; 1.70
Paid work lost	4.29	73.10	−68.81	−210.76; −4.45
Total exacerbation costs	6.48	80.36	−73.88	−219.22; − 5.24
Exacerbation costs as percent of total costs, %	1.98%	32.67%	−30.69%	−81.64%; −0.20%

Costs are in Euros (€).
*95% CI=95% confidence interval, generated by bootstrapping (20,000 samples).
†In the usual-care group, this amount includes other types of medication.
GP=general practitioner; n/a=not applicable; SMART=Symbicort Maintenance And Reliever Therapy.

the difference remained. Only a small proportion of the medication costs were caused by an exacerbation (Table 4), but for the other cost categories the share is substantial.

The mean costs per exacerbation in the entire sample were €390.21 (SD±€727.46, 95% CI: €112.96; €935.12), and the median was €45.86. Excluding the outlying patient, the mean was €179.06 (SD±€207.52, 95% CI: €73.01; €314.01).

Effects

There were no significant differences in health outcomes (Table 5). The ACQ score slightly worsened over time in both groups. SMART users had 1% fewer ACDs, or 3.81 days a year. The net proportion of improved patients was larger (5.8%), but the change in the proportion of well-controlled patients was 2.1% smaller in the SMART group.

CE Planes

The results of the bootstrap analyses were presented in CE planes, in which each dot represents incremental costs and effects in one bootstrap sample (Figure 2). Eighty-eight percent of the dots are below the *x*-axis, which is the probability that SMART induces cost savings. This is

Table 5. Health outcomes.

	SMART (*n*=54)	Usual care (*n*=48)	Difference SMART–usual care	95% CI
Asthma-control days*				
Proportion during run-in, %	68.0	54.4	13.5	
Proportion during trial, %	63.95	56.3	7.7	
Difference, %	–4.04	1.78	–1.04†	–10.17; 8.4
Difference in days per year	–14.76	6.50	–3.81†	–36.8; 30.8
ACQ-5				
Score at start	0.796	0.933		
Score at month 12	0.826	0.967		
Improvement between visits	–0.030	–0.033	0.049†	–0.21; 0.29
Improvement				
Improved‡, % (*n*)	16.7 (9)	14.6 (7)	2.1	–12.0; 16.3
Deteriorated§, % (*n*)	13.0 (7)	16.7 (8)	–3.7	–17.5; 10.0
Net proportion of improved patients‖, %	3.7	–2.1	5.8	–15.6; 27.3
Well-controlled asthma¶				
Proportion at start, % (*n*)	53.7 (29)	39.6 (19)		
Proportion at end, % (*n*)	53.7 (29)	41.7 (20)		
Increase in proportion, %	0	2.1	–2.1	–25.5; 20.8

95%CI=95% confidence interval, generated by bootstrapping (10,000 samples).
*Asthma-control days (daytime and night-time symptom score of 0 and no nightly awakenings).
†Calculated by linear regression with correction for baseline value.
‡Improved patients are defined as patients with ≥0.5 units improvement in their ACQ score.
§Deteriorated patients are defined as patients with ≥0.5 deterioration in their ACQ score.
‖Net proportion of improved patients defined as the proportion of improved patients – proportion of deteriorated patients.
¶Well-controlled are defined as patients with an ACQ score ≤0.75.
ACQ-5=Asthma Control Questionnaire (five-item symptoms only version; 0=no impairment, 6=maximum impairment); SMART=Symbicort Maintenance And Reliever Therapy.

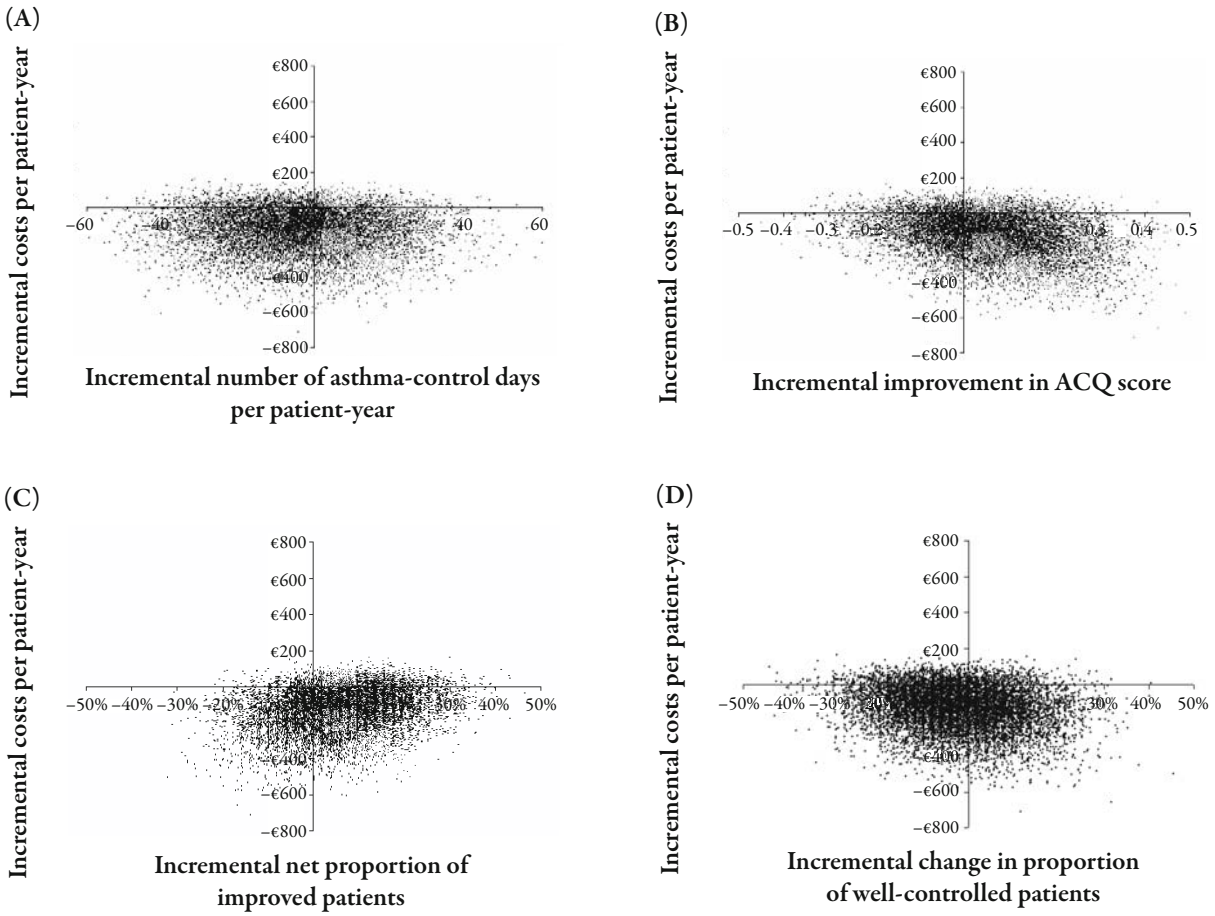
the same in all four CE planes as each sample is represented in all four figures with only the effect measure changing.

For ACDs and the net proportion of improved patients, most of the bootstrap replications are in the southwest quadrant of the CE plane, indicating cost savings, but less health effects for SMART. For the improvement in ACQ score and change in the proportion of well-controlled patients, most dots are in the southeast quadrant, indicating less costs and superior health effects for SMART.

Sensitivity Analysis

Including production losses for every patient who was unable to perform his or her daily activities, leads to a much larger total cost difference of €235.68 in favour of SMART (95%CI: €10.91; €559.66). Using the proportion of improved patients as an outcome measure instead of the net proportion does not lead to a significant difference between the treatment groups (Table 5). The difference between the treatment groups remained stable and not

Figure 2. (**A**) Cost-effectiveness plane, mean difference in costs, and incremental change of the number of asthma control days (SMART vs. usual care). (**B**) Cost-effectiveness plane, mean difference in costs, and incremental improvement of ACQ score (SMART vs. usual care). (**C**) Cost-effectiveness plane, mean difference in costs, and incremental difference in net proportion of improved patients (SMART vs. usual care). (**D**) Cost-effectiveness plane, mean difference in costs, and incremental change in the proportion of well-controlled patients (SMART vs. usual care). ACQ=Asthma Control Questionnaire; SMART=Symbicort Maintentance And Reliever Therapy.



significant if the definition of a well-controlled patient was changed.

DISCUSSION

This study has produced no significant difference in costs in mild-to-moderate persistent asthma patients who received either SMART or guideline-directed usual care in general practice. However, our bootstrap analysis has shown that a substantial cost increase is less likely to occur than substantial savings. Meanwhile, no significant difference was found in the four health outcomes. As patients with mild-to-moderate asthma do not often experience exacerbations, these events could not be used as an indicator of health-related quality of life. Therefore, the number of ACD, the mean change in ACQ between start of study treatment and the end of the study, the net proportion of patients with a clinically relevant improvement in ACQ score, and the proportion of patients with well-controlled asthma according to the ACQ score were

evaluated. Hence, it is concluded that SMART may be a good alternative to usual care, simplifying treatment and potentially improving adherence to maintenance therapy,[4] without compromising health effects or increasing costs. As many of the productivity losses in the control group were attributable to one patient, the difference in absence from work was not indicative of a difference in quality of life.

The present study was different from the previous economic evaluation studies in that a head-to-head comparison of two asthma drugs was not performed. Previous studies compared with SMART to a combination of ICS and an LABA. In the present study a substantial proportion of the control group did not use an LABA; those who did used an LABA most often within a different regimen. Using a different comparator obviously leads to different costs and health effects. The aim of the present study was to describe the health effects and economic consequences of switching all patients with mild-to-moderate persistent asthma who were currently treated with ICS in a general practice setting to SMART. As the control group was receiving usual care, many different medications were used in this group. A substantial proportion of patients had a fixed combination inhaler of an ICS and an LABA, but the majority used a single inhaler with a corticosteroid for maintenance therapy. As patients in the usual-care group continued to use the medication they had before the start of the trial, the medication mix in the control arm is likely to be a good reflection of the medication used in this population in routine daily practice. The present study has shown that switching these patients to SMART reduced the dose of ICS by 58% of that which was taken in the usual-care group without any detrimental health effects.

The present study was powered to detect a clinically relevant difference in PD_{20} histamine; however, this difference was not found in the study (Riemersma RA, et al. submitted). Combining this with the results presented in the present paper, it can be concluded with some confidence that health outcomes are not different for the SMART and usual-care groups.

The sample size is the most important limitation of this economic evaluation. Cost studies typically require a larger number of patients to be able to establish a significant difference.[28] However, the present results are in line with the previous economic evaluations of SMART. None of them presented significantly higher healthcare costs for SMART. The study by Ställberg et al.[14] (n=1565) found societal costs per patient-year that were €13 higher than in patients who were treated with an adjustable combination of budesonide and formoterol, but this difference was not statistically significant.[14] The estimated savings in direct healthcare costs were equivalent to €75 (compared with the free combination) to €125 (compared with the fixed-dose combination) per patient-year. Unfortunately, no confidence intervals were reported. In more severe patients, Lundborg et al.[11] did find significant and larger cost savings when comparing SMART with Symbicort plus formoterol, but their sample size was considerably larger (465 patients). Johansson et al.[10] compared SMART with Seretide plus salbutamol and multiplied trial-wide resource use with unit costs from four different countries. Although they had a large sample of 1051 patients, they found that SMART significantly reduced costs in Germany only—by €118 per year—but not Italy, France, and the UK.[10] Applying Dutch unit costs to the pooled resource utilization data of Johansson et al.[10] would likely result in significant cost savings for severe patients in the Netherlands as well. Significant cost savings were also found for the UK and Australia by Price et al.[12] when they compared SMART with Seretide plus terbutaline,

and for the UK when SMART was compared with Symbicort plus terbutaline.

Asthma-related healthcare resource use was low in the aforementioned studies, but even lower in the present study. No hospitalizations or emergency room visits, and fewer visits to a specialist or a GP were observed. This is consistent with the difference in the severity of the patient populations. In the other economic evaluations, medication costs contributed most to the total costs in both groups. However, medication costs in the present study were lower, due to a lower daily dose used. The major driver of the difference in total costs between the two treatment groups was a difference in productivity costs. A higher price per lost day of paid work was used than in most of the previous studies, ie, €240 compared with between €112 and €158 (excluding the study by Ställberg et al.,[14] who used a similar amount as in the present study).[10-14] The costs in the present study were taken from the standard unit costs that are recommended in pharmacoeconomic guidelines to promote comparability of Dutch economic evaluations. Unit costs of other types of resource use were more or less comparable across the studies.

With regard to health effects, other studies found that SMART lowered the rate of mild and severe exacerbations and lengthened the time to the first exacerbation[5-10,12,13] compared with treatments with higher doses of ICS or maintenance combination therapy. Although a significant difference in exacerbation rate, which was low in both groups, was not established, a large proportion of the difference in production losses was attributed to exacerbations, in particular to one individual patient in the usual-care group who had 15 days of sick leave. This outlier added €104 to the observed difference in mean costs per patient-year; therefore, results for cost savings should be interpreted with caution. Conversely, with or without this patient there is no indication that SMART has the potential to induce large cost increases in users in primary care.

In conclusion, SMART is likely to be an alternative for guideline-directed treatment of mild-to-moderate persistent asthma in general practice, from a health and economic perspective.

ACKNOWLEDGMENTS

This study was funded by AstraZeneca BV, Zoetermeer, The Netherlands.

REFERENCES

1. Global Initiative for Asthma web site. GINA Report, Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma 2008. Available at: www.ginasthma.com. Accessed August 2009.

2. Kips JC, O'Connor BJ, Inman MD, Svensson K, Pauwels RA, O'Byrne PM. A long-term study of the antiinflammatory effect of low-dose budesonide plus formoterol versus high-dose budesonide in asthma. Am J Respir Crit Care Med. 2000;161:996-1001.

3. Lalloo UG, Malolepszy J, Kozma D, et al. Budesonide and formoterol in a single inhaler improves asthma control compared with increasing the dose of corticosteroid in adults with mild-to-moderate asthma. Chest. 2003;123:1480-1487.

4. Stoloff SW, Stempel DA, Meyer J, Stanford RH, Carranza Rosenzweig JR. Improved refill persistence with fluticasone propionate and salmeterol in a single inhaler compared with other controller therapies. J Allergy Clin Immunol. 2004;113:245-251.

5. O'Byrne PM, Bisgaard H, Godard PP, et al. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. Am J Respir Crit Care Med. 2005;171:129-136.

6. Rabe KF, Atienza T, Magyar P, Larsson P, Jorup C, Lalloo UG. Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study. Lancet. 2006;368:744-753.

7. Rabe KF, Pizzichini E, Stallberg B, et al. Budesonide/formoterol in a single inhaler for maintenance and

relief in mild-to-moderate asthma: a randomized, double-blind trial. Chest. 2006;129:246-256.

8. Scicchitano R, Aalbers R, Ukena D, et al. Efficacy and safety of budesonide/formoterol single inhaler therapy versus a higher dose of budesonide in moderate to severe asthma. Curr Med Res Opin. 2004;20:1403-1418.

9. Vogelmeier C, D'Urzo A, Pauwels R, et al. Budesonide/formoterol maintenance and reliever therapy: an effective asthma treatment option? Eur Respir J. 2005;26:819-828.

10. Johansson G, Andreasson EB, Larsson PE, Vogelmeier CF. Cost effectiveness of budesonide/formoterol for maintenance and reliever therapy versus salmeterol/fluticasone plus salbutamol in the treatment of asthma. Pharmacoeconomics. 2006;24:695-708.

11. Lundborg M, Wille S, Bjermer L, et al. Maintenance plus reliever budesonide/formoterol compared with a higher maintenance dose of budesonide/formoterol plus formoterol as reliever in asthma: an efficacy and cost-effectiveness study. Curr Med Res Opin. 2006;22:809-821.

12. Price D, Wiren A, Kuna P. Cost-effectiveness of budesonide/formoterol for maintenance and reliever asthma therapy. Allergy. 2007;62:1189-1198.

13. Miller E, Sears MR, McIvor A, Liovas A. Canadian economic evaluation of budesonide-formoterol as maintenance and reliever treatment in patients with moderate to severe asthma. Can Respir J. 2007;14:269-275.

14. Ställberg B, Ekstrom T, Neij F, et al. A real-life cost-effectiveness evaluation of budesonide/formoterol maintenance and reliever therapy in asthma. Respir Med. 2008;102:1360-1370.

15. Geijer RMM, Chavannes NH, Muris JWM, et al. NHG Standaard Astma bij volwassenen. Huisarts en Wetenschap. 2007;11:537-551.

16. Juniper EF, O'Byrne PM, Roberts JN. Measuring asthma control in group studies: do we need airway calibre and rescue beta2-agonist use? Respir Med. 2001;95:319-323.

17. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. Eur Respir J. 1999;14:902-907.

18. Campbell JL, Kiebert GM, Partridge MR. Development of the satisfaction with inhaled asthma treatment questionnaire. Eur Respir J. 2003;22:127-134.

19. Guyatt GH, Juniper EF, Walter SD, Griffith LE, Goldstein RS. Interpreting treatment effects in randomised trials. BMJ. 1998;316:690-693.

20. Juniper EF, Bousquet J, Abetz L, Bateman ED, GOAL Committee. Identifying "well-controlled" and "not well-controlled" asthma using the Asthma Control Questionnaire. Respir Med. 2006;100:616-621.

21. Oostenbrink JB, Bouwmans CAM, Koopmanschap MA, Rutten FFH. Guide to cost research – Methods and standard costs prices for economic evaluatons in healthcare [in Dutch]. Amstelveen: College voor zorgverzekeringen (Health Care Insurance Board); 2004.

22. Health Care Insurance Board. Available at: www.medicijnkosten.nl (Medication costs). Accessed September 10, 2007.

23. Briggs AH, Wonderling DE, Mooney CZ. Pulling cost-effectiveness analysis up by its bootstraps: a non-parametric approach to confidence interval estimation. Health Econ. 1997;6:327-340.

24. Campbell MK, Torgerson DJ. Bootstrapping: estimating confidence intervals for cost-effectiveness ratios. QJM. 1999;92:177-182.

25. DiCiccio TJ, Efron B. Bootstrap confidence intervals. Stat Sci. 1996;11:189-228.

26. Briggs A, Fenn P. Confidence intervals or surfaces? Uncertainty on the cost-effectiveness plane. Health Econ. 1998;7:723-740.

27. Briggs AH, O'Brien BJ. The death of cost-minimization analysis? Health Econ. 2001;10:179-184.

28. Al MJ, van Hout BA, Michel BC, Rutten FF. Sample size calculation in economic evaluations. Health Econ. 1998;7:327-335.