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ORIGINAL RESEARCH

Cost-Effectiveness of Asthma Step-Up Therapy as an Increased Dose of Extrafine-Particle Inhaled Corticosteroid or Add-On Long-Acting Beta$_2$-Agonist

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ABSTRACT

Introduction: Data from different healthcare systems on relative cost-effectiveness of asthma step-up therapy strategies are required to inform decision-makers and clinicians. Our objective was to compare cost-effectiveness from the United Kingdom National Health Service perspective of three step-up strategies for patients with asthma uncontrolled by inhaled corticosteroid (ICS) monotherapy.

Methods: This was a historical matched cohort cost-effectiveness analysis of anonymized medical records for patients with asthma of age 12–80 years. We conducted two-way comparisons of step-up therapy using increased dose (≥50%) of extrafine-particle ICS or add-on long-acting β_2-agonist (LABA) via fixed-dose combination (FDC) ICS/LABA inhaler or via separate inhaler. The incremental cost-effectiveness ratio (ICER) was calculated using asthma-related direct costs

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during one outcome year and a composite measure of risk-domain asthma control (no asthma-related hospital attendance, acute oral corticosteroids, or consultation for lower respiratory tract infection).

Results: Patients prescribed ICS dose step-up ($n = 3036$) had significantly lower baseline-adjusted, mean asthma-related healthcare costs during the outcome year than those prescribed FDC ICS/LABA ($n = 3036$; mean difference, £124/year). ICS dose step-up had 56% probability of being less costly and marginally less effective (a trade-off), with ICER of £51,449 per additional patient controlled with FDC; and ICS dose step-up had 44% probability of being the preferred treatment strategy (less costly and more effective). In a second comparison, ICS step-up ($n = 3232$) had 100% probability of being cheaper and more effective than adding LABA to ICS via separate inhalers ($n = 6464$).

Conclusion: For asthma step-up therapy, increasing ICS dose using extrafine-particle ICS is significantly less costly from the payer perspective and marginally (non-significantly) less effective than FDC ICS/LABA therapy containing standard fine-particle ICS. These findings apply primarily to the UK healthcare system but warrant consideration when developing guidelines in settings with strong economic constraints.

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Keywords: Asthma; Beclomethasone dipropionate hydrofluoroalkane; Budesonide/formoterol fumarate dehydrate; Cost-effectiveness; Extrafine-particle inhaled corticosteroid; Fixed-dose combination; Fluticasone propionate/salmeterol xinafoate; Long-acting β_2-agonist

INTRODUCTION

An estimated 334 million people worldwide have asthma, including 5.4 million people in the United Kingdom (UK) on current asthma therapy [1, 2]. Asthma is an important cause of healthcare resource utilization and health-related quality of life impairment [3]. The treatment of asthma is expensive, costing the UK National Health Service (NHS) an estimated £1 billion per year in direct costs, mostly attributable to the cost of prescription medications and hospital admissions [2, 4]. Healthcare resource use and the direct costs of asthma are highest for patients with suboptimal asthma control [5–7]. Considering these costs, it is of utmost importance to generate real-life cost-effectiveness data to help decision-makers and clinicians in their decisions regarding the choice between available treatment options.

The goal of asthma therapy is to achieve the two facets of asthma control, namely, current symptomatic control and minimized risk of future acute exacerbations, which can be life threatening [3]. Asthma therapy is prescribed using a stepwise approach, beginning with

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short-acting bronchodilator (reliever medication, such as short-acting β_2-agonist [SABA]) at step 1 and progressing, as needed, to controller or maintenance therapy at step 2 with an anti-inflammatory medication, such as an inhaled corticosteroid (ICS). For patients receiving ICS monotherapy whose asthma remains uncontrolled, asthma management guidelines then recommend at step 3 the addition of a long-acting bronchodilator (e.g., long-acting β_2-agonist [LABA]), with secondary (less-preferred) options of increasing the ICS dose or adding a leukotriene receptor antagonist (LTRA) [3, 8].

These recommendations are based on the results of randomized controlled trials (RCTs) [3, 8]; however, RCT results have limited generalizability to actual clinical practice. By one estimate up to 95% of patients with asthma would not be eligible for RCTs because of restrictive RCT eligibility criteria, such as the exclusion of smokers or obese patients [9]. Moreover, adherence to therapy and inhaler device technique are better in RCTs than among patients in clinical practice [10, 11]. Relevantly for the step-up comparisons between increasing ICS dose and add-on LABA, most RCTs require enrolled patients to demonstrate substantial reversibility of airflow obstruction to a SABA, thereby selecting for bronchodilator responsiveness and excluding the estimated 70% of patients with asthma who fail to demonstrate sufficient bronchodilator reversibility at any given point in time [9].

Cost-effectiveness analyses of asthma therapies are usually based on economic models drawing on data from RCTs of 12–16 weeks' duration [12–15]. However, long-term clinical practice data may be more directly relevant to inform economic decisions regarding treatment choices for asthma, and effectiveness parameters such as annual exacerbation rates may be more appropriate for making treatment decisions [16, 17]. In addition, most economic models relied on RCTs in which standard fine-particle ICS were administered, namely, ICS with particles of median mass aerodynamic diameter (MMAD) of >2–5 μm. Instead, the newer extrafine-particle ICS (MMAD, ~1 μm) may better treat the small airways, where inflammation is often present in asthma, and thus may be more effective than fine-particle ICS, at least for patients with small airway involvement [18, 19].

In a prior historical matched cohort study comparing step-up alternatives for patients with asthma treated in community settings [20], we found that increasing the ICS dose was as effective in controlling exacerbations over the subsequent year as adding a LABA by fixed-dose combination (FDC) ICS/LABA inhaler. The objective of the present historical matched cohort cost-effectiveness analysis was to compare direct asthma-related healthcare costs and cost-effectiveness from the UK NHS perspective of three common step-up options for asthma: increased dose of extrafine-particle ICS, add-on LABA by FDC ICS/LABA inhaler, and add-on LABA by separate inhaler. Our hypothesis was that increasing the dose of an extrafine-particle ICS would be a cost-effective alternative to therapy with ICS plus LABA in combination or separate inhalers for adults with evidence of persistent asthma. Additionally, we hypothesized that FDC ICS/LABA inhalers would be more cost-effective than separate ICS/LABA inhalers.

METHODS

Data Sources and Patients

The anonymized patient data for this matched cohort study were drawn from two UK primary

care electronic datasets used extensively for pharmacoepidemiologic research and described in detail in prior publications: the General Practice Research Database (GPRD), now part of the Clinical Practice Research Datalink, and the Optimum Patient Care Research Database (OPCRD) [21–24]. Approval was given for use of the GPRD data by the GPRD Independent Scientific Advisory Committee. The OPCRD has been approved by Trent Multi Centre Research Ethics Committee for clinical research use, and the study protocol was approved by ADEPT (Anonymised Data Ethics Protocols and Transparency Committee), OPC's independent scientific advisory committee. Informed patient consent was neither required nor possible to obtain for this non-interventional study using anonymized data. The study was conducted according to standards recommended for observational research (further details in the supplementary material) [25].

The study period ran from January 1997 through January 2011. We included patients with asthma and no other chronic respiratory disease who were 12–80 years old. We excluded active smokers who were 61–80 years old because undiagnosed or comorbid chronic obstructive pulmonary disease is more likely in this older age group than in younger patients [3, 8]. Additional inclusion criteria were ICS monotherapy for asthma during one baseline year; a step up in asthma therapy as one of the three options described below; and 2 years of continuous records in the GPRD or the OPCRD, including one baseline year before and one outcome year after the step-up date (defined as the index date). The three step-up options were as follows:

(1) Extrafine ICS step-up: an increase in ICS dose of ≥50% as an extrafine-particle ICS (beclomethasone dipropionate hydrofluoroalkane [HFA]; Qvar®, Teva Pharmaceutical Industries Ltd., Petach Tikva, Israel), by pressurized metered-dose inhaler (pMDI) or breath-actuated pMDI (BAI)
(2) FDC ICS/LABA: addition of LABA (with no change in ICS dose) using a fixed-dose ICS/LABA combination of either fluticasone propionate/salmeterol xinafoate (Seretide®, GlaxoSmithKline, Middlesex, UK), or budesonide/formoterol fumarate dihydrate (Symbicort®, AstraZeneca, London, UK); or
(3) Separate ICS + LABA: addition of LABA by separate pMDI or BAI, with no change in ICS drug, dose, or inhaler.

Resource Use and Costs

Information on asthma-related resource use was extracted from the databases. We calculated total asthma-related direct costs in 2011 sterling (£) from the UK NHS perspective using unit costs obtained from UK national data sources [26–28], summarized in supplementary Table S1, with further details in the supplemental Methods section in the supplementary material.

Effectiveness Measure

We used a composite database measure for risk-domain asthma control as the effectiveness measure, as reported in previous publications [20, 29–31], defining asthma control as including all of the following: (1) no asthma-related hospital attendance or admission, emergency department (ED) attendance, out-of-hours attendance, or outpatient hospital attendance; and (2) no prescription for an acute course of oral corticosteroids [32]; and (3) no primary care consultation for lower respiratory tract infection [33, 34].

Statistical Analyses

We conducted matched cohort analyses, using two-way matching for the three cohorts, to compare outcomes for age- and sex-matched patients with similar asthma severity and baseline asthma control. Patients were matched sequentially on sex, age, the last ICS daily dose prescribed before the index date, asthma control status, mean daily dose of SABA, and the number of primary care consultations for asthma with no oral corticosteroid prescription (details in the supplementary material). Effectiveness and asthma-related costs were compared by two-way comparisons between (1) the ICS step-up cohort versus the FDC ICS/LABA cohort (comparison 1); (2) the ICS step-up cohort versus the separate ICS + LABA cohort (comparison 2); and (3) the separate ICS + LABA cohort versus the FDC ICS/LABA cohort (comparison 3).

The costs of treatments were compared via the differences in mean asthma-related healthcare costs per patient per year during the outcome period, both unadjusted and adjusted for potential confounders (Table S2 in the supplementary material). Two-way comparisons of summary costs between matched cohorts were carried out using conditional logistic regression. Generalized linear models with a log link and gamma distribution were used to estimate adjusted mean asthma-related healthcare costs per year during the outcome period. Differences in adjusted mean costs are reported with 95% confidence intervals (CIs) found by bootstrapping methods, using 1000 random samples taken, with replacement, from the dataset [35].

The effectiveness of treatments for matched cohorts was compared via the difference in the proportion of patients with asthma control during the outcome year, both unadjusted and adjusted for potential confounders. Adjusted proportions were estimated using generalized linear models with a logit link and binomial distribution. Proportions and differences in proportions of patients with asthma control were reported with 95% CIs found by bootstrapping methods, using the 1000 random samples taken, with replacement, from the dataset.

The two-way differences in total asthma-related costs and proportions of patients with asthma control for the 1000 random samples were displayed graphically on cost-effectiveness planes. When the point estimates for differences in costs and effectiveness indicated a trade-off between treatments (Fig. 1, quadrants I and III), we calculated an incremental cost-effectiveness ratio (ICER) as the ratio of the difference in total asthma-related healthcare costs per patient per year (namely, the incremental cost) to the difference in proportions of patients with asthma control (namely, the incremental gain in effectiveness). When all the replicated data were in one quadrant of the cost-effectiveness plane, the ICER was reported with a 95% CI found by bootstrapping methods. When replicated data covered more than one quadrant, we produced a cost-effectiveness acceptability curve (CEAC) in conjunction with the ICER [36–38].

RESULTS

Patients

We identified 5492, 9207, and 20,657 eligible patients who were prescribed extrafine-particle ICS dose step-up, add-on LABA by FDC ICS/LABA inhaler, and add-on LABA to ICS by separate LABA inhaler, respectively. The

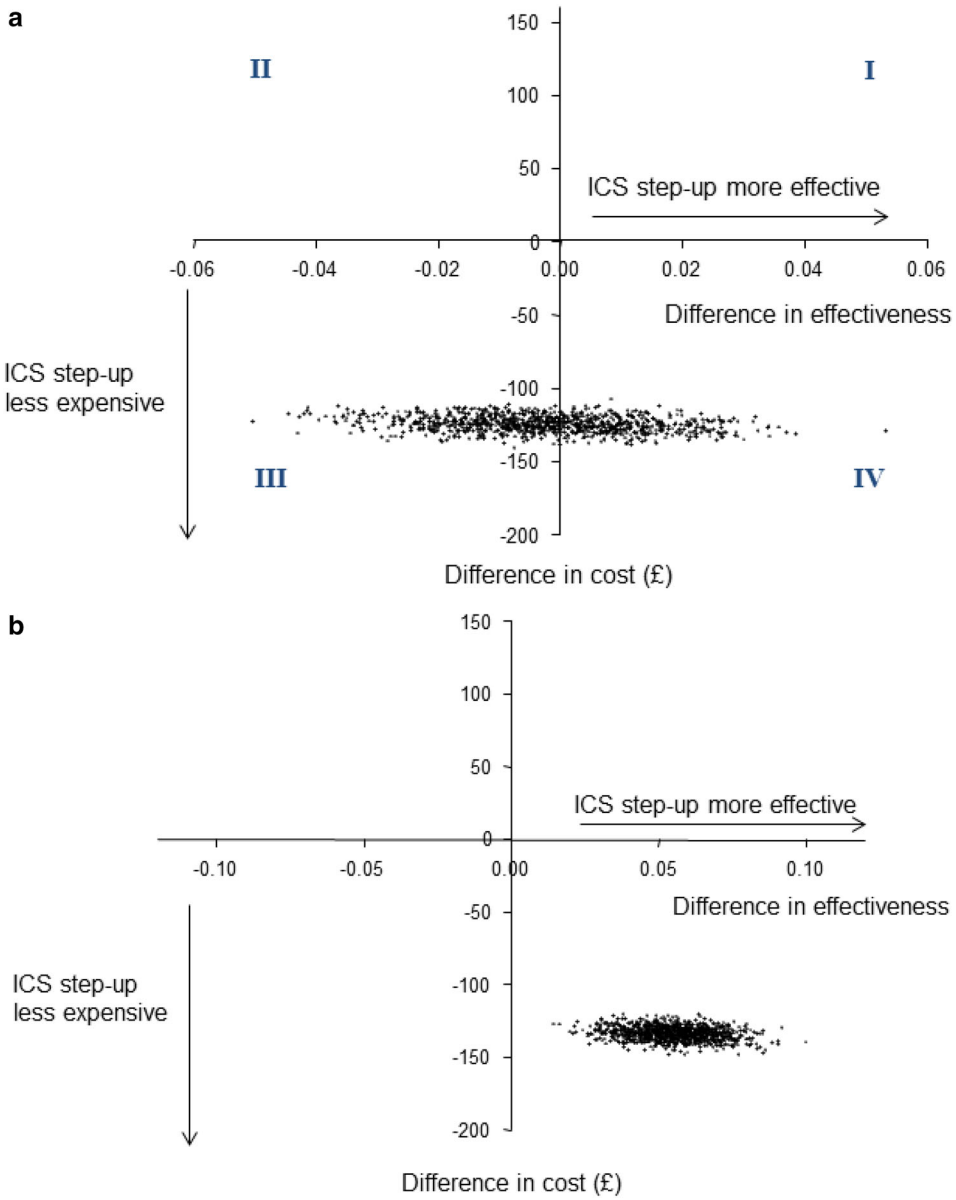

Fig. 1 Cost-effectiveness planes showing the spread of the estimated differences in cost and effectiveness, based on 1000 replicated samples, between **a** the ICS step-up cohort and the FDC ICS/LABA cohort and **b** the ICS step-up cohort and the separate ICS + LABA cohort. Depending where the data points lie, the four quadrants of the cost-effectiveness plane would depict the results of a step-up in asthma therapy by increased dose of extrafine-particle ICS, relative to add-on LABA with ICS in combination (**a**) or separate (**b**) inhalers, as follows: Quadrant I: ICS step-up more costly and more effective (a trade-off); Quadrant II: ICS step-up more costly and less effective (thus, FDC ICS/LABA or separate ICS + LABA dominant); Quadrant III: ICS step-up less costly and less effective (a trade-off); and Quadrant IV: ICS step-up less costly and more effective (ICS step-up dominant). *FDC* fixed-dose combination, *ICS* inhaled corticosteroid, *LABA* long-acting beta$_2$-agonist

matching for the ICS step-up cohort versus the separate ICS + LABA cohort and for the FDC ICS/LABA cohort versus the separate ICS + LABA cohort was in 1:2 ratios because of a baseline imbalance in numbers of unmatched patients. Baseline characteristics of matched patients in comparisons 1 and 2 are in Table S3 in the supplementary material. Approximately 22% of patients in comparisons 1 and 2 were smokers, and approximately 18% were ex-smokers (Table S3).

Full results for comparison 3 (FDC ICS/LABA versus separate ICS + LABA) are reported in Tables S4–S6 in the supplementary material.

In all matched cohorts uncontrolled asthma was associated with increased costs (Table S7).

Comparison 1: Asthma Step-Up Therapy Using an Increased Dose of Extrafine-Particle ICS Versus Add-On LABA by FDC ICS/LABA Inhaler

After matching, there were 3036 patients in the ICS step-up and the FDC ICS/LABA cohorts. Patients' mean (standard deviation) age was 43 (16) years, 60% being women (Table S3 in the supplementary material).

The percentage of patients meeting the risk-domain asthma control measure increased from 65% at baseline to 75% in both cohorts during the outcome year. The complete effectiveness results for comparison 1 have been previously published [20].

During the outcome year, asthma-related resource use was similar in the two cohorts with the exception of expected differences related to study design, such as use of ICS and FDC ICS/LABA inhalers and a greater number of SABA inhalers used by the ICS step-up cohort (Table 1). The mean baseline-adjusted, asthma-related healthcare costs for patients in the ICS step-up cohort were significantly lower than those for patients in the FDC ICS/LABA cohort (mean, £203 vs. £327; Table 2). When adjusted mean costs were combined with the adjusted effectiveness results—using asthma control as the effectiveness measure—there was a 56% probability that stepping up to a higher dose of extrafine-particle ICS would be less costly but less effective (a trade-off) and a 44% probability that ICS step-up would be the preferred treatment strategy (less costly and more effective). The uncertainty around the point estimates is illustrated in the cost-effectiveness plane (Fig. 1a). The point estimate for the ICER was £51,449. The CEAC showed that for no additional cost (willingness to pay = £0) an increased dose of the extrafine-particle ICS was the cost-effective option, since a zero value for the willingness to pay implies that only the cost is important in the cost-effectiveness calculation (Fig. 2).

Comparison 2: Asthma Step-Up Therapy Using an Increased Dose of Extrafine-Particle ICS Versus Add-On LABA by Separate Inhaler

After matching, there were 3232 patients in the ICS step-up cohort and 6464 patients in the separate ICS + LABA cohort. Baseline patient characteristics and asthma-related resource use were similar to those of comparison 1 (Table S3 in the supplementary material).

The percentage of patients meeting the risk-domain asthma control measure increased from 65% at baseline to 75% in the ICS step-up cohort and to 71% in the separate ICS + LABA cohort at outcome.

During the outcome year, most categories of asthma-related resource use and costs were significantly lower for the ICS step-up cohort

Table 1 Mean asthma-related drug prescriptions and unadjusted costs during the outcome year for patients receiving a step-up in ICS dose versus add-on LABA by FDC ICS/LABA inhaler (comparison 1)

Asthma-related resource[b]	Mean (SD) resource use			Mean (SD) resource cost, £		
	ICS dose step-up ($N = 3036$)	FDC ICS/LABA ($N = 3036$)	*P* value[a]	ICS dose step-up ($N = 3036$)	FDC ICS/LABA ($N = 3036$)	*P* value[a]
ICS inhalers	5.7 (4.1)	0.8 (2.3)	<0.001	92 (68)	8 (24)	<0.001
FDC ICS-LABA inhalers	0.9 (3.2)	8.8 (7.3)	<0.001	34 (135)	245 (198)	<0.001
Long-acting β_2-agonist inhalers	0.8 (22.4)	0.2 (4.6)	<0.001	11 (51)	3 (29)	<0.001
Short-acting β_2-agonist inhalers	7.1 (7.7)	5.4 (7.1)	<0.001	27 (58)	22 (55)	<0.001
Leukotriene receptor antagonist prescriptions	0.2 (1.1)	0.2 (1.2)	0.11	6 (41)	7 (40)	0.28
Antibiotic prescriptions[c]	1.0 (1.6)	1.0 (1.5)	0.39	3 (11)	4 (15)	0.30
Oral corticosteroid prescriptions	0.3 (1.0)	0.3 (0.9)	0.067	1 (7)	1 (5)	0.67
Total mean medication costs	–	–	–	174 (182)	290 (220)	<0.001
Total mean medication costs, excluding ICS	–	–	–	49 (92)	37 (77)	<0.001
Primary care asthma consultations	0.9 (1.3)	0.9 (1.3)	0.12	32 (47)	34 (46)	0.12
Total asthma-related hospitalizations	0.0 (0.3)	0.1 (0.3)	0.21	9 (67)	10 (68)	0.34
Asthma-related inpatient	0.0 (0.1)	0.0 (0.1)	0.72	3 (54)	4 (54)	0.72
Asthma-related outpatient	0.0 (0.2)	0.0 (0.3)	0.25	5 (34)	6 (36)	0.25
Asthma-related emergency department visit	0.0 (0.1)	0.0 (0.1)	0.64	0.7 (11)	0.9 (12)	0.64
Total asthma-related primary and secondary care, including ICS costs	–	–	–	215 (226)	334 (254)	<0.001
Total asthma-related primary and secondary care, excluding ICS costs	–	–	–	90 (139)	81 (123)	<0.001

Mean values are reported, despite substantially skewed distributions, because mean values can be multiplied by a target population to estimate total costs and thus are of most interest for policy makers and providers

FDC Fixed-dose combination, *ICS* Inhaled corticosteroid, *LABA* Long-acting β_2-agonist, *SD* Standard deviation

[a] Conditional logistic regression

[b] *Asthma-related* includes all database events coded for asthma and lower respiratory tract infection

[c] Antibiotics prescribed with accompanying lower respiratory tract infection Read code

Table 2 Incremental cost-effectiveness analysis: ICS step-up versus FDC ICS/LABA inhaler (comparison 1) and ICS step-up versus ICS + LABA in separate inhalers (comparison 2)

	Comparison 1		Comparison 2	
	ICS dose step-up (*N* = 3036)	**FDC ICS/LABA (*N* = 3036)**	**ICS dose step-up (*N* = 3232)**	**Separate ICS + LABA (*N* = 6464)**
Risk-domain asthma control, adjusted OR (95% CI)	0.99 (0.88–1.12)[a]	1.00	1.25 (1.13–1.38)[d]	1.00
Risk-domain asthma control, adjusted proportion (95% CI)[b]	0.44 (0.37–0.50)[a]	0.44 (0.37–0.51)[a]	0.61 (0.59–0.63)[d]	0.56 (0.53–0.58)[d]
Difference relative to add-on LABA (95% CI)[b]	0.002 (−0.033 to 0.026)		0.06 (0.03–0.08)	
Adjusted mean asthma-related healthcare costs per patient per year (95% CI)[b,c]	£203 (£197–£210)	£327 (£319–£336)	£204 (£197–£210)	£337 (£332–£344)
Difference relative to add-on LABA (95% CI)[b]	−£124 (−£135 to −£114)		−£134 (−£142 to −£125)	
	Trade-off: ICS step-up significantly less costly but marginally less effective		ICS step-up dominant: less costly and more effective than separate ICS + LABA	
Cost-effectiveness ratio (ICER)	£51,499			

Confidence intervals determined using bootstrapping methods with 1000 random samples

CI confidence interval, *FDC* fixed-dose combination, *ICER* incremental cost-effectiveness ratio, *ICS* Inhaled corticosteroid, *LABA* long-acting β_2-agonist, *OR* Odds ratio

[a] Adjusted for: smoking status (current smoker/ex-smoker/nonsmoker/not specified), outpatient department attendance for asthma/lower respiratory reasons, number of acute oral corticosteroid prescriptions, and oral thrush

[b] Confidence intervals determined using bootstrapping methods with 1000 random samples

[c] Adjusted for baseline asthma-related healthcare costs

[d] Adjusted for number of acute oral corticosteroid prescriptions

(Table 3), and the mean baseline-adjusted, asthma-related healthcare costs for patients in the ICS step-up cohort were significantly lower compared with those for patients remaining on the same ICS dose but adding a separate LABA (£204 vs. £337; Table 2). When costs were combined with the adjusted effectiveness results, there was a 100% probability that stepping up to a higher dose of extrafine-particle ICS would be less costly and more effective than adding a LABA by separate inhaler (Fig. 1b).

DISCUSSION

In this matched cohort cost-effectiveness study, UK patients stepping up to a higher dose of extrafine-particle ICS had significantly lower baseline-adjusted mean asthma-related healthcare costs compared with patients stepping up to an FDC ICS/LABA inhaler (mean difference of £124 per annum) during one outcome year. When these costs were combined with the adjusted effectiveness results, there was a 56% probability that

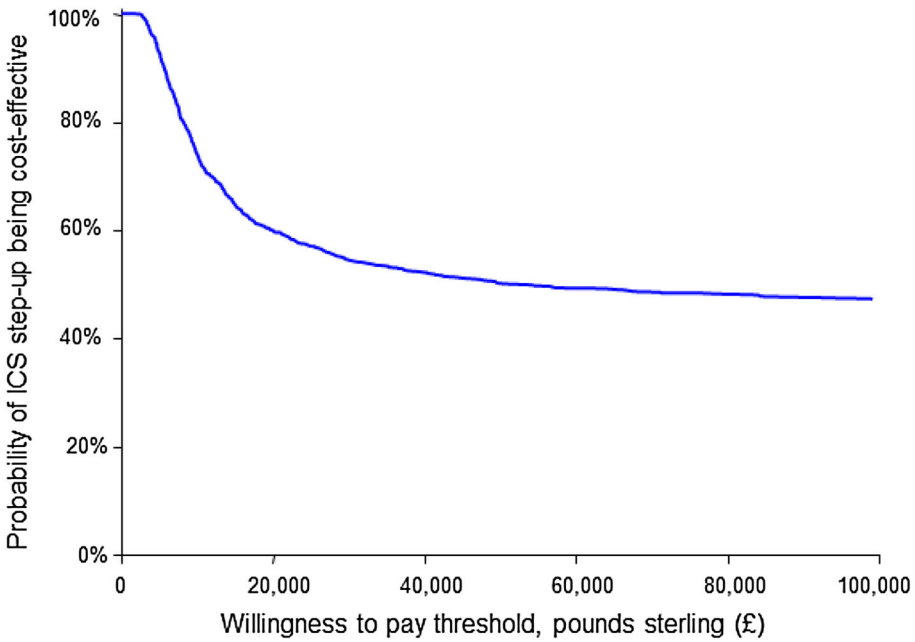

Fig. 2 Cost-effectiveness acceptability curve for an increased dose of extrafine-particle ICS (ICS step-up) relative to add-on LABA in a fixed-dose combination inhaler with ICS (ICS/LABA combination): Probability of ICS step-up being cost-effective from the UK NHS perspective, adjusted results. *ICS* Inhaled corticosteroid, *LABA* Long-acting beta$_2$-agonist, *UK NHS* United Kingdom National Health Service

stepping up to a higher dose ICS would be less costly but less effective (a trade-off); a point estimate for the ICER, the monetary value of the intangible benefit to patients or society beyond the cost to achieve an additional controlled patient using an FDC ICS/LABA inhaler, was £51,449, reflecting the significantly higher costs of FDC therapy and the non-significant difference in effectiveness between treatments. There was a 44% probability that stepping up to a higher dose of extrafine-particle ICS would be the preferred treatment strategy (less costly and more effective). In our second comparison, ICS step-up was the preferred treatment strategy compared with adding LABA via separate inhaler: there was a 100% probability that stepping up to a higher dose of extrafine-particle ICS would be less costly and more effective. Of the two add-on LABA alternatives (comparison 3, reported in the supplementary material) prescribing an FDC ICS/LABA inhaler was more costly but also more effective (with 100% probability) than prescribing a separate add-on LABA inhaler.

This study compared asthma-related direct costs for different step-up strategies in a primary care setting, which is where most patients with asthma receive treatment in the UK, as in many countries [39, 40]. There are only a few studies that have examined real-life comparative costs for asthma step-up therapy [41, 42]. For patients with recent exacerbation or frequent SABA use identified in a recent retrospective cohort study conducted using a large US health insurance dataset, Hagiwara and coworkers [41] found that fluticasone/salmeterol combination was more effective in decreasing exacerbations and SABA use but more expensive than ICS dose step-up with fluticasone. In a broad United States (US) asthma population studied in

Table 3 Mean asthma-related drug prescriptions and unadjusted costs during the outcome year for patients receiving a step-up in ICS dose versus add-on LABA by separate inhaler + ICS (comparison 2)

Asthma-related resource[c]	Mean (SD) resource use			Mean (SD) resource cost, £		
	ICS dose step-up ($N = 3232$)	Separate ICS + LABA ($N = 6464$)	*P* value[a]	ICS dose step-up ($N = 3232$)	Separate ICS + LABA ($N = 6464$)	*P* value[a]
ICS inhalers	5.7 (4.1)	4.5 (4.1)	<0.001	91 (69)	43 (50)	<0.001
Fixed-dose combination ICS/LABA inhalers	0.9 (3.2)	1.6 (4.5)	<0.001	34 (134)	57 (168)	<0.001
Long-acting β_2-agonist inhalers	0.8 (21.8)	5.8 (24.7)	<0.001	11 (52)	155 (150)	<0.001
Short-acting β_2-agonist inhalers	7.1 (8.0)	6.5 (7.7)	<0.001	27 (58)	25 (51)	0.072
Leukotriene receptor antagonist prescriptions	0.2 (1.0)	0.2 (1.2)	0.26	6 (42)	6 (40)	0.85
Antibiotic prescriptions	1.0 (1.7)	1.0 (1.9)	0.54	3 (11)	4 (15)	0.33
Oral corticosteroid prescriptions	0.4 (1.0)	0.4 (1.1)	<0.001	1 (6)	2 (6)	<0.001
Total mean medication costs	–	–	–	174 (182)	292 (242)	<0.001
Total mean medication costs, excluding ICS	–	–	–	49 (92)	192 (173)	<0.001
Primary care asthma consultations	0.9 (1.3)	1.1 (1.4)	<0.001	33 (48)	41 (52)	<0.001
Total asthma-related hospitalizations	0.0 (0.3)	0.1 (0.3)	0.050	8 (62)	13 (93)	0.006
Asthma-related inpatient	0.0 (0.1)	0.0 (0.1)	0.011	3 (49)	7 (80)	0.011
Asthma-related outpatient	0.0 (0.2)	0.0 (0.3)	0.16	4 (32)	5 (36)	0.16
Asthma-related emergency department visit	0.0 (0.1)	0.0 (0.1)	0.94	1 (13)	1 (13)	0.94
Total asthma-related primary and secondary care, including ICS costs	–	–	–	215 (224)	345 (283)	<0.001
Total asthma-related primary and secondary care, excluding ICS costs	–	–	–	90 (136)	246 (209)	<0.001

Mean values are reported, despite substantially skewed distributions, because mean values can be multiplied by a target population to estimate total costs and thus are of most interest for policy makers and providers

ICS inhaled corticosteroid, *LABA* long-acting β_2-agonist, *SD* standard deviation

[a] Conditional logistic regression

[b] *Asthma-related* includes all database events coded for asthma and lower respiratory tract infection

2002–2004, direct medical costs and asthma-related healthcare resource utilization were lower with ICS monotherapy as compared with FDC ICS/LABA therapy (cost-effectiveness was not reported) [42]. Other published cost-effectiveness analyses based on short-term RCT results report that FDC ICS/LABA therapy, while more expensive, usually meets benchmarks for cost-effectiveness [12–15].

Administering LABA by separate inhaler was not a cost-effective alternative in this study as compared with either ICS step-up or an FDC ICS/LABA inhaler. Similar findings were reported in prior RCTs [13]. In addition, administering LABA by separate inhaler is discouraged by asthma guidelines because LABA monotherapy (without ICS) has been associated with serious adverse asthma-related outcomes, including deaths, seen in early trials [8, 43]. Instead, an FDC ICS/LABA inhaler is recommended to ensure that patients take concomitant ICS.

A strength of this study is the large patient population, with over 38,000 patients studied, and the minimal exclusion criteria designed to capture data for a broad general population treated for asthma in primary care. Treatment cohorts were matched according to several criteria reflecting baseline asthma severity and control. Effectiveness measures were adjusted for residual confounding. Nonetheless, we cannot exclude the possibility of unrecognized confounders, including measures that were not available for all patients, such as smoking status and socioeconomic status, or that were not present in the database, such as pack-years of smoking. We were limited to the available database information in developing our asthma control measure; however, it would have been of interest to also include patient-reported outcomes (including actual SABA use rather than inhalers prescribed) in our definition of asthma control, as 58–65% of each cohort were evaluated as controlled at baseline according to our measure. Nevertheless, all patients were prescribed a step-up in therapy at the index date, which suggests that they or their physician did not consider their asthma to be well-controlled.

We had no way to measure patient satisfaction with therapy; however, we inferred from the treatment change data in the companion effectiveness study that there were no major differences in patient satisfaction between ICS step-up and FDC ICS/LABA step-up as the same proportions of patients in the two cohorts changed therapy during the outcome year [20]. Nevertheless, the issue of patient satisfaction with step-up therapy would be an important outcome to explore in a pragmatic trial. Patient satisfaction and patient preferences are potentially important influences on patient adherence to therapy and hence must be factored into clinical prescribing decisions [3, 8]. In addition, ICS doses should be tailored to the level of symptom control, lung function, and exacerbations, all relating to the degree of airways inflammation.

Double counting may have occurred in this analysis because the numerator included the difference in costs of asthma-related resource utilization and the asthma control effectiveness measure was a function of asthma-related events. Therefore, the cost estimates in the ICERs are interpreted as the willingness-to-pay over and above the cost to achieve an additional controlled patient. In other words, ICERs in this case represent the monetary value of the intangible benefit to patients or society beyond the cost to achieve an additional controlled patient over the outcome period [44].

The ICER of £51,000 for prescribing FDC ICS/LABA therapy instead of ICS dose step-up was

calculated using a composite database measure of risk-domain asthma control as the effectiveness measure. The more common calculation of ICER per additional quality-adjusted life-year (QALY), as used by the UK National Institute for Health and Care Excellence (NICE), was not possible from the available data. The cost-effectiveness threshold used by NICE is £20,000 to £30,000 for cost per QALY [45]. Because of our approach in using an intermediate effectiveness measure instead of a composite measure such as QALYs, we cannot make comparisons to results from cost-utility analyses for unrelated interventions or treatments. To increase comparability with unrelated interventions, future pragmatic trials should address treatment preferences to calculate both within-trial cost-per-QALY ratios and projected lifetime cost-per-QALY ratios using assumptions around asthma-specific mortality.

In addition, our study findings apply primarily to the UK healthcare system, and further investigations are needed from other perspectives, using different effectiveness measures, and in the setting of other healthcare systems, as costs are highly variable among countries. Moreover, prescribing preferences can vary according to location. Assessment of indirect costs is needed as well.

We chose to investigate extrafine-particle beclomethasone, with aerosol particle MMAD of 1.1 μm, for the ICS step-up therapy because of its good distribution to the small airways, often a site of persistent inflammation in patients with poorly controlled asthma [18, 46–48]. In a prior, similarly designed cost-effectiveness study of patients initiating ICS therapy for asthma, we found that initiating with an extrafine ICS as compared with standard fine-particle ICS (MMAD of 2.4–3.2 μm, depending on formulation) had ≥84% probability of being the preferred treatment, i.e., less costly and more effective, in both the UK and the USA [49]. Further observational studies are needed to compare the cost-effectiveness of step-up regimens with other extrafine-particle ICS, such as ciclesonide (MMAD of 1.0 μm), and the standard fine-particle ICS, such as fluticasone (MMAD, 2.4–5.4 μm) and budesonide (MMAD, ∼4.0 μm).

CONCLUSIONS

We found that, among available step-up therapy alternatives for adults with persistent asthma on ICS monotherapy cared for in UK clinical practice, adding a LABA via separate inhaler is the least cost-effective option. Increasing extrafine-particle ICS dose is significantly less costly from the payer perspective and marginally (non-significantly) less effective than FDC ICS/LABA therapy containing standard fine-particle ICS. From the UK NHS payer perspective, the cost to achieve an additional controlled patient using an FDC ICS/LABA combination rather than ICS dose step-up using extrafine particles is very high (£51,449). In countries with strong economic constraints, this may lead to questioning the recommendation of FDC ICS/LABA as first choice when treatment step-up is required, especially when considering that extrafine-particle ICS dose step-up has a 44% probability of being the cost-effective option relative to FDC ICS/LABA. These findings warrant further investigation in other healthcare systems and with a range of ICS in pragmatic trials and observational studies.

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Compliance with Ethics Guidelines. This was a retrospective study utilizing anonymized patient data, for which formal consent is not required.

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