Increased Dose of Inhaled Corticosteroid versus Add-On Long-acting β-Agonist for Step-Up Therapy in Asthma

Elliot Israel[1], Nicolas Roche[2], Richard J. Martin[3], Gene Colice[4], Paul M. Dorinsky[5], Dirkje S. Postma[6], Theresa W. Guilbert[7], Willem M. C. van Aalderen[8], Jonathan Grigg[9], Elizabeth V. Hillyer[10], Anne Burden[10], Julie von Ziegenweidt[10], Victoria Thomas[10], and David B. Price[10,11]

[1]Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; [2]Cochin Hospital Group, Assistance Publique-Hôpitaux de Paris, University of Paris Descartes, Paris, France; [3]National Jewish Health and University of Colorado Denver, Denver, Colorado; [4]Washington Hospital Center and George Washington University School of Medicine, Washington, DC; [5]Cipla Europe NV, Antwerp, Belgium; [6]Department of Pulmonary Medicine and Tuberculosis, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; [7]Cincinnati Children's Hospital and Medical Center, Cincinnati, Ohio; [8]Emma Children's Hospital Academisch Medisch Centrum, Amsterdam, The Netherlands; and [9]Blizard Institute, Queen Mary University of London; [10]Research in Real-Life, Ltd, Cambridge, and [11]Academic Primary Care, University of Aberdeen, Aberdeen, United Kingdom

Abstract

Rationale: Guidelines advocate adding long-acting β-agonist (LABA) to inhaled corticosteroid as the preferred step-up therapy to increasing inhaled corticosteroid dose for patients with uncontrolled asthma on inhaled corticosteroid monotherapy. However, less than 5% of patients with asthma qualify for the randomized controlled trials on which guidelines are based. Thus, real-world data are needed to complement the results of randomized trials with narrow entry criteria.

Objectives: To compare the effectiveness of stepping up asthma therapy with an increased dose of various types of inhaled corticosteroid as compared with add-on LABA.

Methods: We performed a historical matched cohort study using large primary care databases to compare asthma step-up therapy with small- and standard size–particle inhaled corticosteroid versus added LABA for patients 12–80 years old. As outcomes, we examined a composite of asthma control and rates of severe exacerbations.

Measurements and Main Results: The odds of asthma control and rates of severe exacerbations over one outcome year were comparable with increased inhaled corticosteroid dose versus added LABA. The adjusted odds ratios (95% confidence interval) for achieving asthma control with increased inhaled corticosteroid dose versus inhaled corticosteroid/LABA were 0.99 (0.88–1.12) for small-particle inhaled corticosteroid (n = 3,036 per cohort) and 0.85 (0.67–1.07) for standard size–particle inhaled corticosteroid (n = 809 per cohort). The adjusted rate ratios (95% confidence interval) for severe exacerbations, compared with inhaled corticosteroid/LABA combination inhaler, were 1.04 (0.91–1.20) and 1.18 (0.92–1.54), respectively. The results were not affected by smoking status.

Conclusions: When applied to a broad primary care population, antiinflammatory therapy using increased doses of small- or standard size–particle inhaled corticosteroid is as effective as adding LABA, as measured by outcomes important to both patients and providers. Real-world populations and outcomes need to be taken into consideration when formulating treatment recommendations.

Keywords: adrenergic β_2-agonists; antiasthmatic agents; bronchodilator agents; disease exacerbation; glucocorticoids

(Received in original form December 17, 2014; accepted in final form March 4, 2015)

Supported by an unrestricted grant from Teva Pharmaceuticals Limited (Petach Tikva, Israel) (data acquisition and analyses). Access to data from the Optimum Patient Care Research Database was cofunded by Research in Real-Life Ltd (RiRL). Data were collected and analyzed by the authors in the research team at RiRL, and the first draft of the manuscript was written by one of the authors. Teva played no role in study conduct or analysis and did not modify or approve the manuscript.

Author Contributions: D.B.P. and A.B. led the study design process; and all authors contributed to the design review. A.B., V.T., and J.v.Z. are responsible for the data acquisition and analyses; E.I. supervised the analysis process. E.V.H. developed the first draft of the manuscript and E.I. supervised all versions. All authors analyzed the data, reviewed drafts of the manuscript, and approved the final draft of the manuscript for submission. All members of the Steering Committee and additional experts who are responsible for this study are listed as authors of the study.

Correspondence and requests for reprints should be addressed to Elliot Israel, M.D., Pulmonary and Critical Care Division, Brigham and Women's Hospital and Harvard Medical School, 75 Francis Street, Boston, MA 02115. E-mail: eisrael@partners.org, eisraelasst@partners.org

This article has an online supplement, which is accessible from this issue's table of contents online at www.atsjournals.org

Ann Am Thorac Soc Vol 12, No 6, pp 798–806, Jun 2015

DOI: 10.1513/AnnalsATS.201412-580OC
Internet address: www.atsjournals.org

For many patients with asthma, the addition of a long-acting bronchodilator to inhaled corticosteroid (ICS) reduces symptoms and decreases the need for short-acting bronchodilators. Whether relief of symptoms by regular bronchodilator therapy might mask processes that lead to asthma deterioration and serious asthma-related outcomes such as hospitalizations, intubations, and deaths had been a concern raised in studies using long-acting β-agonists (LABAs) as monotherapy (1) and led to recommendations that LABAs not be used as monotherapy in asthma (2, 3). However, randomized controlled trials in which the addition of LABA to ICS was compared with increasing the dose of ICS repeatedly suggested that adding a LABA is superior not only regarding symptom control, but more importantly regarding exacerbations (4–11). As a result, international management guidelines recommend the addition of LABA as a preferred step-up therapy for patients whose asthma is not controlled with low to moderate doses of ICS (2, 12).

Observational studies, however, have suggested that only less than 5% of patients with asthma qualify to enroll in randomized controlled asthma trials, which represent the primary source of information for guidelines (13). A substantial proportion of patients are not eligible for asthma trials because they smoke (approximately 20–35%) (14) or have comorbidities. Moreover, the trials that have compared ICS step-up with add-on LABA have almost uniformly been restricted to patients who demonstrate acute reversibility to a β-agonist. This entry criterion enriches the population for β-agonist responders, who do not accurately represent the general asthma population: up to 70% of real-life patients with asthma may not meet the bronchodilator response criteria employed by many trials (13). Furthermore, these trials have frequently included outcomes that "mechanically" favor β-agonist effects, such as improved airflow or reduced β-agonist use. Whether such superiority occurs in a wider range of patients and using real-world outcomes such as clinically defined exacerbations (without airflow determinants), emergency visits, and hospitalizations is unclear. This is particularly important because the safety of long-term LABA therapy as used in real life has been questioned regarding increased serious asthma-related events such as hospitalization and mortality, even for patients receiving concomitant ICS (3, 15–17).

In addition, the relevance of an exacerbation outcome that includes a decline in peak flow, which can be disproportionately affected by β-agonists, has also been questioned (18). In fact, an analysis of almost 2,000 patients who took part in a randomized trial of ICS step-up versus add-on LABA showed that when peak flow was removed from the definition of exacerbations, there was no advantage to add-on LABA over ICS dose step-up (19). In the Gaining Optimal Asthma ControL (GOAL) trial, a 1- to 1.5-fold increase in the ICS dose produced an equal or greater proportion of patients who were well controlled or completely controlled, as did add-on LABA (6).

Real-world data are thus needed to complement the results of randomized controlled trials with narrow entry criteria and enforced adherence to prescribed medication (20). Real-world research can address clinical questions for a wider group of patients, such as the impact over 1 year of starting a LABA as part of a fixed-dose combination versus increasing ICS for all patients managed as having asthma in usual care. By contrast, the questions in RCTs usually focus on a specific subgroup of patients, for example, patients with asthma who have at least 15% reversibility, impaired lung function, limited smoke exposure, good inhaler technique, good adherence, limited exacerbation history, and limited comorbidities and who are managed with regular and detailed follow-up.

We therefore conducted a historical matched cohort study to compare the effectiveness of stepping up asthma therapy with an increased dose of different types of ICS as compared with add-on LABA. In prior work we found evidence of a differential effect based on particle size of the ICS (21–23). Thus we compared ICS dose step-up with representative small-particle ICS and standard size–particle ICS versus add-on LABA by ICS/LABA combination inhaler. Some of the results of this study have been previously reported in the form of abstracts (24, 25).

Methods

Data Source and Patients

We drew on two large, well-validated U.K. primary care electronic databases, the General Practice Research Database (GPRD; now part of the Clinical Practice Research Datalink) (26) and the Optimum Patient Care Research Database (OPCRD), both used for respiratory research and previously well described (*see* the online supplement) (27). Patient characteristics were cross-referenced between the two databases to ensure study of unique individuals.

We studied patients with asthma, aged 12–80 years, who had 2 years of continuous data (1 baseline year followed by 1 outcome year, separated by the index date at which stepping up therapy was recorded) within the study window from January 1997 through January 2011. During the baseline year before stepping up therapy, eligible patients had at least two prescriptions for asthma controller or reliever therapy, including at least one for ICS. Allowed ICS during the baseline year included beclomethasone, budesonide, or fluticasone administered by pressurized metered-dose inhaler (pMDI) or breath-actuated MDI (BAI); patients prescribed an ICS/LABA combination inhaler were excluded. Other exclusion criteria were a recorded diagnosis of chronic obstructive pulmonary disease (COPD) or any chronic respiratory disease other than asthma and, for patients 61–80 years of age, any history of smoking (to minimize the possibility of including patients with COPD misdiagnosed as asthma).

Our primary analysis compared an increase of at least 50% in the dose of small- or standard size–particle ICS (*ICS step-up*) via pMDI or BAI versus fixed dose ICS/LABA (*ICS/LABA combination*) with no change in ICS dose. For the ICS step-up, we captured data for patients prescribed a representative small-particle formulation (beclomethasone dipropionate HFA [Qvar; Teva UK Ltd, Eastbourne, East Sussex, UK]; median mass aerodynamic diameter [MMAD] particle size, 1.1 μm) and a representative standard size–particle ICS (fluticasone propionate, hydrofluoroalkane or chlorofluorocarbon formulation [Flixotide; GlaxoSmithKline UK Ltd, Brentford, Middlesex, UK]; MMAD, 2.4–3.2 μm, depending on formulation). The ICS/LABA combinations were either fluticasone propionate/salmeterol xinafoate (Seretide; GlaxoSmithKline) or budesonide/formoterol fumarate dihydrate (Symbicort; AstraZeneca Ltd, Luton, Bedfordshire, UK).

Outcome Measures

Composite database measures, as previously described (21–23), were used to assess asthma control and relative rates of exacerbations; full details and all end points

are described in Table 1. In brief, we defined *severe exacerbations* according to expert working group recommendations (asthma-related hospital or emergency department attendance, or short course of oral corticosteroids) (28). We defined an end point of risk-domain asthma control (*asthma control*) as an absence of severe exacerbations (as described above) in addition to no general practice (GP) consultations for lower respiratory tract infection, because in practice asthma exacerbations can be confused with lower respiratory infection (29, 30).

Patients who remained on the same dose of ICS throughout the follow-up year were captured in the *treatment stability* measure, which included patients with asthma control and no treatment change (*see* Table 1). Those patients who had a prescribed increase in ICS dose or additional therapy during outcome were recorded as having a *treatment change*. Other end points, including *acute respiratory events*, are defined in Table 1.

Statistical Analysis

We elected to conduct matched cohort analyses because characterization of patients at baseline indicated statistically and clinically significant differences between cohorts (*see* the online supplement). Two-way cohort matching was performed, with ratios determined according to patient numbers to maximize both cohort sizes and the number of matched groupings, and thus the power of statistical tests. The two ICS step-up cohorts were each separately matched 1:1 to the ICS/LABA combination cohort. Matching criteria were applied sequentially and included demographic characteristics and key indicators of asthma severity and control during the baseline year, listed in Table 1. Matching was conducted before the analysis of outcomes and thus was blinded to outcomes.

We described cohort baseline and outcome characteristics using summary statistics. Variables measured on the interval or ratio scale were categorized for the analyses if heavily skewed. Two-way differences between matched cohorts at baseline and outcome were analyzed by conditional logistic regression. We assessed numerous potential confounding variables (*see* the online supplement for additional details).

The adjusted odds of asthma control were compared in two-way analyses using conditional logistic regression. The dichotomous asthma control measure was used as the dependent variable, with treatment and potential confounding factors as explanatory variables. The same modeling approach was used for determining the adjusted odds of achieving treatment stability.

The rates of severe exacerbations during the outcome period were compared between cohorts, using conditional Poisson regression to determine exacerbation rate ratios and using empirical standard errors for more robust confidence intervals; adjustments were made for potential baseline confounders. Adjusted rate ratios were calculated in similar fashion for acute respiratory events and incidence of oropharyngeal candidiasis (thrush). In addition, we conducted a sensitivity analysis comparing severe exacerbation and acute respiratory event rates among nonsmokers in the matched pairs that remained after excluding smokers.

Statistically significant results were defined as $P < 0.05$. Analyses were performed with IBM SPSS Statistics version 19 (SPSS Statistics; IBM, Somers, NY), SAS version 9.2 (SAS Institute, Cary, NC), and Microsoft Office Excel 2007 (Microsoft, Bellevue, WA).

Table 1. Study definitions: database-derived outcome measures and matching criteria

Primary end point
- Asthma control (risk domain), includes *all* of the following:
  1. No asthma-related* hospital attendance or admission, ED attendance, out-of-hours attendance, or outpatient hospital attendance, *and*
  2. No GP consultation for lower respiratory tract infection,† *and*
  3. No prescription for acute course of oral corticosteroids.

Secondary end points
- Number of severe exacerbations,‡ defined as *any* of the following (28):
  1. Asthma-related* hospital attendance or admission or ED attendance, *or*
  2. Acute course of oral corticosteroids
- Number of acute respiratory events, defined as *any* of the following:
  1. Asthma-related* hospital attendance or admission or ED attendance, *or*
  2. Acute course of oral corticosteroids, *or*
  3. GP consultation for lower respiratory tract infection†
- Treatment stability, includes *all* of the following:
  1. Asthma controlled (primary end point; *see above*) *and*
  2. No treatment change, defined as additional therapy or change in therapy as
     a. Increased ICS dose (by ⩾50%), *or*
     b. Use of additional therapy as LABA, LTRA, or theophylline

Matching criteria: Patients were matched sequentially at the index prescription date by:
1. Sex (male/female)
2. Age (±5 yr)
3. Last ICS daily dose prescribed before index date prescription (categorized as 1–50 μg/51–100 μg/101–200 μg/201–300 μg/301–400 μg/>400 μg in extrafine beclomethasone equivalents§)
4. Asthma control (defined as for primary end point) during baseline year (controlled/not controlled)
5. Mean SABA daily dose during baseline year‖ (categorized as 0 μg/1–200 μg/201–400 μg/>400 μg)
6. Asthma consultation(s) without severe exacerbation (0/1/⩾2)

Definition of abbreviations: ED = emergency department; GP = general practice; ICS = inhaled corticosteroid; LABA = long-acting β-agonist; LTRA = leukotriene receptor antagonist; SABA = short-acting β-agonist.

*Asthma-related events in the database were defined as all events with a lower respiratory code, including all asthma codes and lower respiratory tract infection codes.

†Identified as general practice consultations with a lower respiratory tract infection Read code in the database.

‡Hospital attendance/admission and/or oral corticosteroid course within 2-week window were considered as one exacerbation.

§Doses of budesonide and large-particle beclomethasone (Clenil Modulite; Chiesi) were halved, and fluticasone doses of 250 and 500 μg were treated as equivalent to small-particle beclomethasone at 200 and 400 μg.

‖SABA daily dose was defined as total prescribed SABA during baseline year divided by 365.

Results

Small-Particle Inhaled Corticosteroid Dose Step-Up Compared with ICS/LABA Combination Inhaler

After matching, there were 3,036 patients in each cohort (*see* Figures E1 and E2 in the online supplement). The cohorts were well matched for baseline asthma-related measures and comorbidities; statistically

Table 2. Baseline demographic and clinical characteristics of the patients in inhaled corticosteroid (ICS) dose step-up and ICS/long-acting β-agonist combination inhaler cohorts

Characteristic	Small-Particle ICS Step-Up vs. ICS/LABA Combination Inhaler		Standard Size–Particle ICS Step-Up vs. ICS/LABA Combination Inhaler	
	ICS Dose Step-Up (*n* = 3,036)	ICS/LABA Combination (*n* = 3,036)	ICS Dose Step-Up (*n* = 809)	ICS/LABA Combination (*n* = 809)
Female sex, n (%)*	1,811 (59.7)	1,811 (59.7)	508 (62.8)	508 (62.8)
Age at index date (yr), mean (SD)*	42.7 (16.4)	42.6 (16.5)†	42.8 (17.6)	42.7 (17.4)
Nonsmokers 61–80 yr, n (%)	417 (13.7)	429 (14.1)	128 (15.8)	128 (15.8)
Asthma control, n (%)*	1,978 (65.2)	1,978 (65.2)	495 (61.2)	495 (61.2)
Mean daily SABA dose, n (%)*				
0 μg/d	145 (4.8)	145 (4.8)	43 (5.3)	43 (5.3)
1–200 μg/d	1,241 (40.9)	1,241 (40.9)	306 (37.8)	306 (37.8)
201–400 μg/d	754 (24.8)	754 (24.8)	202 (25.0)	202 (25.0)
>400 μg/d	896 (29.5)	896 (29.5)	258 (31.9)	258 (31.9)
Last ICS dose before index date (μg/d), mean (SD)*‡	199 (44)	200 (51)§	260 (138)	290 (218)§
Index date dose of ICS (μg/d), mean (SD)	402 (89)	202 (59)§	674 (289)	294 (227)
Asthma consultation/no severe exacerbation, n (%)*				
0	1,122 (37.0)	1,122 (37.0)	199 (24.6)	199 (24.6)
1	1,063 (35.0)	1,063 (35.0)	313 (38.7)	313 (38.7)
2	568 (18.7)	506 (16.7)‖	187 (23.1)	176 (21.8)
⩾3	283 (9.3)	345 (11.4)	110 (13.6)	121 (15.0)
Smoking status, n (%)¶				
Current smoker	592 (22.5)	575 (20.6)§	118 (14.6)	152 (20.5)§
Ex-smoker	477 (18.2)	516 (18.4)	140 (17.3)	128 (17.2)
Nonsmoker	1,559 (59.3)	1,706 (61.0)	549 (68.0)	463 (62.3)
Rhinitis, n (%)**	765 (25.2)	780 (25.7)	203 (25.1)	203 (25.1)
Gastroesophageal reflux, n (%)**	346 (11.4)	349 (11.5)	96 (11.9)	77 (9.5)
Cardiac disease, n (%)**	162 (5.3)	129 (4.2)†	86 (10.6)	46 (5.7)§
Year of index prescription, mean (SD)	2005 (2.6)	2005 (2.1)‖	2007 (1.3)	2005 (2.2)§
Years since first asthma code, median (IQR)	8.5 (2.6–15.9)	7.8 (1.9–15.4)	9.5 (3.1–17.1)	7.3 (1.8–14.3)§
Peak expiratory flow (% predicted), mean (SD)¶	85.1 (19.7)	83.7 (19.1)	82.9 (20.4)	84.5 (19.6)
Severe exacerbations, n (%)				
0	2,270 (74.8)	2,275 (74.9)	579 (71.6)	587 (72.6)
1	534 (17.6)	546 (18.0)	142 (17.6)	147 (18.2)
2	159 (5.2)	147 (4.8)	61 (7.5)	49 (6.1)
⩾3	73 (2.4)	68 (2.2)	27 (3.3)	26 (3.2)
Antibiotic prescriptions for LRTI, n (%)				
0	2,542 (83.7)	2,540 (83.7)	664 (82.1)	658 (81.3)
1	369 (12.2)	352 (11.6)	104 (12.9)	112 (13.8)
⩾2	125 (4.1)	144 (4.7)	41 (5.1)	39 (4.8)

Definition of abbreviations: ICS = inhaled corticosteroid; IQR = interquartile range; LABA = long-acting β-agonist; LRTI = lower respiratory tract infection; SABA = short-acting β-agonist.

*Matching variable.

†$P \leqslant 0.05$, conditional logistic regression for two-way comparisons between cohorts.

‡For matching purposes, doses of budesonide and large-particle beclomethasone (Clenil Modulite; Chiesi) were halved, and fluticasone doses of 250 and 500 μg were treated as equivalent to extrafine beclomethasone at 200 and 400 μg, respectively. Instead, baseline year ICS doses are reported as halved budesonide doses and actual extrafine beclomethasone and fluticasone doses.

§$P < 0.001$, conditional logistic regression for two-way comparisons between cohorts.

‖$P < 0.01$, conditional logistic regression for two-way comparisons between cohorts.

¶Recorded smoking data were available for 2,628 (86.6%) and 2,797 (92.1%) of patients in small-particle ICS step-up and ICS/LABA combination cohorts, respectively, and for 807 (99.8%) and 743 (91.8%) in standard size–particle ICS step-up and ICS/LABA combination cohorts, respectively; recorded peak expiratory flow data were available for 2,116 (69.7%) and 2,022 (66.6%) in small-particle ICS step-up and ICS/LABA combination cohorts, respectively, and for 536 (66.3%) and 552 (68.2%) in standard size–particle ICS step-up and ICS/LABA combination cohorts, respectively.

**Rhinitis, gastroesophageal reflux disease, and cardiac disease diagnoses were captured through database Read codes.

significant differences between cohorts at baseline were small and not clinically important (Table 2 and Table E1). The mean ICS dose prescribed on the index date for the ICS step-up cohort was twice that for the ICS/LABA combination cohort (402 vs. 202 μg/d; $P < 0.001$).

The percentage of patients in each cohort who met the database composite measure of asthma control increased from 65% during the baseline year (Table 2) to 75% during the outcome year (Table 3). Patients who experienced one or more severe exacerbations per year fell from 25% during baseline to 16–17% during outcome (Tables 2 and 3).

The adjusted odds ratio for asthma control with small-particle ICS step-up, as compared with ICS/LABA combination, was 0.99 (Figure 1), and exacerbation rates during the outcome year were comparable between cohorts as well. The adjusted rate ratio (95% confidence interval) for severe exacerbations, as compared with ICS/LABA combination, was 1.04 (0.91–1.20; Figure 1). The adjusted odds of treatment stability (asthma control plus no treatment change) with small-particle ICS step-up was 1.12 (1.00–1.24) compared with ICS/LABA combination (Figure 1).

Over the outcome year, patients in both cohorts required additional therapy (18.1 and 20.4% of ICS step-up and ICS/LABA combination cohorts, respectively; Table 3).

Table 3. Results during the outcome year for matched cohorts comparing inhaled corticosteroid (ICS) dose step-up and ICS/long-acting β-agonist combination step-up cohorts

Outcome	Small-Particle ICS Step-Up vs. ICS/LABA Combination Inhaler			Standard Size–Particle ICS Step-Up vs. ICS/LABA Combination Inhaler		
	ICS Dose Step-Up (*n* = 3,036)	ICS/LABA Combination (*n* = 3,036)		ICS Dose Step-Up (*n* = 809)	ICS/LABA Combination (*n* = 809)	
Asthma control, n (%)	2,278 (75.0)	2,275 (74.9)		556 (68.7)	591 (73.1)	
Severe exacerbation, n (%)						
0	2,530 (83.3)	2,553 (84.1)		645 (79.7)	667 (82.4)	
1	371 (12.2)	352 (11.6)		99 (12.2)	94 (11.6)	
2	77 (2.5)	78 (2.6)		42 (5.2)	27 (3.3)	
⩾3	58 (1.9)	53 (1.7)		23 (2.8)	21 (2.6)	
Acute respiratory event, n (%)						
0	2,310 (76.1)	2,322 (76.5)		574 (71.0)	602 (74.4)	
1	505 (16.6)	507 (16.7)		141 (17.4)	136 (16.8)	
2	136 (4.5)	119 (3.9)		53 (6.6)	35 (4.3)	
⩾3	85 (2.8)	88 (2.9)		41 (5.1)	36 (4.4)	
Treatment stability, n (%)	1,979 (65.2)	1,903 (62.7)		467 (57.7)	487 (60.2)	
			P* Value			***P* Value***
⩾1 asthma-related hospital attendance, n (%)	12 (0.4)	15 (0.5)	0.57	2 (0.2)	5 (0.6)	0.27
⩾1 antibiotic prescriptions for LRTI, n (%)	364 (12.0)	365 (12.0)	0.64	129 (15.9)	108 (13.3)	0.12
⩾1 prescriptions for oral corticosteroids, n (%)	498 (16.4)	468 (15.4)	0.18	161 (19.9)	137 (16.9)	0.050
Treatment change, n (%)†	550 (18.1)	620 (20.4)	<0.001	190 (23.5)	179 (22.1)	0.52
ICS dose exposure (μg/d), median (IQR)‡	274 (164–438)	164 (93–230)	<0.001	370 (247–575)	181 (99–337)	<0.001
Mean ICS dose exposure, n (%)‡						
0–100 μg/d	290 (9.6)	962 (31.7)	<0.001	51 (6.3)	214 (26.5)	<0.001
101–200 μg/d	727 (23.9)	1,085 (35.7)		116 (14.3)	245 (30.3)	
201–400 μg/d	1,203 (39.6)	746 (24.6)		243 (30.0)	190 (23.5)	
>400 μg/d	816 (26.9)	243 (8.0)		399 (49.3)	160 (19.8)	
Daily SABA dose (μg/d), median (IQR)	219 (110–548)	164 (55–384)	<0.001	274 (110–548)	219 (55–438)	<0.001
Spacer device prescribed, n (%)	448 (14.8)	356 (11.7)	<0.001	175 (21.6)	100 (12.4)	<0.001
Oropharyngeal candidiasis, n (%)§	143 (4.7)	139 (4.6)	0.80	49 (6.1)	40 (4.9)	0.34
Possible pneumonia, n (%)‖	6 (0.2)	6 (0.2)	1.0	3 (0.4)	2 (0.2)	0.66
Definite pneumonia, n (%)‖	3 (0.1)	2 (0.1)	0.66	2 (0.2)	1 (0.1)	0.57

Definition of abbreviations: ICS = inhaled corticosteroid; IQR = interquartile range; LABA = long-acting β-agonist; LRTI = lower respiratory tract infection; SABA = short-acting β-agonist.

Data are presented as n (%) unless otherwise specified.

*Conditional logistic regression.

†Patients could have more than one change in therapy as either or both increased ICS dose or additional therapy during the year. Additional therapy could include combination ICS/LABA inhaler (for ICS step-up cohort), separate LABA inhaler, leukotriene receptor antagonist, and theophylline.

‡The dose of budesonide was halved for equivalence with extrafine beclomethasone and fluticasone, for which actual doses were used in the analyses. Daily ICS dose exposure was calculated as the dispensed amount divided by 365.

§Diagnosis of or therapy for oropharyngeal candidiasis (thrush).

‖Possible pneumonia was defined as a pneumonia Read code in the database; definite pneumonia was defined as pneumonia read code plus either a chest radiograph or hospital admission within 1 month.

As expected, the median daily SABA dose was significantly higher in the ICS step-up cohort (219 vs. 164 μg/d; $P < 0.001$). A total of 12 and 15 patients in the ICS step-up and ICS/LABA combination cohorts, respectively, were hospitalized with a recorded code for asthma or lower respiratory condition.

Standard Size–Particle Inhaled Corticosteroid Dose Step-Up Compared with ICS/LABA Combination Inhaler

After matching there were 809 patients in each cohort (*see* Figure E3). Three hundred and thirteen patients in the ICS/LABA comparison cohort were also in that cohort for the comparison with small-particle ICS step-up (described previously). The standard size–particle ICS step-up and ICS/LABA combination cohorts were well matched at baseline (Table 2). The mean ICS dose prescribed on the index date for the ICS step-up cohort was 2.3 times that for the ICS/LABA combination cohort (674 vs. 294 μg/d; $P < 0.001$).

During the outcome year, the percentage of patients achieving asthma control increased from 61% at baseline (Table 2) to 69 and 73% during outcome in ICS step-up and ICS/LABA combination cohorts, respectively (Table 3), and the percentage of patients with one or more exacerbations per year decreased from 28% at baseline to 20 and 18%, respectively, during the outcome year (Tables 2 and 3).

The adjusted odds of asthma control were comparable in the two cohorts, as was the odds of treatment stability (Figure 2). The adjusted rate ratio (95% confidence interval) for severe exacerbations, as compared with ICS/LABA combination, was 1.18 (0.92–1.54) for increased standard size–particle ICS dose (Figure 2).

The percentage of treatment changes was similar between cohorts (Table 3). A total of two and five patients in the ICS step-up and ICS/LABA combination cohorts, respectively, were hospitalized with a recorded code for asthma or lower respiratory condition.

Subanalysis: Results for Nonsmokers

After smokers were excluded, a total of 2,040 (67%) matched pairs of nonsmokers remained in the small-particle ICS and ICS/LABA combination cohorts, and 571 (71%) matched pairs of nonsmokers remained in the standard size–particle ICS and ICS/LABA combination cohorts. As in the main analyses, exacerbation rates decreased from baseline across all treatment cohorts during the outcome year, and adjusted exacerbation rate ratios showed no significant differences between cohorts for the two comparisons (*see* Tables E2 and E3).

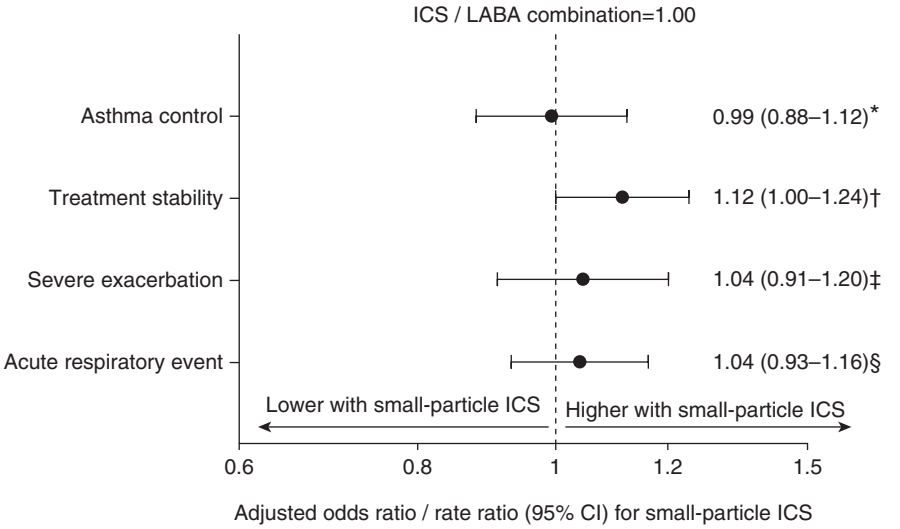

Figure 1. Adjusted outcome measures comparing a step-up in asthma therapy using increased dose of small-particle ICS versus ICS/LABA combination inhaler. *Definition of abbreviations*: CI = confidence interval; ICS = inhaled corticosteroid; LABA = long-acting β-agonist. Treatment stability was defined as asthma control and no change in therapy. *Adjusted for smoking status (current smoker/ex-smoker/nonsmoker/not specified), outpatient department attendance for asthma/lower respiratory reasons (yes/no), number of oral corticosteroid prescriptions, and oral thrush (yes/no). †Adjusted for smoking status, cardiac disease diagnosis (yes/no), and number of oral corticosteroid prescriptions. ‡Adjusted for numbers of primary care consultations and oral corticosteroid prescriptions. §Adjusted for year of index date, smoking status, medication possession ratio (number of days' supply of ICS/365 × 100%) for ICS (<80%/≥80%), and numbers of primary care consultations, oral corticosteroid prescriptions, and courses of antibiotics for lower respiratory tract infection.

Discussion

In these matched cohort analyses of large primary care databases, stepping up asthma therapy by increasing the ICS dose—with either small- or standard size–particle ICS—was as effective as adding a LABA via fixed-dose ICS/LABA combination inhaler for patients 12–80 years old. During the 1 year of follow-up, the rates of exacerbations decreased, the percentages of patients with asthma control increased, and all secondary end points improved to a similar extent for ICS dose step-up and ICS/LABA combination cohorts.

This study has several strengths. The analyses included large numbers of patients representative of the general asthma population who received usual care in a routine UK clinical setting, where most asthma in the United Kingdom is managed (31). We examined a baseline year to characterize patients and asthma-related measures; the cohorts were well matched for baseline asthma severity and control, and similar proportions (25%) of patients in each cohort had concomitant rhinitis, a risk factor for poor asthma control (32). Patients were monitored for a full outcome year to minimize the influence of seasonal variations in asthma and to capture infrequent outcomes such as severe exacerbations (28). The composite outcome measures, used in prior research (21–23), comprised data that are in line with factors identified by expert working groups as being reflective of asthma control and exacerbations (28, 29). Moreover, the results of sensitivity analyses comparing exacerbation rates for nonsmokers, conducted because the response to ICS is attenuated in smokers (33), supported the main analyses.

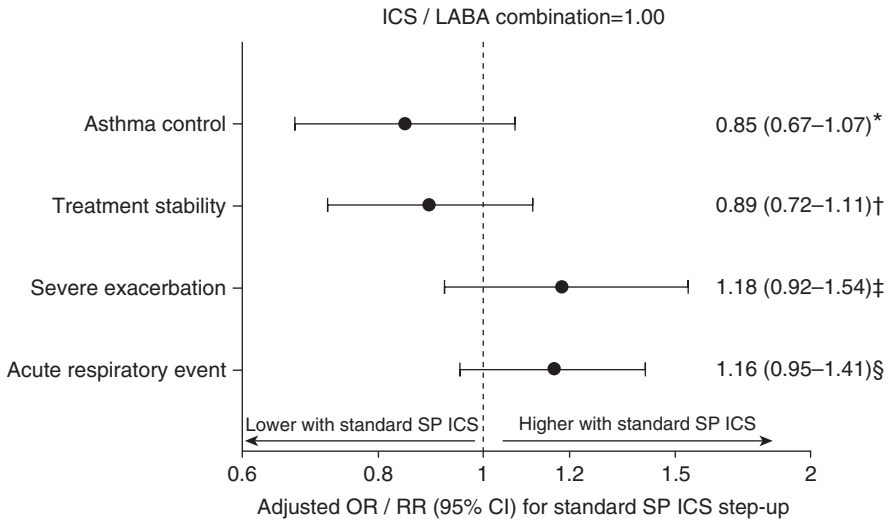

Figure 2. Adjusted outcome measures comparing a step-up in asthma therapy using increased dose of standard size–particle ICS versus ICS/LABA combination inhaler. *Definition of abbreviations*: CI = confidence interval; ICS = inhaled corticosteroid; LABA = long-acting β-agonist; OR = odds ratio; RR = rate ratio; SP = size particle. Treatment stability was defined as asthma control and no change in therapy. *Adjusted for non-asthma-related consultations and acute respiratory events during baseline. †Adjusted for number of nonasthma consultations, adherence to ICS therapy, and antibiotic use. ‡Adjusted for number of baseline severe exacerbations. §Adjusted for gastroesophageal reflux diagnosis and/or therapy (yes/no), baseline acute respiratory events, and nonasthma consultations.

These data are in contrast to the results of prior randomized controlled trials, which suggested that adding LABA produces better outcomes than increasing ICS in a population still symptomatic on lower dose ICS (4–11). However, as mentioned previously, those randomized trials excluded patients with prevalent comorbidities and studied β-agonist–responsive patients, who represent a minority of the asthma population. Furthermore, as discussed in the analysis by regulatory agencies, the outcomes in the trials, even those that looked at exacerbations, included indices that are disproportionately affected by agents that affect airway caliber (18).

Our study can be criticized on the basis of the fact that the data were not collected prospectively. However, treatment and prescribing data are considered to be reliably recorded in UK general practice, and the Clinical Practice Research Datalink (formerly the GPRD) is the world's largest data set of anonymized longitudinal data from primary care and is well validated, managed with quality controls, and used frequently for pharmacoepidemiologic research (26, 34).

It is possible that physicians choose to step up asthma therapy with add-on LABA for patients with asthma they consider to be more severe than that of patients for whom they prescribe ICS dose step-up. We thus conducted a matched cohort analysis to reduce the possibility of prescribing bias. All the indices of baseline asthma severity listed in Table 2, including peak expiratory flow, history of exacerbations, and prior medication use, suggest that asthma was of similar severity in the matched cohorts. Our matching criteria are applied sequentially; this approach produces two cohorts of matched pairs of patients, different from propensity score matching, which produces two cohorts with similar distributions of the multiple covariates used to construct the score (35). Although slight baseline differences in asthma severity between treatment cohorts might still be present, they are unlikely to be of clinical significance. Confounding was minimized by adjusted analyses. Furthermore, the fact that both of our analyses with different corticosteroid molecules produced similar results suggests that it is unlikely that a systematic bias occurred. Nonetheless, the possibility of unrecognized confounding remains.

Our study analyses were limited to the information available in the databases. It would have been useful to compare lung function from baseline to outcome year; however, lung function is not regularly measured in UK primary care. Moreover, patient ethnicity is not recorded, limiting the ability to generalize our findings by ethnic background. Finally, it would have been of interest to measure and compare adherence to therapy between cohorts. However, while we could not accurately measure actual adherence via database prescribing records, the findings of this noninterventional study reflect the clinical outcomes of real-life adherence as occurs in primary care practice.

We found that ICS step-up and add-on LABA step-up did not differ when we accounted for exacerbations requiring oral corticosteroids or an emergency department visit or hospitalization. This was true for each of the individual components composing an exacerbation and is somewhat reassuring regarding the adverse effects of LABAs. We cannot comment directly on daily symptom control, as this is not available in the databases. There was a slightly greater median use of β-agonists in the ICS cohorts of 55 μg/day, which represents an additional two-thirds of a puff of β-agonist use per day. This is not surprising because one would expect a greater decrease in reliever β-agonist use with LABA therapy (18). However, it can be inferred from the data that there were no major differences resulting in patient dissatisfaction with asthma control, as the same proportions of patients in ICS step-up and LABA step-up cohorts changed therapy during the outcome year.

As with all asthma treatment approaches, it is important to consider the risk-to-benefit ratio when comparing higher doses of ICS versus combination therapy (11). We found that the incidence of oropharyngeal candidiasis (thrush) was similar (~5%) in the ICS step-up and ICS/LABA cohorts. Rates of pneumonia were low and similar; and the numbers of antibiotic prescriptions for lower respiratory tract infection were similar in both two-way comparisons.

Areas of interest for future research include comparisons of other asthma therapy step-up strategies, such as add-on leukotriene modifiers and add-on LABA using a separate inhaler. In addition, patients who remain on the baseline ICS

dose throughout the follow-up period could serve as a valuable control group for comparison with step-up cohorts.

In conclusion, results of this matched cohort observational study indicate that stepping up antiinflammatory therapy with an increased dose of ICS is as effective as adding a LABA via fixed-dose ICS/LABA combination inhaler for a broad primary care asthma population. Further research is needed to identify subgroups of patients most likely to benefit from one step-up strategy or the other. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: The authors thank Professor Neil Barnes for advice during study design development. The authors also thank Alison Chisholm and Muzammil Ali for assistance and input on data analyses and interpretation.

References

1 Lazarus SC, Boushey HA, Fahy JV, Chinchilli VM, Lemanske RF Jr, Sorkness CA, Kraft M, Fish JE, Peters SP, Craig T, *et al*.; Asthma Clinical Research Network for the National Heart, Lung, and Blood Institute. Long-acting β_2-agonist monotherapy vs continued therapy with inhaled corticosteroids in patients with persistent asthma: a randomized controlled trial. *JAMA* 2001;285:2583–2593.

2 British Thoracic Society, Scottish Intercollegiate Guidelines Network. British Guideline on the Management of Asthma (SIGN 141), October 2014 [accessed 2014 Nov 20]. Available from: http://www.sign.ac.uk/pdf/SIGN141.pdf

3 Beasley R, Perrin K, Weatherall M, Wijesinghe M. Call for withdrawal of LABA single-therapy inhaler in asthma. *Lancet* 2010;376:750–751.

4 Greening AP, Ind PW, Northfield M, Shaw G; Allen & Hanburys Limited UK Study Group. Added salmeterol versus higher-dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroid. *Lancet* 1994;344:219–224.

5 Shrewsbury S, Pyke S, Britton M. Meta-analysis of increased dose of inhaled steroid or addition of salmeterol in symptomatic asthma (MIASMA). *BMJ* 2000;320:1368–1373.

6 Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJ, Pauwels RA, Pedersen SE; GOAL Investigators Group. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma ControL study. *Am J Respir Crit Care Med* 2004;170:836–844.

7 Pauwels RA, Löfdahl CG, Postma DS, Tattersfield AE, O'Byrne P, Barnes PJ, Ullman A; Formoterol and Corticosteroids Establishing Therapy (FACET) International Study Group. Effect of inhaled formoterol and budesonide on exacerbations of asthma. *N Engl J Med* 1997;337:1405–1411.

8 Shepherd J, Rogers G, Anderson R, Main C, Thompson-Coon J, Hartwell D, Liu Z, Loveman E, Green C, Pitt M, *et al*. Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long-acting β_2 agonists for the treatment of chronic asthma in adults and children aged 12 years and over. *Health Technol Assess* 2008;12:iii–iv, 1–360.

9 O'Byrne PM, Naya IP, Kallen A, Postma DS, Barnes PJ. Increasing doses of inhaled corticosteroids compared to adding long-acting inhaled β_2-agonists in achieving asthma control. *Chest* 2008;134:1192–1199.

10 Masoli M, Weatherall M, Holt S, Beasley R. Moderate dose inhaled corticosteroids plus salmeterol versus higher doses of inhaled corticosteroids in symptomatic asthma. *Thorax* 2005;60:730–734.

11 Ducharme FM, Ni Chroinin M, Greenstone I, Lasserson TJ. Addition of long-acting β_2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma. *Cochrane Database Syst Rev* [serial on the Internet]. 2010 [accessed 2015 Mar];4:CD005533. Available from: http://summaries.cochrane.org/

12 Global Initiative for Asthma. Global strategy for asthma management and prevention, revised 2014 [accessed 2014 Nov 20]. Available from: www.ginasthma.org

13 Travers J, Marsh S, Williams M, Weatherall M, Caldwell B, Shirtcliffe P, Aldington S, Beasley R. External validity of randomised controlled trials in asthma: to whom do the results of the trials apply? *Thorax* 2007;62:219–223.

14 Thomson NC, Chaudhuri R, Heaney LG, Bucknall C, Niven RM, Brightling CE, Menzies-Gow AN, Mansur AH, McSharry C. Clinical outcomes and inflammatory biomarkers in current smokers and exsmokers with severe asthma. *J Allergy Clin Immunol* 2013;131:1008–1016.

15 Mcivor RA, Pizzichini E, Turner MO, Hussack P, Hargreave FE, Sears MR. Potential masking effects of salmeterol on airway inflammation in asthma. *Am J Respir Crit Care Med* 1998;158:924–930.

16 Drazen JM, O'Byrne PM. Risks of long-acting β-agonists in achieving asthma control. *N Engl J Med* 2009;360:1671–1672.

17 Gibson PG, Powell H, Ducharme FM. Differential effects of maintenance long-acting β-agonist and inhaled corticosteroid on asthma control and asthma exacerbations. *J Allergy Clin Immunol* 2007;119:344–350.

18 Chowdhury BA, Dal Pan G. The FDA and safe use of long-acting β-agonists in the treatment of asthma. *N Engl J Med* 2010;362:1169–1171.

19 O'Byrne PM, Bisgaard H, Godard PP, Pistolesi M, Palmqvist M, Zhu Y, Ekström T, Bateman ED. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. *Am J Respir Crit Care Med* 2005;171:129–136.

20 Roche N, Reddel H, Martin R, Brusselle G, Papi A, Thomas M, Postma D, Thomas V, Rand C, Chisholm A, *et al*.; Respiratory Effectiveness Group. Quality standards for real-world research: focus on observational database studies of comparative effectiveness. *Ann Am Thorac Soc* 2014;11:S99–S104.

21 Price D, Martin RJ, Barnes N, Dorinsky P, Israel E, Roche N, Chisholm A, Hillyer EV, Kemp L, Lee AJ, *et al*. Prescribing practices and asthma control with hydrofluoroalkane–beclomethasone and fluticasone: a real-world observational study. *J Allergy Clin Immunol* 2010;126:511–518.e1–10.

22 Colice G, Martin RJ, Israel E, Roche N, Barnes N, Burden A, Polos P, Dorinsky P, Hillyer EV, Lee AJ, *et al*. Asthma outcomes and costs of therapy with extrafine beclomethasone and fluticasone. *J Allergy Clin Immunol* 2013;132:45–54.

23 Barnes N, Price D, Colice G, Chisholm A, Dorinsky P, Hillyer EV, Burden A, Lee AJ, Martin RJ, Roche N, *et al*. Asthma control with extrafine-particle hydrofluoroalkane–beclomethasone vs. large-particle chlorofluorocarbon–beclomethasone: a real-world observational study. *Clin Exp Allergy* 2011;41:1521–1532.

24 Price DB, Martin R, Barnes N, Roche N, Lee AJ, Dorinsky P, Burden A, von Ziegenweidt J, Chisholm A, Hillyer EV, *et al*. Real-world effectiveness of asthma step-up options: matched comparison of extrafine hydrofluoroalkane–beclomethasone AND inhaled corticosteroid/long-acting β-agonist [abstract]. *J Allergy Clin Immunol* 2012;129:AB61.

25 Israel E, Colice G, Grigg J, Martin R, van Aalderen W, Dorinsky P, Postma D, Roche N, Burden A, von Ziegenweidt J, *et al*. Real-world effectiveness and cost-effectiveness of asthma step-up options: A UK comparison of extrafine hydrofluoroalkane–beclomethasone and combination therapy [abstract]. *Eur Respir J* 2013;42:3826.

26 Clinical Practice Research Datalink. NHS National Institute for Health Research (NIHR) and the Medicines and Healthcare products Regulatory Agency (MHRA) [accessed 2014 Nov 20]. Available from: http://www.cprd.com/home/

27 Optimum Patient Care Research Database. Optimum Patient Care [accessed 2014 Nov 20]. Available from: http://www.optimumpatientcare.org/Html_Docs/OPCRD.html

28 Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, Casale TB, Chanez P, Enright PL, Gibson PG, *et al*.; American Thoracic Society/European Respiratory Society Task Force on Asthma Control and Exacerbations. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med* 2009;180:59–99.

29 Akinbami LJ, Sullivan SD, Campbell JD, Grundmeier RW, Hartert TV, Lee TA, Smith RA. Asthma outcomes: healthcare utilization and costs. *J Allergy Clin Immunol* 2012;129(3, Suppl):S49–S64.
30 Vanderweil SG, Tsai CL, Pelletier AJ, Espinola JA, Sullivan AF, Blumenthal D, Camargo CA Jr. Inappropriate use of antibiotics for acute asthma in United States emergency departments. *Acad Emerg Med* 2008;15:736–743.
31 Lancet Respiratory Medicine. Primary care at the heart of respiratory medicine in the UK [editorial]. *Lancet Respir Med* 2014;2:83.
32 Greiner AN, Hellings PW, Rotiroti G, Scadding GK. Allergic rhinitis. *Lancet* 2011;378:2112–2122.
33 Lazarus SC, Chinchilli VM, Rollings NJ, Boushey HA, Cherniack R, Craig TJ, Deykin A, DiMango E, Fish JE, Ford JG, *et al*.; National Heart Lung and Blood Institute's Asthma Clinical Research Network. Smoking affects response to inhaled corticosteroids or leukotriene receptor antagonists in asthma. *Am J Respir Crit Care Med* 2007; 175:783–790.
34 Clinical Practice Research Datalink. Boston Collaborative Drug Surveillance Program [accessed 2014 Nov 20]. Available from: http://www.bu.edu/bcdsp/gprd/
35 Joffe MM, Rosenbaum PR. Invited commentary: propensity scores. *Am J Epidemiol* 1999;150:327–333.