Original Article

Effect of Stepping Up to High-Dose Inhaled Corticosteroids in Patients With Asthma: UK Database Study

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What is already known about this topic? It is unclear whether patients with poorly controlled asthma benefit from stepping up to high-dose inhaled corticosteroids (ICSs) and whether patients with high blood eosinophil count benefit from high-dose ICSs.

What does this article add to our knowledge? We found no evidence that a step-up to high-dose ICSs is effective in preventing future asthma exacerbations.

How does this study impact current management guidelines? Our results support the current Global Initiative for Asthma steps of management (medium-dose ICS/long-acting β-agonist step 4).

BACKGROUND: It is unclear whether patients with asthma benefit from stepping up to high-dose inhaled corticosteroids (ICSs).

OBJECTIVE: To determine the effectiveness of stepping up to high-dose ICSs.

METHODS: A historic cohort study of patients with asthma (≥13 years old), identified from 2 large UK electronic medical record databases, was conducted. Patients who remained on medium-dose ICSs were compared with those who stepped up from medium- to high-dose ICSs, whereas patients who stepped up from low- to medium-dose ICSs were compared with those who stepped up from low- to high-dose ICSs. Time to first severe exacerbation (primary outcome) between treatment groups was compared using multivariable Cox proportional hazards models, and the number of exacerbations and antibiotics courses was analyzed using negative binomial regression. Inverse probability of treatment weighting was used to handle confounding.

RESULTS: The mean follow-up time to first exacerbation was 2.7 ± 2.7 years for those who remained on stable medium-dose ICSs and 2.0 ± 2.2 years for those who stepped up from medium- to high-dose ICSs. A similar pattern was noted for those who stepped up from low- to medium-dose ICSs (2.6 ± 2.5 years) and from low- to high-dose ICSs (2.3 ± 2.5 years). Patients who stepped up from medium- to high-dose ICSs (n =

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Conflicts of interest: I. D. Pavord reports grants from the National Institute for Health Research and personal fees from Aerocrine, Almirall, Boehringer Ingelheim, Chiesi, Circassia, Genentech, GlaxoSmithKline (GSK), Knopp, Novartis, Regeneron, Sanofi, and Teva, outside the submitted work, and is a member of the GOLD Science Committee. T. N. Tran is an employee of AstraZeneca, who is a funder of this study, which is conducted collaboratively with the Observational and Pragmatic Research Institute (OPRI) Pte Ltd. R. C. Jones declares grants from AstraZeneca, GSK, and Novartis; and personal fees for consultancy, speaker's fees, or travel support from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Nutricia, OPRI Pte Ltd, and Pfizer. J. Nuevo is an employee of AstraZeneca, which is a funder of this study. M. van den Berge reports grants paid to the university from AstraZeneca, Teva, GSK, and Chiesi, outside the submitted work. G. G. Brusselle has received honoraria for lectures from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Novartis, and Teva and is a member of advisory boards for AstraZeneca, Boehringer Ingelheim, GSK, Novartis, Sanofi/Regeneron, and Teva. A. N. Menzies-Gow has attended advisory boards for AstraZeneca, GSK, Novartis, Sanofi, and Teva; has received speaker fees from AstraZeneca, Novartis, Roche, Teva, and Sanofi; has participated in research with AstraZeneca for which his institution has been remunerated; has attended international conferences with Teva;

Abbreviations used
COPD- chronic obstructive pulmonary disease
CPRD- Clinical Practice Research Datalink
HR- hazard ratio
ICS- inhaled corticosteroid
ID- index date
IPTW- inverse probability of treatment weighting
LABA- long-acting β-agonist
MPR- medication possession ratio
OCS- oral corticosteroid
OPCRD- Optimum Patient Care Research Database

6879) had a higher risk of exacerbations during follow-up compared with those who remained on medium-dose ICSs (n = 51,737; hazard ratio, 1.17; 95% CI, 1.12-1.22). This was similar in patients stepping up from low- to high-dose (n = 3232) compared with low- to medium-dose (n = 12,659) ICSs (hazard ratio, 1.10; 95% CI, 1.04-1.17). A step-up to high-dose ICSs was also associated with a higher number of asthma exacerbations and antibiotics courses. No significant difference in associations was found across subgroups of patients with different blood eosinophil counts. CONCLUSIONS: We found no evidence that a step-up to high-dose ICSs is effective in preventing future asthma exacerbations. **(J Allergy Clin Immunol Pract 2023;11:532-43)**

Key words: *Asthma; Exacerbations; Corticosteroids; High dose; Step-up*

INTRODUCTION

Asthma is a chronic inflammatory disease characterized by variable narrowing of the airways. The clinical spectrum of asthma ranges from mild, intermittent symptoms to severe, refractory disease with frequent exacerbations; however, most patients with asthma have mild disease.[1]

Poor control of asthma symptoms can have a significant impact on day-to-day quality of life, with patients reporting considerable impairment in physical, work-related, and social activities.[2,3] Inhaled corticosteroids (ICSs) are the mainstay of asthma treatment and have been shown to reduce severe exacerbations, hospitalization, and death.[4,5] The Global Initiative for Asthma 2021 guidelines recommend that asthma treatment be adjusted in a stepwise approach in accordance with individual patient needs, with an increase to high-dose ICSs a possible option.[6] Beasley et al[7] however critically reviewed available evidence for a therapeutic dose-response relationship of ICSs on oral corticosteroid sparing in adult asthma and concluded that there is no evidence at present to suggest that stepping up to high-dose ICSs is beneficial. Others concluded that the addition of a long-acting β-agonist (LABA) is more effective than increasing the dose of ICSs in improving asthma control and that by increasing the dose of ICSs, clinical improvement is likely to be of small magnitude.[8] Clearer evidence on the efficacy of this approach is important because high-dose ICS regimens are costly and long-term ICS use has been associated with side effects including osteoporosis, glaucoma, skin thinning, and suppression of hypothalamic-pituitary-adrenal axis.[9,10]

Eosinophilic infiltration of the airway mucosa is a common feature in asthma and is thought to play an important role in the pathogenesis of asthma attacks.[11,12] Airway eosinophilia is a known predictor of responsiveness to steroid therapy in asthma and chronic obstructive pulmonary disease (COPD).[13-15] Peripheral blood eosinophil count, a more convenient alternative to sputum eosinophil count, is a biomarker associated with increased risk of asthma exacerbations and poorer asthma control.[16-18] It remains unknown whether patients with a high blood eosinophil count benefit from increased doses of ICSs within real-world populations.

Our hypothesis was that stepping up to higher-dose ICSs would prevent future asthma exacerbations in a real-world observational population. We tested this hypothesis by assessing time to severe exacerbation, and average number of exacerbations and antibiotic courses (during a 1- and 3-year period) in those who remained on stable medium-dose ICSs versus those

and has had consultancy agreements with AstraZeneca, Sanofi, and Vectura. D. Skinner and V. Carter are employees of OPRI Pte Ltd at the time of the study, which conducted this study in collaboration with Optimum Patient Care and AstraZeneca. OPRI Pte Ltd has also conducted paid research on behalf of the following organizations in the past 3 years: Aerocrine, AKL Research and Development Ltd, Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Mapi Group, Meda, Mylan, Mundipharma, Napp, Novartis, Orion, Regeneron, Roche, Takeda, Teva, and Zentiva (a Sanofi company). J. W. H. Kocks reports grants, personal fees, and nonfinancial support from AstraZeneca, GSK, and Boehringer Ingelheim; grants and personal fees from Chiesi Pharmaceuticals and Teva; grants from Mundipharma; and personal fees from MSD and COVIS Pharma, outside the submitted work; and holds 72.5% of shares in the General Practitioners Research Institute. D. B. Price has advisory board membership with AstraZeneca, Boehringer Ingelheim, Chiesi, Mylan, Novartis, Regeneron Pharmaceuticals, Sanofi Genzyme, and Thermofisher; consultancy agreements with Airway Vista Secretariat, AstraZeneca, Boehringer Ingelheim, Chiesi, EPG Communication Holdings Ltd, FIECON Ltd, Fieldwork International, GSK, Mylan, Mundipharma, Novartis, OM Pharma SA, PeerVoice, Phadia AB, Spirosure, Inc, Strategic North Limited, Synapse Research Management Partners S.L., Talos Health Solutions, Theravance, and WebMD Global LLC; grants and unrestricted funding for investigator-initiated studies (conducted through OPRI Pte Ltd) from AstraZeneca, Boehringer Ingelheim, Chiesi, Mylan, Novartis, Regeneron Pharmaceuticals, Respiratory Effectiveness Group, Sanofi Genzyme, Theravance, and UK National Health Service; payment for lectures/speaking engagements from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GSK, Kyorin, Mylan, Mundipharma, Novartis, Regeneron Pharmaceuticals, and Sanofi Genzyme; payment for travel/accommodation/meeting expenses from AstraZeneca, Boehringer Ingelheim, Mundipharma, Mylan, Novartis, and Thermofisher; stock/stock options from AKL Research and Development Ltd, which produces phytopharmaceuticals; owns 74% of the social enterprise Optimum Patient Care Ltd (Australia and UK) and 92.61% of OPRI Pte Ltd (Singapore); 5% shareholding in Timestamp, which develops adherence monitoring technology; is peer reviewer for grant committees of the UK Efficacy and Mechanism Evaluation programme, and Health Technology Assessment; and was an expert witness for GSK.

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who stepped up from medium- to high-dose ICSs and also for 2 ICS step-up strategies.

METHODS

Study design and data sources

A historical cohort study was conducted in UK patients with asthma. Patients who stepped up from medium- to high-dose ICSs were compared with those who remained on medium-dose ICSs, whereas patients who stepped up from low- to high-dose ICSs were compared with those who stepped up from low- to medium-dose ICSs. Prescribed doses of different ICSs were classified into low, medium, and high dose as presented in Table I. All prescriptions for ICSs, alone or in a combination inhaler, were considered. ICS prescriptions were assessed during a baseline period of 1 year, which was considered long enough to confirm consistent ICS exposure (Figure 1).

Data were extracted from the Optimum Patient Care Research Database (OPCRD)[19] and Clinical Practice Research Datalink (CPRD)[20] databases. The OPCRD comprises anonymized, longitudinal medical record data for more than 11 million patients from 815 UK primary care practices. It was established in 2005, contains regularly inputted data from 1988 and retrospectively inputted data from 1950, and is maintained by Optimum Patient Care Ltd (OPC UK), a UK-based social enterprise.[21] The OPCRD is approved by the UK National Health Service for clinical research use (Research Ethics Committee reference: 15/EM/0150). CPRD, established in 1987, is a large computerized primary care database, containing deidentified, longitudinal data from 16 million registered patients from more than 700 UK practices. Both the OPCRD and the CPRD are well validated and used frequently for medical and health research.[21,22] The OPCRD and CPRD + hospital episode statistics data sets for this study were constructed separately, checked for overlap, and combined for analyses, to exclude patients with duplicate data. The study protocol was approved by the CPRD Independent Scientific Advisory Committee (approval no. 16_236) and registered with the European Union electronic Register of Post-Authorization Studies (EUPAS register no. EUPAS15869). Approval for this study was granted by the Anonymised Data Ethics Protocols and Transparency Committee, the independent scientific advisory committee for the OPCRD (ADEPT2016).

Study population

Patients who met the following criteria were eligible for inclusion: (1) diagnostic Read code for asthma; (2) active asthma defined as having 2 or more prescriptions for asthma reliever and/or maintenance medication in the baseline year before index date (ID); (3) blood eosinophil count available within 2 years before ID, recorded without a prescription of an acute course of oral corticosteroids (OCSs; defined as the OCS courses with evidence of lower respiratory consultation in the baseline year) within 2 weeks before the measurement; (4) aged 13 years or more at ID; and (5) 1 or more year of continuous data before ID. Patients with a Read code for other chronic respiratory conditions (eg, cystic fibrosis, lung cancer, and pulmonary fibrosis) were excluded. Patients with COPD were included; however, a sensitivity analysis excluding these patients was performed. All code lists are available from the authors on request.

Study outcomes

The primary outcome was time to first (severe) asthma exacerbation, defined by the American Thoracic Society/European Respiratory Society Task Force[23] as the occurrence of any of the following during the assessment period: asthma-related hospital admission or emergency department attendance, or an acute course of OCSs with evidence of respiratory review. Primary care recorded hospital admissions and accident & emergency attendances were used for the purposes of this study. However, exacerbations and hospitalizations treated in secondary/specialist care are included if reported to the primary care physician. OCSs/hospitalizations that occurred within 2 weeks of each other were considered the same exacerbation. Secondary outcomes included the number of exacerbations and number of antibiotic courses prescribed at a respiratory consultation (because high-dose ICS therapy may impact risk of bacterial infections).[24,25] The assessment period for all outcomes started from the date of step-up to a higher-dose ICS or a randomly chosen eligible prescription date for those who remained on medium-dose ICSs and continued until patients left the practice, died, or until the last date of data collection for the assessment of time to first exacerbation and for 1 and 3 years for the secondary outcomes (Figure 1). Time to first moderate/severe exacerbation was assessed over the longest possible time frame for each patient to maximize the chance of identifying all first exacerbations. Number of exacerbations and number of antibiotic prescriptions at a respiratory consultation were assessed during the standard 1-year follow-up period, but also during a 3-year follow-up period to ensure all events were captured and to provide confidence in robustness of our findings (by comparison of rates).

TABLE I. Definition of daily ICS dose categories in microgram per day (GINA 2020)

Substance	Low dose	Medium dose	High dose
Beclomethasone			
Fine particle	≤500	>500-1000	>1000
Extrafine particle	≤200	>200-400	>400
Ciclesonide	≤160	>160-320	>320
Fluticasone furoate	100		200
Fluticasone propionate	≤250	>250-500	>500
Budesonide	≤400	>400-800	>800

GINA, Global Initiative for Asthma.

Data analyses

All statistical analyses were carried out using Stata version SE 14.2 and MP 15.1 (StataCorp, College Station, Texas). Descriptive statistics of baseline variables (ie, demographic and clinical characteristics) were computed for all patients and stratified by baseline eosinophil count (<150, 150-349, ≥350 cells/μL). Continuous variables were summarized using mean and SD (for normally distributed variables) and/or median and interquartile range, whereas categorical variables were summarized using count and percentage. The standardized mean difference was used to quantify the difference in baseline variables between treatment arms (medium-medium vs medium-high and low-medium vs low-high).[26] A standardized mean difference less than or equal to 10% indicated sufficient balance.

Primary outcome: Time to first exacerbation

Inverse probability of treatment weighting (IPTW) was used to account for confounding by indication because matching the treatment arms resulted in selection of patients with less severe disease. A propensity score, generated from a logistic regression model including all baseline variables with less than 20% of values missing

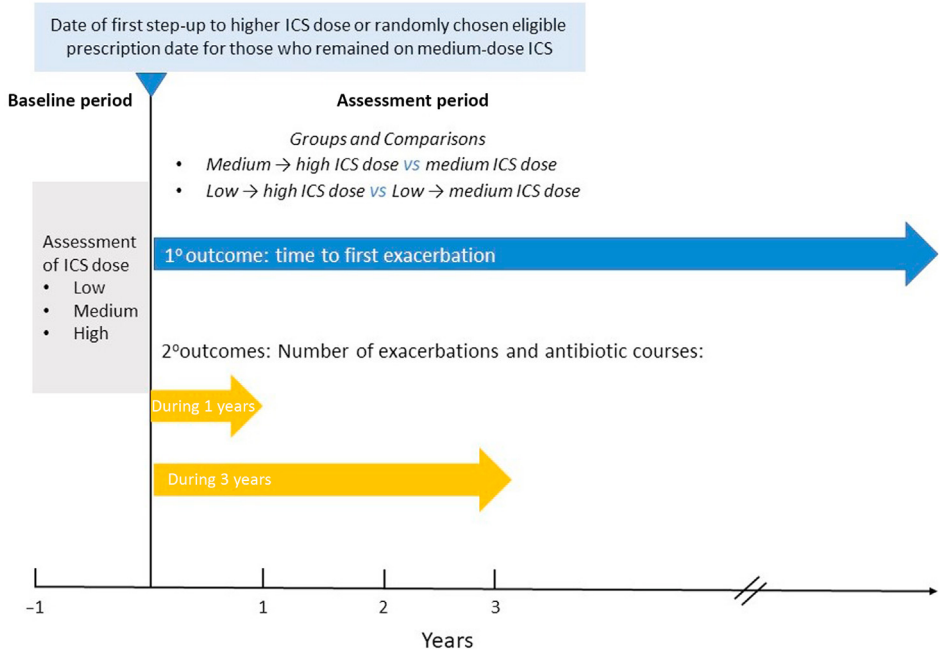

FIGURE 1. Study design.

(Table II; see Table E1 in this article's Online Repository at www.jaci-inpractice.org), was used to weight the data with the inverse of the treatment probability. Weighted standardized mean differences were calculated to verify the balancing effect of the IPTW approach. Unadjusted incidence rates of asthma exacerbations per 100 follow-up years were calculated for the different treatment arms. Multivariable Cox proportional hazards regression analysis with adjustment for residual confounders (see Table E2 in this article's Online Repository at www.jaci-inpractice.org) was used to compare time to first asthma exacerbation (primary outcome) during the outcome period between treatment arms (medium-medium vs medium-high ICSs and low-medium vs low-high ICSs). An intention-to-treat design was used with right-censoring at loss to follow-up or death.

Secondary outcomes

These analyses were restricted to patients with at least 1 and 3 years of continuous follow-up. Negative binomial regression was used to compare the number of exacerbations and antibiotic courses between treatment arms that occurred within these time periods.

Patients improving/worsening

This analysis was restricted to patients with at least 1-year follow-up. The proportion of patients who improved, remained stable, or worsened was calculated for each treatment arm by comparing the number of exacerbations experienced in the baseline period to the number of exacerbations experienced in the first year of the outcome period. Those patients with less exacerbations were categorized as improved, those with the same number of exacerbations were categorized as stable, and those with more exacerbations were categorized as worse. Logistic regression was used to compare worsening/improving between treatment arms (medium-medium vs medium-high ICSs and low-medium vs low-high ICSs) by blood eosinophil count.

Sensitivity analyses

Results are also presented by blood eosinophil count (<150, 150-349, ≥350 cells/μL).[17] These cutoff values were selected because of the way data were recorded in electronic medical records (ie, 10^9/L to 1 decimal place). Thus, it is unknown whether a value of 0.3 × 10^9/L (between 250 and 349 cells/μL) would fall below or above the recommended cutoff point of 300 cells/μL. Differences between strata were tested by including an interaction term with exposure group in the full (unstratified) models.

Sensitivity analyses were conducted as follows: (1) including only patients with good ICS adherence (medication possession ratio [MPR] ≥ 70%; with MPR calculated by dividing the total of 1 day's supply by the total number of days evaluated, multiplied by 100%) to rule out potential bias resulting from the level of or any changes in adherence; (2) excluding exacerbations that occurred in the first 30 days of follow-up to confirm any effect seen is not the result of high-dose inhaler use as the first step of treatment when patients present with exacerbations; (3) excluding patients with COPD to confirm that a medical history of COPD does not significantly impact the results; and (4) excluding patients who had a change in substance, particle size, or device type at ID to evaluate the impact on the results.

RESULTS

The study included 51,737 patients who remained on medium-dose ICSs and 6879 patients who stepped up from medium- to high-dose ICSs, and 12,659 and 3232 patients who stepped up from low- to medium- and low- to high-dose ICSs, respectively (Figure 2). The demographic and clinical characteristics of patients by treatment arm are presented in Table II and Table E1 (for baseline characterization by eosinophil group, see Tables E3-E5 in this article's Online Repository at www.jaci-inpractice.org). A higher proportion of patients who stepped up from medium- to high-dose ICSs were 60 years or

TABLE II. Baseline characterization of all patients

Variable	Medium-medium (N = 51,737)	Medium-high (N = 6879)	*P*	SMD	Low-medium (N = 12,659)	Low-high (N = 3232)	*P*	SMD
Index year								
Mean ± SD	2008 ± 3.7	2009 ± 3.5	<.001	26.9	2009 ± 3.4	2008 ± 3.6	<.001	16.2
Median (IQR)	2008 (2005-2011)	2009 (2006-2012)			2009 (2006-2011)	2008 (2005-2011)		
Age (y)								
Mean ± SD	57.5 ± 17.0	61.8 ± 16.1	<.001	26.4	58.0 ± 17.3	61.1 ± 16.6	<.001	18.4
Median (IQR)	59.0 (45.0-70.0)	64.0 (51.0-74.0)			60.0 (46.0-71.0)	63.0 (50.0-74.0)		
Age (y), n (%)								
<20	811 (1.6)	50 (0.7)	<.001	25.0	253 (2.0)	33 (1.0)	<.001	17.6
≥20-<39	7,524 (14.5)	651 (9.5)			1,720 (13.6)	348 (10.8)		
≥40-<59	18,110 (35.0)	2,049 (29.8)			4,262 (33.7)	967 (29.9)		
≥60-<79	20,536 (39.7)	3,215 (46.7)			5,160 (40.8)	1,445 (44.7)		
≥80	4,756 (9.2)	914 (13.3)			1,264 (10.0)	439 (13.6)		
Sex								
Male, n (%)	18,856 (36.4)	2,516 (36.6)	.834	0.3	4,211 (33.3)	1,120 (34.7)	.136	2.9
Smoking status, n (%)								
N (% nonmissing)	50,951 (98.5)	6,796 (98.8)	<.001	11.3	12,417 (98.1)	3,175 (98.2)	<.001	8.8
Nonsmoker	24,049 (47.2)	2,933 (43.2)			6,018 (48.5)	1,360 (42.8)		
Current smoker	10,082 (19.8)	1,209 (17.8)			2,197 (17.7)	671 (21.1)		
Ex-smoker	16,820 (33.0)	2,654 (39.1)			4,202 (33.8)	1,144 (36.0)		
BMI, n (%)								
N (% nonmissing)	50,467 (97.5)	6,765 (98.3)	<.001	4.4	12,419 (98.1)	3,153 (97.6)	.082	0.9
<18.5	1,012 (2.0)	142 (2.1)			224 (1.8)	79 (2.5)		
≥18.5-<25	13,881 (27.5)	1,790 (26.5)			3,340 (26.9)	830 (26.3)		
≥25-<30	17,344 (34.4)	2,197 (32.5)			4,234 (34.1)	1,069 (33.9)		
≥30	18,230 (36.1)	2,636 (39.0)			4,621 (37.2)	1,175 (37.3)		
COPD diagnosis, n (%)								
Yes	5,844 (11.3)	1,509 (21.9)	<.001	28.9	1,207 (9.5)	702 (21.7)	<.001	34.0
Nasal polyps, n (%)								
Yes	1,694 (3.3)	216 (3.1)	.556	0.8	328 (2.6)	78 (2.4)	.568	1.1
Charlson comorbidity index, n (%)								
0	18,809 (36.4)	2,031 (29.5)	<.001	16.3	3,573 (28.2)	1,021 (31.6)	<.001	1.7
1-4	27,525 (53.2)	3,887 (56.5)			7,610 (60.1)	1,760 (54.5)		
≥5	5,403 (10.4)	961 (14.0)			1,476 (11.7)	451 (14.0)		
FEV_1 % predicted, n (%)								
N (% nonmissing)	20,969 (40.5)	3,922 (57.0)	<.001	14.8	5,516 (43.6)	1,663 (51.5)	<.001	27.4
≥80%	9,658 (46.1)	1,546 (39.4)			2,294 (41.6)	521 (31.3)		
50%-<80%	8,434 (40.2)	1,676 (42.7)			2,475 (44.9)	759 (45.6)		
30%-<50%	2,319 (11.1)	561 (14.3)			603 (10.9)	309 (18.6)		
<30%	558 (2.7)	139 (3.5)			144 (2.6)	74 (4.4)		

No. of exacerbations (ATS), n (%)								
None	40,012 (77.3)	5,324 (77.4)	.244	0.6	10,959 (86.6)	2,575 (79.7)	<.001	19.0
1	7,504 (14.5)	1,000 (14.5)			1,253 (9.9)	426 (13.2)		
2	2,622 (5.1)	319 (4.6)			293 (2.3)	157 (4.9)		
3	1,006 (1.9)	141 (2.0)			106 (0.8)	53 (1.6)		
≥4	593 (1.1)	95 (1.4)			48 (0.4)	21 (0.6)		
Blood eosinophil count (cells/μL), n (%)								
<150	24,148 (46.7)	3,234 (47.0)			5,965 (47.1)	1,480 (45.8)		
150-349	13,115 (25.3)	1,605 (23.3)			2,871 (22.7)	782 (24.2)		
≥350	14,474 (28.0)	2,040 (29.7)	<.001	5.1	3,823 (30.2)	970 (30.0)	.167	2.3
ICS substance before ID, n (%)								
Beclomethasone	16,800 (32.5)	1,338 (19.5)	<.001	10.5	7,566 (59.8)	2,186 (67.6)	<.001	16.9
Fluticasone	22,419 (43.3)	4,279 (62.2)			2,735 (21.6)	601 (18.6)		
Budesonide	12,518 (24.2)	1,262 (18.3)			2,358 (18.6)	445 (13.8)		
Cumulative ICS dose prescribed over baseline year (μg/d, beclomethasone equivalent), n (%)*								
≤400	20,046 (38.7)	1,100 (16.0)	<.001	65.2	6,839 (54.0)	1,519 (47.0)	<.001	22.0
>400-800	18,536 (35.8)	2,159 (31.4)			4,004 (31.6)	990 (30.6)		
>800-1600	11,103 (21.5)	2,838 (41.3)			1,613 (12.7)	565 (17.5)		
>1600	2,052 (4.0)	782 (11.4)			203 (1.6)	158 (4.9)		

ATS, American Thoracic Society; *BEC*, blood eosinophil count; *BMI*, body mass index; *IQR*, interquartile range; *SMD*, standardized mean difference.

P, *P* value for the Kruskal-Wallis equality-of-populations rank test or the Pearson χ^2 test of independent categories, where appropriate.

*In the United Kingdom, an ICS prescription can be made for inhalers with authorized repeats. These repeats must be issued by a prescribing physician, are recorded in patient electronic medical records, and included in databases such as OPCRD. However, there is no close monitoring of the number of repeats given until patients run out, so it is possible for more prescriptions to be given than the prescribed dose. Further details on UK prescribing can be found at the NHS website.[27]

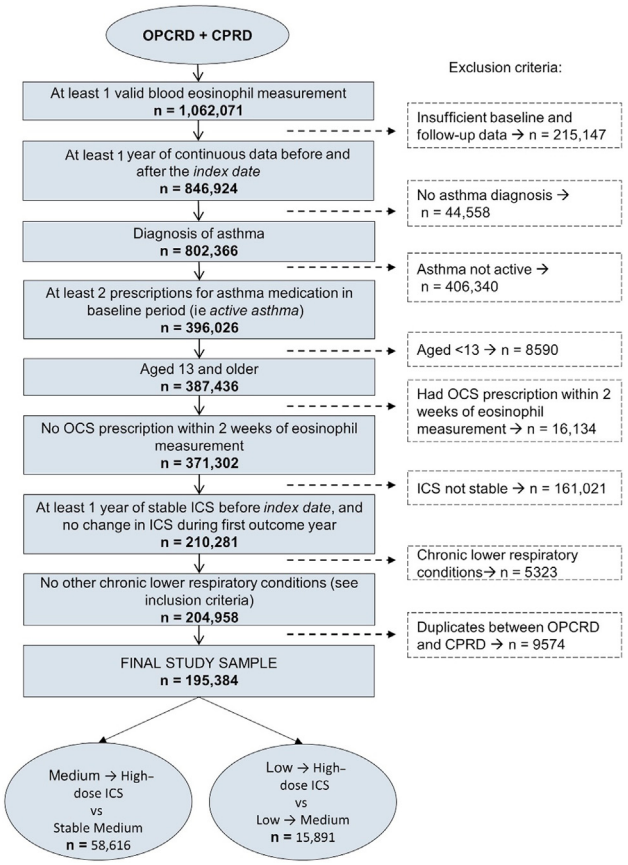

FIGURE 2. Flowchart of study population. In accordance with study design, the assessment period differed by patient and by group. The start of the assessment window was the date of step-up to a higher ICS dose for those who stepped up therapy or a randomly chosen eligible prescription date for those who remained on medium-dose ICSs. Efficacy was assessed from (median dates [IQR]) 2008 (2005-2011), 2009 (2006-2012), 2009 (2006-2011), and 2008 (2005-2011) for stable medium, medium-to-high, low-to-medium, and low-to-high ICS dose groups, respectively. *IQR*, Interquartile range.

older (60% vs 48.9%), ex-smokers (39.1% vs 33%), and had a diagnosis of COPD (21.9% vs 11.3%) compared with patients on stable medium-dose ICSs (Table II). Step-up from medium- to high-dose ICSs was more likely in those prescribed fluticasone, whereas step-up from low- to high-dose ICSs was more likely in those prescribed beclomethasone (Table II). After IPTW, 94% (45 of 48; medium-medium vs medium-high ICSs) and 100% (low-medium vs low-high ICSs) of the measured baseline characteristics were well balanced between treatment arms (see Table E6 in this article's Online Repository at www.jaci-inpractice.org).

The proportion of patients who had a change in ICS substance, particle size, or device type at ID was higher in patients stepping up to high-dose ICSs than in the comparison arms (medium-high vs medium-medium: 45% vs 3%; low-high vs low-medium: 74% vs 57%; both $P < .00001$). In most cases, the change was to fluticasone/salmeterol, which was also the most frequently prescribed inhaler at ID in these patients.

Primary outcome: Time to first exacerbation

The mean follow-up time from ID to first exacerbation or censoring due to loss-to-follow-up was 2.7 ± 2.7 and 2.0 ± 2.2 years in those who remained on stable medium-dose ICSs and those who stepped up from medium- to high-dose ICSs, respectively. For those patients who stepped up from low- to medium- and low- to high-dose ICSs, mean follow-up time was 2.6 ± 2.5 and 2.3 ± 2.5 years, respectively. Follow-up times were similar when treatment arms were stratified by baseline eosinophil count (Table III). There was a crude incidence of 18.9 exacerbations per 100 follow-up years in those who remained on medium-dose ICSs, and a higher incidence of 27.5 per 100 follow-up years in those who stepped up from medium- to high-dose ICSs. This resulted in an adjusted IPTW-weighted hazard ratio (HR) of 1.17 (95% CI, 1.12-1.22). There was a crude incidence of 17.7 exacerbations per 100 follow-up years in those who stepped up from low- to medium-dose ICSs, and a higher incidence of 23.0 per 100 follow-up years in those who stepped up from low- to high-dose ICSs. In the adjusted IPTW-weighted model, the latter had a 10% higher hazard rate of exacerbations in the follow-up period compared with the former (HR, 1.10; 95% CI, 1.04-1.17) (Table III). Similar results were obtained when data were assessed using conventional regression and crude propensity score covariate adjustments (data not shown).

The increased risk of exacerbations with high-dose ICSs was also found in patients with good adherence (MPR $\geq$ 70%) to ICSs in the year before ID (see Table E7 in this article's Online Repository at www.jaci-inpractice.org), when exacerbations that occurred within the first 30 days of follow-up were excluded, and when patients with a history of COPD were excluded (medium-to-high ICS dose vs medium-to-medium ICS dose: HR, 1.18; 95% CI, 1.12-1.24; low-to-high ICS dose vs low-to-medium ICS dose: HR, 1.10; 95% CI, 1.03-1.17). When patients with a change in substance, particle size, or device type at ID were excluded from the analyses, an increased risk of exacerbations was observed in medium-high versus medium-medium (HR, 1.18; 95% CI, 1.08-1.28) but not in low-high versus low-medium (HR, 1.02; 95% CI, 0.84-1.24).

Secondary outcomes

A step-up to high-dose ICSs was associated with a high number of asthma exacerbations and antibiotics courses prescribed for a lower respiratory condition compared with medium-dose ICSs over 1 and 3 years of follow-up (Table IV). Similar results were shown in patients with good adherence (see Table E8 in this article's Online Repository at www.jaci-inpractice.org). No significant difference in associations was found across subgroups of patients with different blood eosinophil counts (Table IV).

Patients improving/worsening

When individual changes in weighted exacerbation rate from baseline to first outcome year were analyzed, a higher number of patients worsened than improved in all treatment arms (Figure 3). The risk of worsening was higher in patients stepping up to high-dose ICSs than in the comparison arms (medium-high vs medium-medium: 23.0% vs 18.2%, IPT-weighted odds ratio [95% CI], 1.35 [1.24-1.46], $P < .0001$; low-high vs low-medium: 21.4% vs 18.6%, 1.19 [1.06-1.32], $P = .0023$). The proportion of patients who improved did not differ between treatment arms (Figure 3). Overall, patients with high blood

TABLE III. Follow-up time, asthma exacerbation and incidence rates (/year) by treatment arm, and adjusted HRs for patients stepping up to high-dose ICS relative to comparison arms, using intention-to-treat analyses (censored at loss to follow-up), stratified by baseline BEC

			Follow-up (y)*		Follow-up (y), analyses†		Incidence		IRR vs stable medium‡		HR (adjusted)	
Study arm	**BEC**	**No. of patients**	**N**	**Mean ± SD**	**N**	**Mean ± SD**	**Events**	**IR**	**IRR (95% CI)**	***P***	**HR (95% CI)**	***P***
Medium-high vs medium-medium ICS												
Stable medium	<150	14,459	66,081.2	4.6 ± 3.4	38,916.1	2.7 ± 2.7	7,211	18.5				
	150-349	24,120	1,11,452.4	4.6 ± 3.3	65,238.3	2.7 ± 2.7	12,098	18.5				
	≥350	13,099	62,843.4	4.8 ± 3.4	34,945.9	2.7 ± 2.7	6,969	19.9				
	Total	51,678	2,40,377.0	4.7 ± 3.3	1,39,100.3	2.7 ± 2.7	26,278	18.9				
Medium->high	<150	2,037	7,409.3	3.6 ± 2.8	4,038.7	2.0 ± 2.2	1,098	27.2	1.47 (1.38-1.56)	<.0001	1.13 (1.04-1.23)§	.0038
	150-349	3,232	12,556.1	3.9 ± 3.0	6,594.3	2.0 ± 2.2	1,794	27.2	1.47 (1.40-1.54)	<.0001	1.18 (1.10-1.25)§	<.0001
	≥350	1,602	6,375.2	4.0 ± 3.1	3,282.5	2.0 ± 2.2	937	28.5	1.43 (1.34-1.53)	<.0001	1.18 (1.08-1.28)‖	.0003
	Total	6,871	26,340.6	3.8 ± 2.9	13,915.5	2.0 ± 2.2	3,829	27.5	1.46 (1.41-1.51)	<.0001	1.17 (1.12-1.22)§	<.0001
Low-high vs low-medium ICS												
									IRR vs low to medium¶			
Low->medium	<150	3,818	15,288.2	4.0 ± 3.0	9,602.0	2.5 ± 2.4	1,696	17.7				
	150-349	5,955	24,075.2	4.0 ± 3.0	15,275.2	2.6 ± 2.5	2,644	17.3				
	≥350	2,869	12,190.7	4.2 ± 3.1	7,406.7	2.6 ± 2.5	1,365	18.4				
	Total	12,642	51,554.0	4.1 ± 3.0	32,283.9	2.6 ± 2.5	5,705	17.7				
Low->high	<150	967	4,097.0	4.2 ± 3.2	2,195.1	2.3 ± 2.4	515	23.5	1.33 (1.20-1.47)	<.0001	1.07 (0.96-1.20)	.2249
	150-349	1,479	6,277.7	4.2 ± 3.2	3,540.2	2.4 ± 2.5	787	22.2	1.28 (1.18-1.39)	<.0001	1.10 (1.01-1.21)	.0276
	≥350	781	3,424.5	4.4 ± 3.3	1,830.6	2.3 ± 2.4	439	24.0	1.30 (1.17-1.45)	<.0001	1.11 (0.98-1.26)#	.0916
	Total	3,227	13,799.2	4.3 ± 3.2	7,565.8	2.3 ± 2.5	1,741	23.0	1.30 (1.23-1.37)	<.0001	1.10 (1.04-1.17)	.0017

BEC, Blood eosinophil count; *IR*, incidence rate; *IRR*, incidence rate ratio.

*Total follow-up time in current general practice.

†Follow-up time after ID until first exacerbation or censoring due to loss to follow-up (continued until patients left the practice, died, or until the last date of data collection).

‡Medium to high vs stable medium.

§Adjusted for number of respiratory consultations.

‖Adjusted for time since last acute respiratory event.

¶Low to high vs low to medium.

#Adjusted for number of acute OCS courses (courses with evidence of lower respiratory consultation in the baseline year).

TABLE IV. Average event rate in a year and IPTW-adjusted rate ratios of asthma exacerbations and antibiotics courses over a 1- and 3-y period

			Baseline year		First follow-up year				First 3 follow-up years			
Outcome	BEC	Arm	N	Mean/%	N	Mean/%	Adjusted ratio (95% CI)	*P*	N	Mean/%	Adjusted ratio (95% CI)	*P*
Medium-high vs medium-medium ICSs												
Exacerbations, n*	<150	Med-med	14,474	0.34	12,553	0.38	1.28 (1.14-1.44)	<.0001	8,651	0.37	1.21 (1.07-1.36)	.0020
		Med-high	2,040	0.32	1,672	0.53			1,030	0.51		
	150-349	Med-med	24,148	0.34	21,074	0.40	1.10 (1.01-1.20)	.0279	14,805	0.40	1.13 (1.03-1.24)	.0066
		Med-high	3,234	0.35	2,711	0.50			1,679	0.51		
	≥350	Med-med	13,115	0.40	11,590	0.46	1.14 (1.01-1.28)	.0376	8,243	0.46	1.11 (0.99-1.26)	.0805
		Med-high	1,605	0.45	1,354	0.59			862	0.58		
	Total	Med-med	51,737	0.36	45,217	0.41	1.15 (1.09-1.22)	<.0001	31,699	0.41	1.14 (1.07-1.21)	<.0001
		Med-high	6,879	0.36	5,737	0.53			3,571	0.53		
Antibiotic courses, n†	<150	Med-med	14,474	0.66	14,474	0.59	1.15 (1.05-1.26)	.0025	14,474	0.50	1.10 (1.01-1.18)	.0206
		Med-high	2,040	0.84	2,040	0.81			2,040	0.63		
	150-349	Med-med	24,148	0.63	24,148	0.57	1.06 (0.99-1.13)	.1156	24,148	0.48	1.09 (1.03-1.16)	.0062
		Med-high	3,234	0.83	3,234	0.74			3,234	0.61		
	≥350	Med-med	13,115	0.65	13,115	0.56	1.08 (0.97-1.19)	.1484	13,115	0.49	1.05 (0.96-1.15)	.3081
		Med-high	1,605	0.92	1,605	0.79			1,605	0.63		
	Total	Med-med	51,737	0.64	51,737	0.57	1.09 (1.04-1.15)	.0003	51,737	0.49	1.07 (1.02-1.11)	.0042
		Med-high	6,879	0.86	6,879	0.77			6,879	0.62		
Low-high vs low-medium ICSs												
Exacerbations, n*	<150	Low-med	3,823	0.17	3,244	0.32	1.13 (0.93-1.37)	.2262	2,106	0.31	1.06 (0.91-1.24)	.4536
		Low-high	970	0.31	805	0.47			558	0.49		
	150-349	Low-med	5,965	0.19	5,034	0.32	1.23 (1.08-1.40)	.0016	3,272	0.33	1.09 (0.95-1.25)	.2010
		Low-high	1,480	0.28	1,260	0.46			857	0.43		
	≥350	Low-med	2,871	0.23	2,451	0.35	1.08 (0.90-1.31)	.4056	1,636	0.34	1.16 (0.96-1.39)	.1168
		Low-high	782	0.35	674	0.49			455	0.47		
	Total	Low-med	12,659	0.19	10,729	0.33	1.17 (1.06-1.28)	.0012	7,014	0.33	1.11 (1.01-1.21)	.0269
		Low-high	3,232	0.31	2,739	0.47			1,870	0.46		
Antibiotic courses, n†	<150	Low-med	3,823	0.61	3,823	0.55	1.17 (1.04-1.32)	.0118	3,823	0.45	1.12 (1.00-1.25)	.0520
		Low-high	970	0.79	970	0.77			970	0.61		
	150-349	Low-med	5,965	0.63	5,965	0.55	1.06 (0.96-1.17)	.2287	5,965	0.45	1.07 (0.99-1.17)	.0938
		Low-high	1,480	0.86	1,480	0.72			1,480	0.59		
	≥350	Low-med	2,871	0.64	2,871	0.49	1.05 (0.91-1.20)	.5009	2,871	0.43	1.05 (0.94-1.17)	.3819
		Low-high	782	0.80	782	0.60			782	0.52		
	Total	Low-med	12,659	0.62	12,659	0.54	1.09 (1.02-1.16)	.0078	12,659	0.45	1.08 (1.02-1.14)	.0107
		Low-high	3,232	0.83	3,232	0.70			3,232	0.58		

BEC, Blood eosinophil count.

*ATS/ERS Task Force definition: Respiratory-related hospital admission or emergency attendance or acute OCS course (courses with evidence of lower respiratory consultation in the baseline year).

†Antibiotics course prescribed at a respiratory consultation.

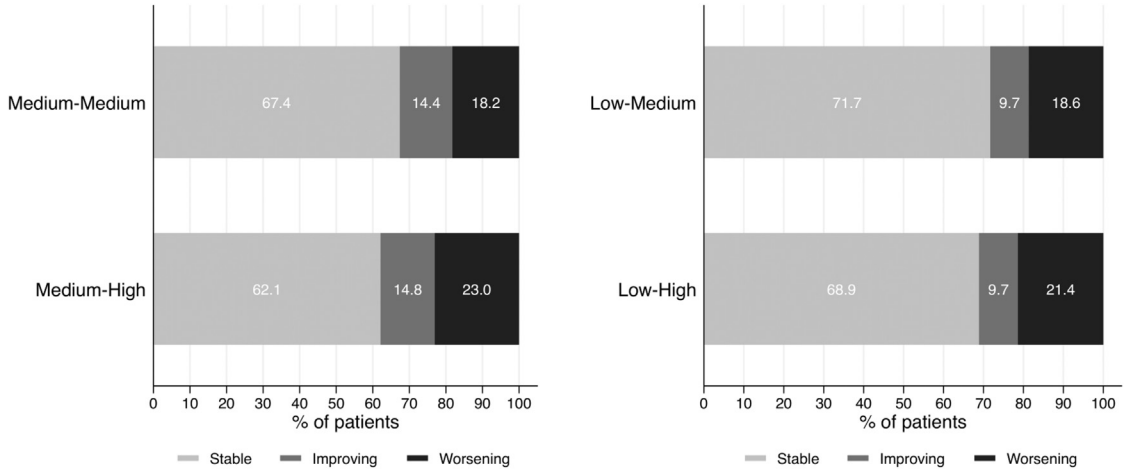

FIGURE 3. Change in number of exacerbations from baseline to outcome (IPTW) for medium-high vs medium-medium (*left*) and low-high vs low-medium ICS groups (*right*).

eosinophil count (≥350 cells/μL) improved more frequently than patients with a low count (<150 cells/μL; IPTW odds ratio [95% CI] medium-high vs medium-medium: 1.23 [1.08-1.39], P = .001; low-high vs low-medium: 1.29 [1.06-1.56], P = .010).

DISCUSSION

We report the results of a real-life historic cohort study that used longitudinal medical records from primary care databases to assess the effect of stepping up to high-dose ICSs in asthma. Our results do not support our original hypothesis because we found no evidence that a step-up to high-dose ICSs is effective in reducing time to first moderate/severe asthma exacerbations in UK patients (aged ≥13 years). We observed a higher risk of exacerbations in the follow-up period in those who stepped up to high-dose ICSs. In addition, a step-up to high-dose ICSs was associated with higher rates of asthma exacerbations and antibiotic courses prescribed for a lower respiratory condition over 1 and 3 years of follow-up.

Our findings, in a broad asthma population, support the findings of Beasley et al[7] who concluded that 80% to 90% of the maximum obtainable benefit of ICSs is seen with a "low" dose with minimal additional clinical benefit from "high"-dose ICSs in patients with moderate to severe asthma. The increased exacerbations in those who stepped up to high-dose ICSs in our study may reflect prescribing practices rather than a real increase. OCSs are used excessively in the United Kingdom and globally, and clinicians often resort to OCSs to gain control of asthma.[28] Because an exacerbation was partly defined by prescription of an OCS course in our study, increased exacerbations may not be a failure of increasing ICSs but rather a matter of clinical practice, which was less prominent in the eosinophilic phenotype.

When individual changes in exacerbation rate from baseline to first outcome year within the study arms were analyzed, a higher proportion of patients showed an increase in exacerbation rate in the high-dose ICS arms than in the comparison arms and there were more patients worsening than improving. The within-patient change in the number of exacerbations is important additional information because these results do not compare groups of patients with potential differences in exacerbation risk that were not captured by the patient information variables used to calculate propensity scores. Our findings may be explained by several factors. General practitioners may increase ICSs to a high dose when patients present with moderate asthma exacerbations that prompt a necessary therapy change but are not severe. Results were similar when exacerbations in the first 30 days of follow-up were excluded from the analyses. The observation of a higher exacerbation risk after stepping up the ICS dose could also be due to increased monitoring after the intervention. Our finding of a higher risk of exacerbations in those who stepped up to high-dose ICSs, along with more patients in this group worsening than improving, could even suggest a harmful effect of this treatment option. Previous evidence suggests that ICSs increase the risk of pneumonia and lower respiratory tract infection in a dose-responsive manner.[24,25] Prospective research including a broad population of patients with asthma is required to further investigate this.

We found a similar increased risk of exacerbations with high-dose ICSs in patients with good adherence (MPR ≥ 70%) to ICSs in the year before ID. Others have found that good 12-year ICS adherence (≥80%) was associated with increased OCS use, add-on therapies, and asthma-related health care visits in those with adult-onset asthma.[29] Improved adherence may reduce exacerbation risk for those who are responsive to ICSs, but poor adherence may also indicate poor responsiveness in terms of reducing exacerbation risk. In particular, ICS-responsive patients with poor adherence to medium-dose ICSs may use the option to improve adherence (in the medium-medium arm) and may therefore be poorly comparable with patients with a similar indication for an increase in dosage who are not responsive to medium-dose ICSs and therefore receive an increase in dose. Therapy could be stepped up in instances where low adherence is mistaken for low therapy effectiveness. In addition, higher-dose ICSs have been suggested to threaten patient compliance.[30] This illustrates the importance of patients' habits in terms of therapeutic compliance in real-life studies.

Overall, the proportion of patients with improved exacerbation rates was higher in patients with high blood eosinophil counts. This suggests that some patients with a high blood

eosinophil count may benefit from a step-up in ICS dose, which is in line with Clinical Study in Asthma Patients Receiving Triple Therapy in a Single Inhaler (CAPTAIN).[31] Indeed, there is evidence that treatment tailored using the sputum eosinophil count results in fewer asthma attacks than traditional management in adults with asthma.[32] There is also growing evidence that patients with high blood eosinophil counts may benefit from stepping up from low- to medium-dose ICSs.[15] It has recently been suggested that a small number (<1%) of patients with asthma with a high blood eosinophil count do not respond sufficiently to treatment with medium- or high-dose ICSs; the rate of severe asthma exacerbations was higher in these patients than in those without a high blood eosinophil count.[17,33] However, we found no evidence that increasing to high-dose ICSs would be more effective in patients with a high blood eosinophil count. This may suggest that maximum therapeutic benefit among patients with high blood eosinophil count is obtained at low or medium doses of ICSs, and patients with high eosinophil counts who have severe refractory asthma require alternative treatment options. Further research accounting for the existing associations between higher eosinophils and increased risk of exacerbations is required.

Our real-life study found that a step-up to high-dose ICSs was frequently associated with other changes in therapy, which may have influenced the associations. Sensitivity analyses excluding patients who had a change in substance, particle size, or device type at ID also showed no effectiveness of a step-up to high-dose ICSs. Most patients on high-dose ICSs were prescribed fluticasone. The fact that beneficial effects might differ between ICS substances cannot be excluded. Future study should investigate whether our findings hold true when stepping from stable low-dose ICS to higher-dose ICS regimens and from ICSs to ICS/LABA and when ICS groups are further categorized as ICS-formoterol, ICS alone, and ICS/LABA in alignment with currently recommended Global Initiative for Asthma controller/preferred reliever and controller/alternative reliever pathways, although it should be noted that currently no high-dose ICS/LABA maintenance and reliever therapy exists. Analyses by age groups, sex, race and ethnicity, concomitant conditions, and health care populations in those who improved and those who did not improve may also shed more light on our seemingly paradoxical findings.

This study has many strengths including the large sample size and the use of extensive statistical methods to adjust for confounding between the comparison arms. Some limitations, however, need consideration. First, despite applying extensive statistical methods to handle confounding including IPTW and excluding the first 30 days after stepping up, it is possible that some other unknown and unmeasured characteristics (eg, physician/patient behavior) are causing residual confounding by indication, which could explain the greater exacerbations reported after stepping up. However, confounding by severity was mitigated by use of IPTW when assessing the impact of stepping up ICS dose on time to first moderate/severe exacerbation. Furthermore, including all prescriptions for ICSs, either alone or in combination inhalers, may have skewed our findings, although use of cumulative ICS dose/d (beclomethasone equivalent) in the baseline year to categorize groups may have mitigated this effect somewhat. Second, the data sets represent information collected for clinical and routine use rather than for research purposes; however, extensive quality control and validity checks are conducted at practice level. Third, patients with available blood eosinophil counts may not be representative of the asthma population because eosinophil counts are typically measured from full blood cell counts requested for a specific medical reason. Fourth, the relationship between blood and airway eosinophils might differ by severity. A large time window between eosinophil and outcome measurements may influence results. Finally, there was no intervention in the stable medium-dose ICS arm, which may have skewed the effect seen in those who stepped up from medium- to high-dose ICSs comparatively, because an intervention (eg, step-up to higher-dose ICSs) could lead to increased awareness and recording of exacerbations in the outcome period. However, this is unlikely because we have previously reported that addition of a long-acting muscarinic antagonist was associated with a decreased rate of exacerbations and other acute respiratory events in the year after the intervention in a similar population using a pre-post design.[34]

CONCLUSIONS

We found no evidence that a step-up to high-dose ICSs is effective in preventing future asthma exacerbations in UK patients and support the current Global Initiative for Asthma steps of management (medium-dose ICS/long-acting beta agonist step 4)[6] and the introduction of alternative treatment strategies for those who remain uncontrolled including biologic therapies. Our results do not exclude the need to increase the ICS dose, but rather encourage physicians to consider whether such an increase is necessary and beneficial and serve as a reminder to follow up patients stepped-up to higher-dose ICS to gauge response.

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The data set supporting the conclusions of this article was derived from the CPRD (www.cprd.com) and the OPCRD (www.opcrd.co.uk). The CPRD has broad National Research Ethics Service Committee ethics approval for purely observational research using the primary care data and established data linkages. The OPCRD has ethical approval from the National Health Service (NHS) Research Authority to hold and process anonymized research data (Research Ethics Committee reference: 15/EM/0150). This study was approved by the Anonymised Data Ethics Protocols and Transparency Committee, the independent scientific advisory committee for the OPCRD, and the Independent Scientific Advisory Committee for the CPRD. The authors do not have permission to give public access to the study data set; researchers may request access to CPRD or OPCRD data for their own purposes. Access to CPRD can be made via the CPRD website (https://www.cprd.com/researcher/) or via the enquiries email enquiries@cprd.com. Access to OCPRD can be made via the OCPRD website (https://opcrd.co.uk/our-database/data-requests/) or via the enquiries email info@opcrd.co.uk.

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