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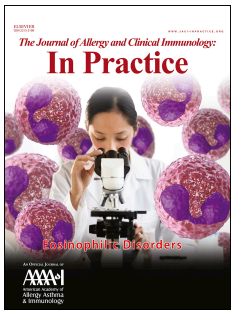

Effect of stepping up to high-dose inhaled corticosteroids in patients with asthma: UK Database Study

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PII: S2213-2198(22)01143-6

DOI: https://doi.org/10.1016/j.jaip.2022.10.040

Reference: JAIP 4492

To appear in: *The Journal of Allergy and Clinical Immunology: In Practice*

Received Date: 5 October 2021

Revised Date: 19 October 2022

Accepted Date: 20 October 2022

Please cite this article as: Pavord, FMedSci ID, Tran TN, Jones RC, Nuevo J, van den Berge M, Brusselle GG, Menzies-Gow AN, Skinner D, Carter V, Kocks JWH, Price DB, Effect of stepping up to high-dose inhaled corticosteroids in patients with asthma: UK Database Study, *The Journal of Allergy and Clinical Immunology: In Practice* (2022), doi: https://doi.org/10.1016/j.jaip.2022.10.040.

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Effect of stepping up to high-dose inhaled corticosteroids in patients with asthma: UK Database Study

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Conflicts of Interest

Ian D Pavord reports grants from NIHR and personal fees from Aerocrine, Almirall, Boehringer Ingelheim, Chiesi, Circassia, Genentech, GlaxoSmithKline, Knopp, Novartis, Regeneron, Sanofi and Teva, outside the submitted work, and is a member of the GOLD Science Committee.

Trung N Tran is an employee of AstraZeneca, who is a funder of this study that is conducted collaboratively with the OPRI Pte Ltd.

Rupert C Jones declares grants from AstraZeneca, GlaxoSmithKline, and Novartis; and personal fees for consultancy, speaker's fees, or travel support from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Nutricia, Observational and Pragmatic Research Institute, and Pfizer.

Javier Nuevo is an employee of AstraZeneca, which is a funder of this study.

Maarten van den Berge reports grants paid to the University from AstraZeneca, TEVA, GlaxoSmithKline, and Chiesi, outside the submitted work.

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Guy G Brusselle has received honoraria for lectures from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis, and Teva. He is a member of advisory boards for AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Sanofi/Regeneron, and Teva.

Andrew N Menzies-Gow has attended advisory boards for AstraZeneca, GlaxoSmithKline, Novartis, Sanofi and Teva, and has received speaker fees from AstraZeneca, Novartis, Roche, Teva and Sanofi. He has participated in research with AstraZeneca for which his institution has been remunerated and has attended international conferences with Teva. He has had consultancy agreements with AstraZeneca, Sanofi, and Vectura.

Derek Skinner and Victoria Carter are employees of Observational and Pragmatic Research Institute (OPRI) at the time of the study, which conducted this study in collaboration with Optimum Patient Care and AstraZeneca. OPRI has also conducted paid research on behalf of the following organisations in the past 3 years: Aerocrine, AKL Research and Development Ltd, Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Mapi Group, Meda, Mylan, Mundipharma, Napp, Novartis, Orion, Regeneron, Roche, Takeda, Teva, Zentiva (a Sanofi company).

Janwillem W. H. Kocks reports grants, personal fees and non-financial support from AstraZeneca, grants, personal fees and non-financial support from Boehringer Ingelheim, grants and personal fees from Chiesi Pharmaceuticals, grants, personal fees and non-financial support from GSK, grants from Mundipharma, grants and personal fees from TEVA, personal fees from MSD, personal fees from COVIS Pharma, outside the submitted work; and holds 72.5% of shares in the General Practitioners Research Institute.

David B Price has advisory board membership with AstraZeneca, Boehringer Ingelheim, Chiesi, Mylan, Novartis, Regeneron Pharmaceuticals, Sanofi Genzyme, Thermofisher; consultancy agreements with Airway Vista Secretariat, AstraZeneca, Boehringer Ingelheim, Chiesi, EPG Communication Holdings Ltd, FIECON Ltd, Fieldwork International, GlaxoSmithKline, 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

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unrestricted funding for investigator-initiated studies (conducted through Observational and Pragmatic Research Institute 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, GlaxoSmithKline, Kyorin, Mylan, Mundipharma, Novartis, Regeneron Pharmaceuticals and Sanofi Genzyme; payment for travel/accommodation/meeting expenses from AstraZeneca, Boehringer Ingelheim, Mundipharma, Mylan, Novartis, 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 Observational and Pragmatic Research Institute 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 GlaxoSmithKline

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Highlights Box

What is already known about this topic?

It is unclear whether patients with poorly controlled asthma benefit from stepping up to high-dose ICS and whether patients with high blood eosinophil count benefit from high-dose ICS.

What does this article add to our knowledge?

We found no evidence that a step-up to high-dose ICS is effective in preventing future asthma exacerbations.

How does this study impact current management guidelines?

Our results support the current GINA steps of management (medium-dose ICS/LABA step 4).

Keywords: asthma; exacerbations; corticosteroids; high dose; step-up

Funding: The OPCRD is established and maintained by Optimum Patient Care (OPC) Ltd. This study was funded by AstraZeneca and conducted collaboratively with the OPRI Pte Ltd.

Abbreviations

A&E: Accident & emergency; ADEPT: Anonymised Data Ethics Protocols and Transparency Committee; CI: Confidence interval; COPD: Chronic obstructive pulmonary disease; CPRD: Clinical Practice Research Datalink; EUPAS: European Union electronic Register of Post-Authorization studies; GINA: Global Initiative for Asthma; HR: Hazard ratio; ICS: Inhaled corticosteroid; ID: Index date; IPTW: Inverse probability of treatment weighting; IQR: Interquartile range; ISAC: Independent Scientific Advisory Committee; OCS: Oral corticosteroid; OPCRD: Optimum Patient Care Research Database; RCT: Randomized controlled trial; SD: Standard deviation; SMD: Standardized mean difference; UK: United Kingdom

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Abstract

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

Objective: To determine the effectiveness of stepping up to high-dose ICS.

Methods: A historic cohort study of asthma patients (≥13 years old), identified from two large UK electronic medical record databases, was conducted. Patients who remained on medium-dose ICS were compared to those who stepped up from medium- to high-dose ICS, while patients who stepped up from low- to medium-dose were compared to those who stepped up from low- to high-dose ICS. Time to first severe exacerbation (primary outcome) between treatment groups was compared using multivariable Cox proportional hazards models, and number of exacerbations and antibiotics courses were 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 (SD 2.7) years for those who remained on stable medium-dose ICS and 2.0 (SD 2.2) years for those who stepped up from medium-to high-dose ICS. A similar pattern was noted for those who stepped-up from low- to medium-ICS dose (2.6 (SD 2.5) years) and from low- to high-dose ICS (2.3 (SD 2.5) years). Patients who stepped up from medium- to high-dose ICS (n=6,879) had a higher risk of exacerbations during follow-up compared to those who remained on medium-dose ICS (n=51,737; hazard ratio [HR] 1.17, 95% confidence interval 1.12-1.22). This was similar in patients stepping up from low- to high-dose (n=3,232) compared to low-to medium-dose (n=12,659) ICS (HR 1.10 [1.04-1.17]). A step-up to high-dose ICS was also associated with higher number of asthma exacerbations and antibiotics courses. No significant difference in associations was found across subgroups of patients with different blood eosinophil counts (BEC).

Conclusion: We found no evidence that a step-up to high-dose ICS is effective in preventing future asthma exacerbations.

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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 (ICS) are the mainstay of asthma treatment and have been shown to reduce severe exacerbations, hospitalization, and death.[4,5] The Global Initiative for Asthma (GINA) 2021 guidelines recommend that asthma treatment is adjusted in a stepwise approach in accordance with individual patient needs, with an increase to high-dose ICS a possible option.[6] Beasley et al. however, critically reviewed available evidence for a therapeutic dose-response relationship of ICS on oral corticosteroid sparing in adult asthma and concluded that there is no evidence at present to suggest that stepping up to high-dose ICS is beneficial.[7] Others concluded that the addition of a LABA is more effective than increasing the dose of ICS in improving asthma control and that by increasing the dose of ICS, clinical improvement is likely to be of small magnitude.[8] Clearer evidence on the efficacy of this approach is important as 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 ICS within real-world populations.

Our hypothesis was that stepping up to higher dose ICS 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 ICS versus those who stepped up from medium- to high-dose ICS and also for two ICS step-up strategies.

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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 ICS were compared to those who remained on medium-dose ICS, while patients who stepped up from low- to high-dose ICS were compared to those who stepped up from low- to medium-dose ICS. Prescribed doses of different ICS were classified into low-, medium-, and high-dose as displayed in **Table 1**. All prescriptions for ICS, alone or in a combination inhaler, were considered. ICS prescriptions were assessed during a baseline period of one year, which was considered long enough to confirm consistent ICS exposure (**Figure 1**).

Data were extracted from the Optimum Patient Care Research Database (OPCRD; https://opcrd.co.uk/) and Clinical Practice Research Datalink (CPRD; https://www.cprd.com/) databases. The OPCRD comprises anonymized, longitudinal medical record data for >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.[19] 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 de-identified, longitudinal data from 16 million registered patients from >700 UK practices. Both the OPCRD and CPRD are well-validated and used frequently for medical and health research.[19,20] The OPCRD and CPRD + hospital episode statistics datasets 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 (ISAC approval number 16_236) and registered with the European Union electronic Register of Post-Authorization Studies (EUPAS Register number EUPAS15869). Approval for this study was granted by the Anonymised Data Ethics

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Protocols and Transparency (ADEPT) 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 prescriptions for asthma reliever and/or maintenance medication in the baseline year prior to ID, 3) blood eosinophil count available within two years prior to ID, recorded without a prescription of an acute course of oral corticosteroids (OCS; defined as the OCS courses with evidence of lower respiratory consultation in the baseline year) within two weeks prior to the measurement, 4) aged ≥13 years at ID, and 5) ≥1 year of continuous data prior to ID. Patients with a Read code for other chronic respiratory conditions (e.g. cystic fibrosis, lung cancer, 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 upon request.

Study outcomes

The primary outcome was time to first (severe) asthma exacerbation, defined by the American Thoracic Society/European Respiratory Society Task Force[21] as the occurrence of any of the following during the assessment period: asthma-related hospital admission or emergency department (ED) attendance, or an acute course of OCS with evidence of respiratory review. Primary care recorded hospital admissions and A&E 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. OCS/hospitalizations that occurred within two 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 (as high-dose ICS therapy may impact risk of bacterial infections.[22,23] The assessment period for all outcomes started from the date of step-up to a higher ICS dose or a randomly chosen eligible prescription date for those who remained on medium-dose ICS 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

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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).

Data analyses

All statistical analyses were carried out using Stata version SE 14.2 and MP 15.1 (StataCorp, College Station, TX). Descriptive statistics of baseline variables (i.e. 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 standard deviation (SD; for normally distributed variables) and/or median and interquartile range (IQR), while categorical variables were summarized using count and percentage. The standardized mean difference (SMD) was used to quantify the difference in baseline variables between treatment arms (medium-medium vs. medium-high and low-medium vs. low-high).[24] An SMD ≤10% indicated sufficient balance.

Primary outcome: time to first exacerbation

Inverse probability of treatment weighting (IPTW) was used to account for confounding by indication as 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 <20% of values missing (**Table 2** and **Table E1**), was used to weight the data with the inverse of the treatment probability. Weighted SMDs 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 **(Table E2)** was used to compare time to first asthma exacerbation (primary

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outcome) during the outcome period between treatment arms (medium-medium vs. medium-high ICS and low-medium vs. low-high ICS). 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 one and three 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 one-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 ICS and low-medium vs. low-high ICS) by blood eosinophil count.

Sensitivity analyses

Results are also presented by blood eosinophil count (<150, 150-349, ≥350 cells/µL).[17] These cut-off values were selected due to the way data were recorded in electronic medical records (i.e. 10^9/L to one 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 cut-off 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 (MPR≥70%; with MPR calculated by dividing the total of one 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.

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Results

The study included 51,737 patients who remained on medium-dose ICS and 6,879 patients who stepped up from medium- to high-dose ICS, and 12,659 and 3,232 patients who stepped up from low- to medium and low- to high-dose ICS, respectively (**Figure 2**). The demographic and clinical characteristics of patients by treatment arm are displayed in **Table 2** and **Table E1** (see **Tables E3-E5** for baseline characterization by eosinophil group). A higher proportion of patients who stepped up from medium- to high-dose ICS were aged ≥60 years (60% vs. 48.9%), ex-smokers (39.1% vs. 33%), and had a diagnosis of COPD (21.9% vs. 11.3%) compared to patients on stable medium-dose ICS (**Table 2**). Step up from medium- to high-dose ICS was more likely in those prescribed fluticasone, while step up from low- to high-dose ICS was more likely in those prescribed beclomethasone (**Table 2**). After IPT weighting, 94% (45/48; medium-medium vs. medium-high ICS) and 100% (low-medium vs. low-high ICS) of the measured baseline characteristics were well balanced between treatment arms (**Table E6**).

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 ICS than in the comparison arms (medium-high vs. medium-medium: 45% vs. 3%; low-high vs. low-medium: 74% vs. 57%; both p<0.00001). In most cases the change was to fluticasone/salmeterol, which was also the most frequent inhaler prescribed at ID in these patients.

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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 (SD 2.7) and 2.0 (SD 2.2) years in those who remained on stable medium-dose ICS and those who stepped up from medium- to high-dose ICS, respectively. For those patients who stepped up from low- to medium- and low- to high-dose ICS, mean follow-up time was 2.6 (SD 2.5) and 2.3 (SD 2.5) years, respectively. Follow-up times were similar when treatment arms were stratified by baseline eosinophil count (**Table 3**). There was a crude incidence of 18.9 exacerbations per 100 follow-up years in those who remained on medium-dose ICS, and a higher incidence of 27.5 per 100 follow-up years in those

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who stepped up from medium- to high-dose ICS. This resulted in an adjusted IPTW-weighted hazard ratio (HR) of 1.17 (95% confidence interval [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 ICS, and a higher incidence of 23.0 per 100 follow-up years in those who stepped up from low- to high-dose ICS. In the adjusted IPTW-weighted model, the latter had a 10% higher hazard rate of exacerbations in the follow-up period compared to the former (HR 1.10 [1.04-1.17]) (Table 3). 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 ICS was also found in patients with good adherence (MPR≥70%) to ICS in the year prior to ID (Table E7), 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 [1.12-1.24]; low-to-high ICS dose vs. low-to-medium ICS dose: HR 1.10 [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 vs. medium-medium (HR 1.18 [1.08-1.28]) but not in low-high vs. low-medium (HR 1.02 [0.84-1.24]).

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Secondary outcomes

A step-up to high-dose ICS was associated with high number of asthma exacerbations and antibiotics courses prescribed for a lower respiratory condition compared to medium-dose ICS over one and three years of follow-up (**Table 4**). Similar results were shown in patients with good adherence (**Table E8**). No significant difference in associations was found across subgroups of patients with different blood eosinophil counts (**Table 4).**

Patients improving/worsening

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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 ICS 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<0.0001; low-high vs. low-medium: 21.4% vs.18.6%, 1.19 [1.06-1.32], p=0.0023). The proportion of patients who improved did not differ between treatment arms (**Figure 3**). Overall, patients with high blood 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=0.001; low-high vs. low-medium: 1.29 [1.06-1.56]), p=0.010).

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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 ICS in asthma. Our results do not support our original hypothesis as we found no evidence that a step-up to high-dose ICS 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 ICS. Additionally, a step-up to high-dose ICS was associated with higher rates of asthma exacerbations and antibiotic courses prescribed for a lower respiratory condition over one and three years of follow-up.

Our findings, in a broad asthma population, support the findings of Beasley et al. who concluded that 80-90% of the maximum obtainable benefit of ICS is seen with a 'low' dose with minimal additional clinical benefit from 'high' dose ICS in patients with moderate to severe asthma.[7] The increased exacerbations in those who stepped up to high-dose ICS in our study may reflect prescribing practices rather than a real increase. OCS is used excessively in the UK and globally, and clinicians often resort to OCS to gain control of asthma.[25] As an exacerbation was partly defined by prescription of an OCS course in our study, increased exacerbations may not be a failure of increasing ICS 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 number of exacerbations is important additional information as 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. GPs may increase ICS to a high dose when patients present with moderate asthma exacerbations that prompt a necessary therapy change but are not severe. Results

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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 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 ICS, along with more patients in this group worsening than improving, could even suggest a harmful effect of this treatment option. Previous evidence suggests that ICS increases the risk of pneumonia and lower respiratory infection in a dose-responsive manner.[22,23] Prospective research including a broad population of asthma patients is required to further investigate this.

We found a similar increased risk of exacerbations with high-dose ICS in patients with good adherence (MPR≥70%) to ICS in the year prior to ID. Others have found that good 12-year ICS adherence (≥80%) was associated with increased OCS use, add-on therapies and asthma-related healthcare visits in those with adult onset asthma.[26] Improved adherence may reduce exacerbation risk for those who are responsive to ICS, 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 ICS 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 ICS 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 ICS has been suggested to threaten patient compliance.[27] 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 CAPTAIN, Indeed, there is evidence that treatment tailored using the sputum eosinophil count results in fewer asthma attacks than traditional management in adults with asthma.[28] There is also growing evidence that patients with high blood eosinophil counts may benefit from stepping up from low- to medium-dose ICS.[15] It has recently been suggested that a small number (<1%) of asthma patients with a high blood eosinophil count do not respond sufficiently to treatment with medium- or high-dose ICS; the rate of severe asthma exacerbations was higher in these patients compared to those without a high blood eosinophil count.[17,30]

However, we found no evidence that increasing to high-dose ICS 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 ICS, 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 ICS 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 ICS. Most patients on high-dose ICS were prescribed fluticasone. The fact that beneficial effects might differ between ICS substances cannot be excluded. Future study should investigate if our findings hold true when stepping from stable low ICS to higher dose ICS regimens and from ICS to ICS/LABA and when ICS groups are further categorized as ICS-formoterol, ICS alone and ICS/LABA in alignment with currently recommended GINA 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/ethnicity, concomitant conditions and healthcare populations in those that improved and those that 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 (e.g. 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 inverse probability of treatment weighting when assessing the impact of stepping up ICS dose on time to first moderate/severe exacerbation.

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Furthermore, including all prescriptions for ICS, either alone or in combination inhalers may have skewed our findings, although use of cumulative ICS dose/day (beclomethasone equivalent) in the baseline line year to categorize groups may have mitigated this effect somewhat. Second, the datasets 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 as eosinophil counts are typically measured from full blood 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 ICS comparatively, as an intervention (e.g. step-up to higher dose ICS) could lead to increased awareness and recording of exacerbations in the outcome period. However, this is unlikely as 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.[31]

In conclusion, we found no evidence that a step-up to high-dose ICS is effective in preventing future asthma exacerbations in UK patients and support the current GINA 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 ICS dose, but rather encourage physicians to consider if such an increase is necessary and beneficial and serve as a reminder to follow-up patients stepped up to higher ICS dose in order to gauge response.

Acknowledgments

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The authors wish to acknowledge the input of Dr Marjan Kerkhof and Dr Jaco Voorham for their contributions to the study. We would like to acknowledge Dr Julia Granerod (PhD) of the Observational and Pragmatic Research Institute (OPRI), Singapore, for her medical writing support, and Ms. Shilpa Suresh (MSc) of the Observational and Pragmatic Research Institute (OPRI), Singapore, for editorial and formatting assistance that supported the development of this publication.

Data Availability Statement

The dataset supporting the conclusions of this article was derived from the Clinical Practice Research Datalink (www.cprd.com) and the Optimum Patient Care Research Database (www.opcrd.co.uk). The CPRD has broad National Research Ethics Service Committee (NRES) 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 anonymised research data (Research Ethics Committee reference: 15/EM/0150). This study was approved by the Anonymised Data Ethics Protocols and Transparency (ADEPT) committee – the independent scientific advisory committee for the OPCRD, and the Independent Scientific Advisory Committee (ISAC) for the CPRD. The authors do not have permission to give public access to the study dataset; 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

Authors Contributions

David B. Price agrees to be accountable for all content and aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Derek Skinner, Victoria Carter and David B Price had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors were

involved in data acquisition or analysis and interpretation, as well as the critical revision of the manuscript for important intellectual content. All authors were involved in the conception and design of the study, were responsible for drafting the manuscript and provided additional administrative, technical, and material support. The study was supervised by Ian Pavord, Trung Tran and David B Price. All authors approved the final version of this manuscript and agree to be accountable for all aspects of the work.

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Table 1. Definition of daily ICS dose categories in µg 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

ICS: Inhaled corticosteroids

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533 **Table 2. Baseline characterization of all patients**
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Variable		Medium-Medium (N= 51,737)	Medium-High (N= 6,879)	P	SMD	Low-Medium (N= 12,659)	Low-High (N= 3,232)	P	SMD
Index year	Mean (SD)	2008 (3.7)	2009 (3.5)	<0.001	26.9	2009 (3.4)	2008 (3.6)	<0.001	16.2
	Median (IQR)	2008 (2005-2011)	2009 (2006-2012)			2009 (2006-2011)	2008 (2005-2011)		
Age (years)	Mean (SD)	57.5 (17.0)	61.8 (16.1)	<0.001	26.4	58.0 (17.3)	61.1 (16.6)	<0.001	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	<20, n (%)	811 (1.6)	50 (0.7)	<0.001	25.0	253 (2.0)	33 (1.0)	<0.001	17.6
	≥20 <39, n (%)	7,524 (14.5)	651 (9.5)			1,720 (13.6)	348 (10.8)		
	≥40 <59, n (%)	18,110 (35.0)	2,049 (29.8)			4,262 (33.7)	967 (29.9)		
	≥60 <79, n (%)	20,536 (39.7)	3,215 (46.7)			5,160 (40.8)	1,445 (44.7)		
	≥80, n (%)	4,756 (9.2)	914 (13.3)			1,264 (10.0)	439 (13.6)		
Gender	Male, n (%)	18,856 (36.4)	2,516 (36.6)	0.834	0.3	4,211 (33.3)	1,120 (34.7)	0.136	2.9
Smoking status	N (% non-missing)	50,951 (98.5)	6,796 (98.8)	<0.001	11.3	12,417 (98.1)	3,175 (98.2)	<0.001	8.8
	Non-smoker, n (%)	24,049 (47.2)	2,933 (43.2)			6,018 (48.5)	1,360 (42.8)		
	Current smoker, n (%)	10,082 (19.8)	1,209 (17.8)			2,197 (17.7)	671 (21.1)		
	Ex-smoker, n (%)	16,820 (33.0)	2,654 (39.1)			4,202 (33.8)	1,144 (36.0)		
BMI	N (% non-missing)	50,467 (97.5)	6,765 (98.3)	<0.001	4.4	12,419 (98.1)	3,153 (97.6)	0.082	0.9
	<18.5, n (%)	1,012 (2.0)	142 (2.1)			224 (1.8)	79 (2.5)		
	≥18.5-<25, n (%)	13,881 (27.5)	1,790 (26.5)			3,340 (26.9)	830 (26.3)		
	≥25-<30, n (%)	17,344 (34.4)	2,197 (32.5)			4,234 (34.1)	1,069 (33.9)		
	≥30, n (%)	18,230 (36.1)	2,636 (39.0)			4,621 (37.2)	1,175 (37.3)		
COPD diagnosis	Yes, n (%)	5,844 (11.3)	1,509 (21.9)	<0.001	28.9	1,207 (9.5)	702 (21.7)	<0.001	34.0
Nasal polyps	Yes, n (%)	1,694 (3.3)	216 (3.1)	0.556	0.8	328 (2.6)	78 (2.4)	0.568	1.1
Charlson Comorbidity Index	0, n (%)	18,809 (36.4)	2,031 (29.5)	<0.001	16.3	3,573 (28.2)	1,021 (31.6)	<0.001	1.7
	1-4, n (%)	27,525 (53.2)	3,887 (56.5)			7,610 (60.1)	1,760 (54.5)		
	≥5, n (%)	5,403 (10.4)	961 (14.0)			1,476 (11.7)	451 (14.0)		
FEV_1 % predicted	N (% non-missing)	20,969 (40.5)	3,922 (57.0)	<0.001	14.8	5,516 (43.6)	1,663 (51.5)	<0.001	27.4
	≥80%, n (%)	9,658 (46.1)	1,546 (39.4)			2,294 (41.6)	521 (31.3)		
	50-<80%, n (%)	8,434 (40.2)	1,676 (42.7)			2,475 (44.9)	759 (45.6)		
	30-<50%, n (%)	2,319 (11.1)	561 (14.3)			603 (10.9)	309 (18.6)		
	<30%, n (%)	558 (2.7)	139 (3.5)			144 (2.6)	74 (4.4)		
Number of exacerbations (ATS)	None, n (%)	40,012 (77.3)	5,324 (77.4)	0.244	0.6	10,959 (86.6)	2,575 (79.7)	<0.001	19.0
	1, n (%)	7,504 (14.5)	1,000 (14.5)			1,253 (9.9)	426 (13.2)		
	2, n (%)	2,622 (5.1)	319 (4.6)			293 (2.3)	157 (4.9)		
	3, n (%)	1,006 (1.9)	141 (2.0)			106 (0.8)	53 (1.6)		

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Variable		Medium-Medium (N= 51,737)	Medium-High (N= 6,879)	P	SMD	Low-Medium (N= 12,659)	Low-High (N= 3,232)	P	SMD
	≥4, n (%)	593 (1.1)	95 (1.4)			48 (0.4)	21 (0.6)		
Blood eosinophil count (cells/µL)	<150, n (%)	14,474 (28.0)	2,040 (29.7)	<0.001	5.1	3,823 (30.2)	970 (30.0)	0.167	2.3
	150-349, n (%)	24,148 (46.7)	3,234 (47.0)			5,965 (47.1)	1,480 (45.8)		
	≥350, n (%)	13,115 (25.3)	1,605 (23.3)			2,871 (22.7)	782 (24.2)		
ICS substance prior to ID	Beclomethasone, n (%)	16,800 (32.5)	1,338 (19.5)	<0.001	10.5	7,566 (59.8)	2,186 (67.6)	<0.001	16.9
	Fluticasone, n (%)	22,419 (43.3)	4,279 (62.2)			2,735 (21.6)	601 (18.6)		
	Budesonide, n (%)	12,518 (24.2)	1,262 (18.3)			2,358 (18.6)	445 (13.8)		
Cumulative ICS dose prescribed over baseline year (µg/day, beclomethasone equivalent)†	<=400, n (%)	20,046 (38.7)	1,100 (16.0)	<0.001	65.2	6,839 (54.0)	1,519 (47.0)	<0.001	22.0
	>400-800, n (%)	18,536 (35.8)	2,159 (31.4)			4,004 (31.6)	990 (30.6)		
	>800-1600, n (%)	11,103 (21.5)	2,838 (41.3)			1,613 (12.7)	565 (17.5)		
	>1600, n (%)	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; COPD = Chronic obstructive pulmonary disease; FEV_1 = Forced expiratory volume in one second; ICS = Inhaled corticosteroids; IQR = Interquartile range; P = P-value for the Kruskal-Wallis equality-of-populations rank test or the Pearson's chi-square test of independent categories, where appropriate; SD = Standard deviation; SMD = Standardized mean difference

†In the UK an ICS prescription can be made for inhalers with authorised repeats. These repeats must be issued by a prescribing physician, are recorded in patient electronic medical records (EMRs) and included in databases such as Optimum Patient Care Research Database (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 https://www.nhs.uk/nhs-app/nhs-app-help-and-support/prescriptions-in-the-nhs-app/ordering-a-prescription/.

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543 **Table 3. Follow-up time, asthma exacerbation and incidence rates (/year) by treatment arm, and adjusted hazard ratios for patients stepping up to high-**
544 **dose ICS relative to comparison arms, using intention-to-treat analyses (censored at loss to follow-up), stratified by baseline blood eosinophil count**

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Study arm	BEC	N patients	Follow-up (years)*		Follow-up (years), analyses**		Incidence		Incidence Rate Ratio vs stable medium†		Hazard Ratio (adjusted)***	
			N	Mean (SD)	N	Mean (SD)	Events	IR	IRR (95% CI)	P-value	HR (95% CI)	P-value
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	111452.4	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	240377.0	4.7 (3.3)	139100.3	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)	<0.0001	1.13 (1.04-1.23)[a]	0.0038
	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)	<0.0001	1.18 (1.10-1.25)[a]	<0.0001
	≥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)	<0.0001	1.18 (1.08-1.28)[b]	0.0003
	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)	<0.0001	1.17 (1.12-1.22)[a]	<0.0001
Low-high vs. low-medium ICS												
									Incidence Rate Ratio 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)	<0.0001	1.07 (0.96-1.20)	0.2249
	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)	<0.0001	1.10 (1.01-1.21)	0.0276
	≥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)	<0.0001	1.11 (0.98-1.26)[c]	0.0916
	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)	<0.0001	1.10 (1.04-1.17)	0.0017

*Total follow-up time in current general practice; **Follow-up time after index date 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) ***Adjusted for: a. number of respiratory consultations; b: time since last acute respiratory event; c:

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number of acute OCS courses (courses with evidence of lower respiratory consultation in the baseline year); † Medium to high vs stable medium; ‡ Low to high vs low to medium
BEC = Blood eosinophil count; CI = Confidence interval; HR = Hazard ratio; IR = Incidence rate; IRR = Incidence rate ratio; SD = Standard deviation

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549 **Table 4. Average event rate in a year and IPT-weighted adjusted rate ratios of asthma exacerbations and antibiotics courses over a one- and three-year**
550 **period**

Outcome	BEC	Arm	Baseline year		First follow-up year				First 3 follow-up years			
			N	Mean/%	N	Mean/ %	Adj. Ratio (95% CI)	P-value	N	Mean/ %	Adj. Ratio (95% CI)	P-value
Medium-high vs. medium-medium ICS												
Exacerbations, number*	<150	Med-Med	14,474	0.34	12,553	0.38	1.28 (1.14-1.44)	<0.0001	8,651	0.37	1.21 (1.07-1.36)	0.0020
		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)	0.0279	14,805	0.40	1.13 (1.03-1.24)	0.0066
		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)	0.0376	8,243	0.46	1.11 (0.99-1.26)	0.0805
		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)	<0.0001	31,699	0.41	1.14 (1.07-1.21)	<0.0001
		Med-High	6,879	0.36	5,737	0.53			3,571	0.53		
Antibiotic courses, number**	<150	Med-Med	14,474	0.66	14,474	0.59	1.15 (1.05-1.26)	0.0025	14,474	0.50	1.10 (1.01-1.18)	0.0206
		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)	0.1156	24,148	0.48	1.09 (1.03-1.16)	0.0062
		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)	0.1484	13,115	0.49	1.05 (0.96-1.15)	0.3081
		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)	0.0003	51,737	0.49	1.07 (1.02-1.11)	0.0042
		Med-High	6,879	0.86	6,879	0.77			6,879	0.62		
Low-high vs. low-medium ICS												
Exacerbations, number*	<150	Low-Med	3,823	0.17	3,244	0.32	1.13 (0.93-1.37)	0.2262	2,106	0.31	1.06 (0.91-1.24)	0.4536
		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)	0.0016	3,272	0.33	1.09 (0.95-1.25)	0.2010
		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)	0.4056	1,636	0.34	1.16 (0.96-1.39)	0.1168
		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)	0.0012	7,014	0.33	1.11 (1.01-1.21)	0.0269
		Low-High	3,232	0.31	2,739	0.47			1,870	0.46		
Antibiotic courses, number**	<150	Low-Med	3,823	0.61	3,823	0.55	1.17 (1.04-1.32)	0.0118	3,823	0.45	1.12 (1.00-1.25)	0.0520
		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)	0.2287	5,965	0.45	1.07 (0.99-1.17)	0.0938
		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)	0.5009	2,871	0.43	1.05 (0.94-1.17)	0.3819
		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)	0.0078	12,659	0.45	1.08 (1.02-1.14)	0.0107
		Low-High	3,232	0.83	3,232	0.70			3,232	0.58		

551 *ATS/ERS Task Force definition: Respiratory related hospital admission or emergency attendance or acute OCS course (courses with evidence of lower respiratory consultation
552 in the baseline year); **Antibiotics course prescribed at a respiratory consultation; BEC = Blood eosinophil count; CI = Confidence interval

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Legend to Figures

Figure 1: Study design

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 ICS. 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. **Abbreviations:** CPRD: Clinical Practice Research Datalink; ICS: Inhaled corticosteroid; OCS: Oral Corticosteroids; OPCRD: Optimum Patient Care Research Database.

Figure 3: Change in number of exacerbations from baseline to outcome (IPT-weighted) for medium-high vs. medium-medium (left) and low-high vs. low-medium ICS groups (right). **Abbreviations:** ICS: Inhaled corticosteroid

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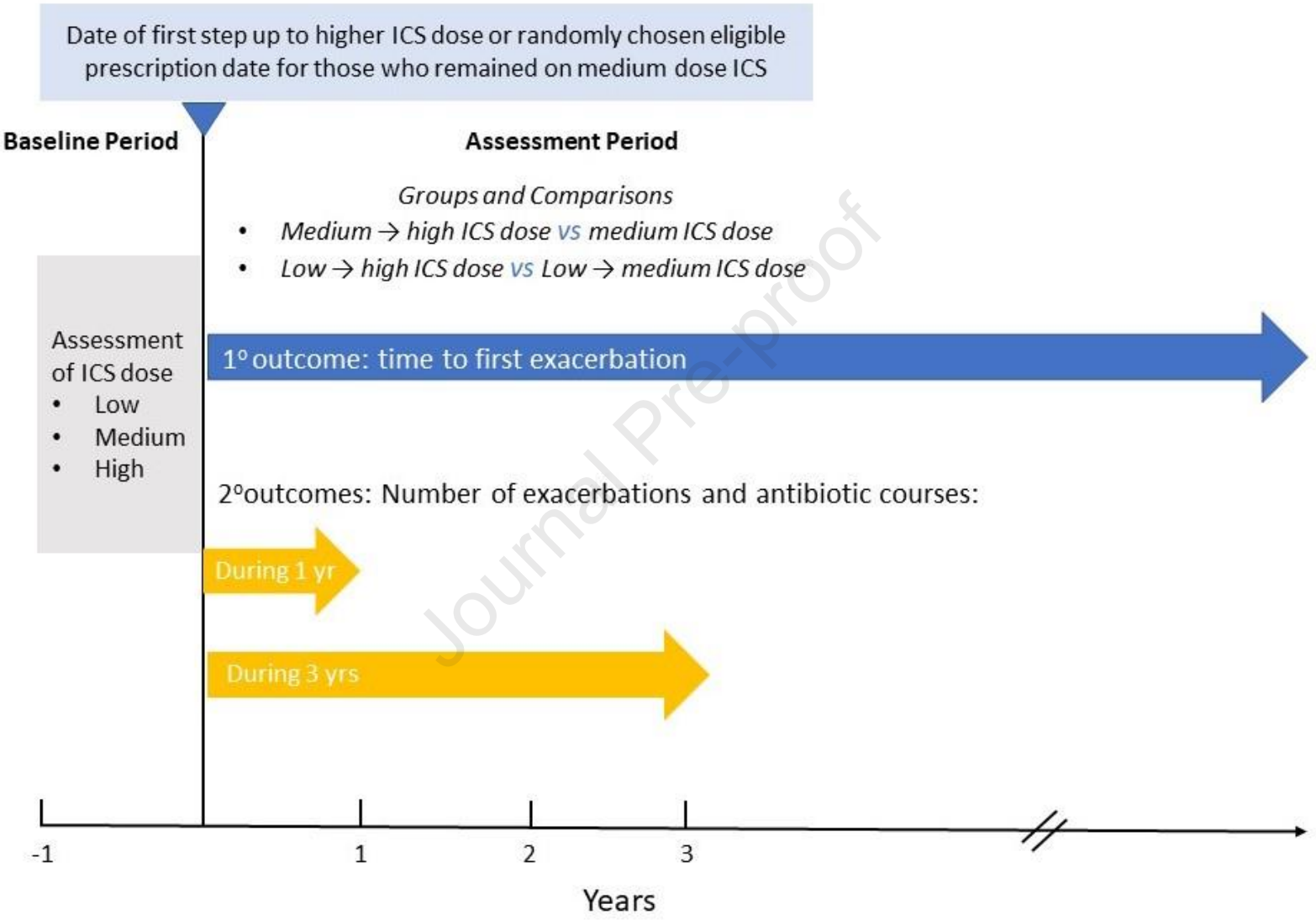

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Figure 2

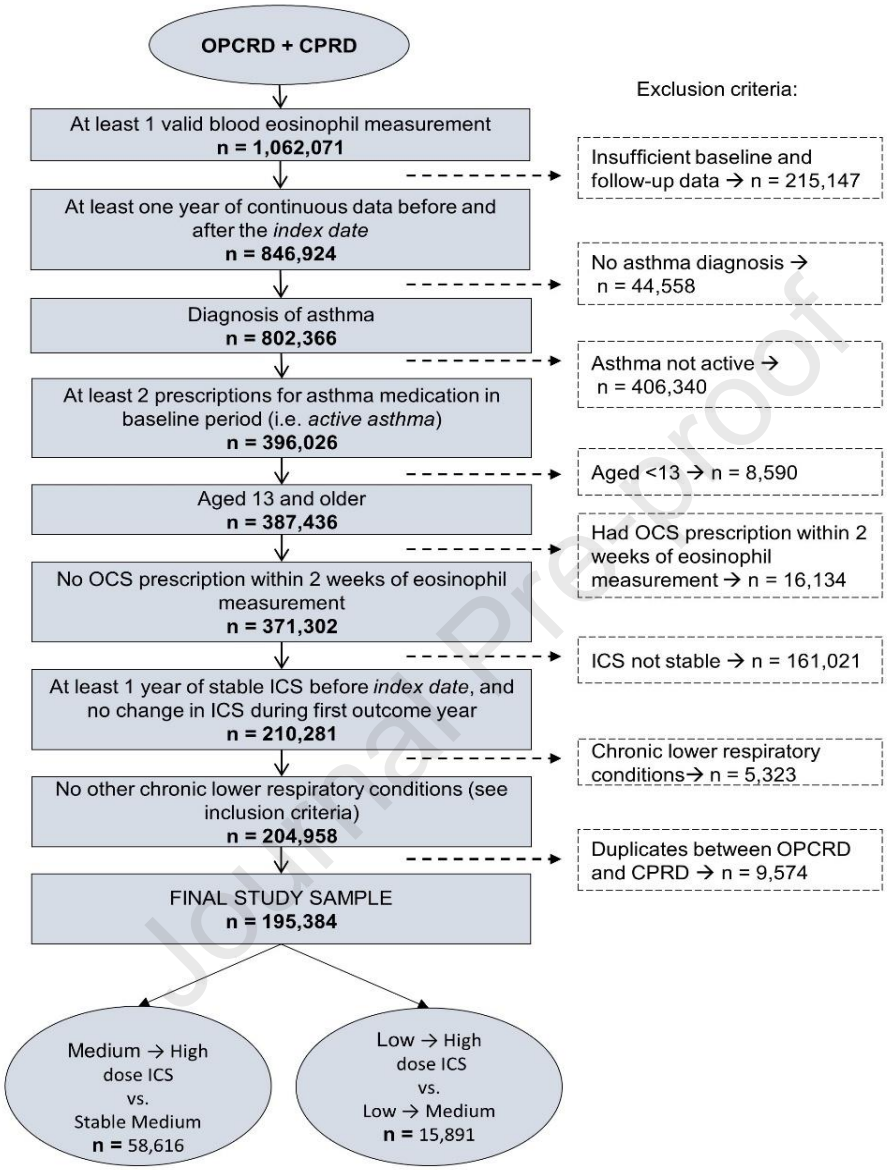

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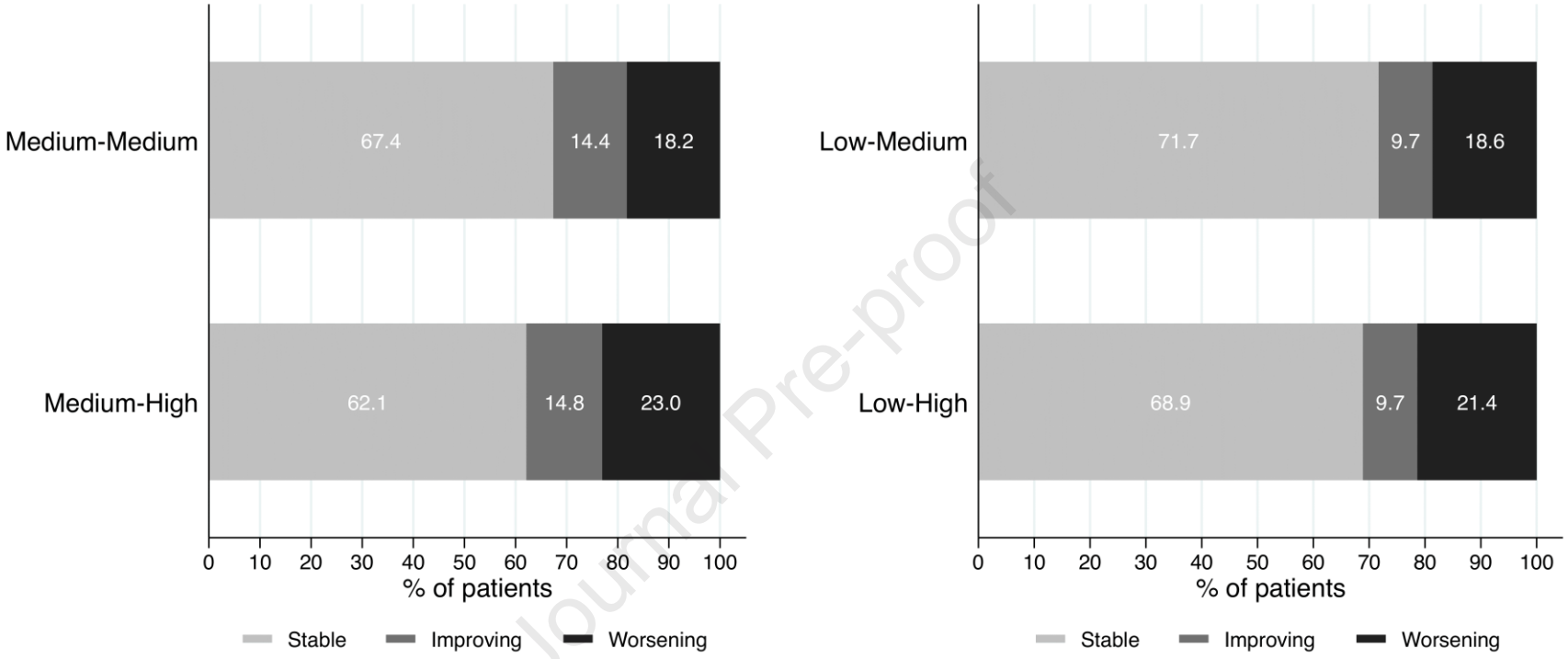
Figure 3



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