doi.org/10.36721/PJPS/2026.40.16412.1

# Eosinophil-guided inhaled corticosteroid de-escalation and its impact on acute exacerbations in stable chronic obstructive pulmonary disease (COPD) patients receiving triple inhaled therapy: A single-center randomized controlled trial

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**Abstract**: **Background**: Acute exacerbations of COPD increase hospitalization and death risk. Randomized evidence on blood eosinophil-guided inhaled corticosteroid (ICS) dose reduction in stable triple-therapy patients is lacking. **Objectives**: To evaluate whether blood eosinophil stratification modifies the effect of budesonide dose reduction (from 160 µg to 80 µg per actuation) on acute exacerbations in stable COPD patients receiving budesonide/ glycopyrrolate/formoterol (BGF) triple therapy. **Methods**: This double-blind randomized controlled trial enrolled 600 stable COPD patients on maintenance BGF for ≥12 weeks with ≥1 prior exacerbation. Patients were stratified by blood eosinophils (<300 vs ≥300 cells/µL) and randomized 1:1 to ICS reduction (budesonide 80 µg) or maintenance (budesonide 160 µg) for 52 weeks. The primary outcome was the annualized rate of moderate-to-severe exacerbations, analyzed using negative binomial regression with interaction testing. The trial was registered with the China Clinical Trial Registration Center (MR-51-22-003984). **Results**: In the ITT population, the annualized exacerbation rate was higher with ICS reduction, but the difference was not significant (IRR=1.17, P=0.064). A significant treatment-by-eosinophil interaction was present (P=0.006). At eosinophils ≥300 cells/µL, dose reduction increased exacerbations (IRR=1.57, P=0.002) and shortened time to first exacerbation (HR=1.69, P=0.002). At eosinophils <300 cells/µL, no difference was observed (IRR=1.03). Pneumonia (5.74% vs 10.40%, P=0.049) and local adverse events were less frequent with dose reduction. **Conclusion**: Blood eosinophils significantly modify the effect of ICS dose reduction (P_interaction=0.006). Dose reduction is not recommended when eosinophils ≥300 cells/µL. When eosinophils <300 cells/µL, cautious dose reduction may be considered to reduce adverse events without increasing exacerbations.

**Keywords**: Acute exacerbation; Blood eosinophils; Chronic obstructive pulmonary disease; Inhaled corticosteroid dose reduction

*Submitted 10-03-2026 – Revised 03-04-2026 – Accepted 13-04-2026*

## INTRODUCTION

Chronic obstructive pulmonary disease is a common chronic airway disease and acute exacerbations drive symptom worsening, increased risks of hospitalization and death and impose a substantial healthcare burden (Agusti *et al.*, 2023). Preventing acute exacerbations is a core goal of long-term management. Differences in inflammatory phenotypes lead to inconsistent treatment responses (Christenson, 2023). For patients with a history of exacerbations and persistent symptoms, triple inhaled therapy combining long-acting bronchodilators with inhaled corticosteroids is commonly used to reduce moderate-to-severe exacerbations and improve health status (Zayed *et al.*, 2019, Rabe *et al.*, 2020).

Inhaled corticosteroids have anti-inflammatory effects, but the benefits are heterogeneous; long-term exposure to higher doses is associated with pneumonia, oral candidiasis and hoarseness, suggesting that treatment intensity needs to be balanced between efficacy and safety (Miravitlles *et al.*, 2021). Blood eosinophils are readily available and reproducible and are used to assess the potential benefit of inhaled corticosteroids for exacerbation prevention, providing an actionable tool for phenotype-guided therapy (Singh *et al.*, 2022).

Stable patients often develop a need to reduce corticosteroid exposure after long-term triple inhaled therapy when exacerbation control is stable and decisions are often influenced by pneumonia risk and prior exacerbations (Chalmers *et al.*, 2020). Fixed-dose triple formulations improve adherence, thereby increasing inhaled corticosteroid exposure (Quint *et al.*, 2023). Existing evidence is mostly derived from inhaled corticosteroid withdrawal or step-down studies; the intervention approaches are not consistent with reducing the inhaled corticosteroid dose within a triple formulation alone, and non-uniform treatment backgrounds limit the generalizability of the conclusions (Rogliani *et al.*, 2020).

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Blood eosinophils may alter the impact of dose reduction on exacerbations: patients with high eosinophils are more likely to rely on the anti-inflammatory benefits of corticosteroids and thus be sensitive to dose reduction, whereas those with low eosinophils may reduce infection-related risk without increasing exacerbations (Georgiou *et al.*, 2024). The lack of randomized controlled evidence with prespecified stratification and interaction testing in stable patients receiving triple inhaled therapy makes dose-reduction strategies difficult to standardize and also limits judgments on risk-benefit rebalancing.

Therefore, a single-center, double-blind, blood eosinophil-stratified randomized controlled trial was conducted to compare high-dose maintenance versus low-dose de-escalation of budesonide in stable chronic obstructive pulmonary disease patients who continued to receive budesonide/glycopyrrolate/formoterol (BGF), with 52-week follow-up and the annualized rate of moderate-to-severe acute exacerbations as the primary endpoint. The study tested whether the de-escalation effect varied by blood eosinophil stratification and evaluated changes in pneumonia and local adverse events, providing evidence for individualized de-escalation.

## MATERIALS AND METHODS

### *Study design*

This study was a double-blind, parallel-group, randomized controlled trial stratified by blood eosinophil count. The study was conducted in the Department of Respiratory and Critical Care Medicine of The People's Hospital of Linshui. Screening and enrollment were performed from April 1, 2022, to March 31, 2024; follow-up ended on March 31, 2025 and the follow-up duration for each participant was 52 weeks. This study was implemented after review and approval by the hospital ethics committee (approval No. LYLL2022009). All participants signed written informed consent before any study-related procedures. The trial was registered with the China Clinical Trial Registration Center (Registration Number: ChiCTR2200058145; registered March 30, 2022).

### *Study population*

The study population comprised COPD patients followed up in outpatient clinics and after hospital discharge.

***Inclusion criteria***: 40–80 years; pulmonary function rechecked during the screening period, with post-bronchodilator FEV1/FVC<0.70; smoking history ≥10 pack-years; stable maintenance treatment with budesonide/glycopyrrolate/formoterol (BGF) for 12 weeks prior to screening; ≥1 moderate or severe acute exacerbation within 12 months before screening; CAT ≥10; no moderate/severe acute exacerbation within 6 weeks before screening and no use of systemic corticosteroids or antibiotics for respiratory tract infection within 4 weeks before screening; able to complete follow-up and sign informed consent.

***Exclusion criteria***: asthma; bronchiectasis with recurrent expectoration of purulent sputum; interstitial lung disease, active pulmonary tuberculosis; lung cancer or history of treatment for other malignancies within the past 5 years; radiographically confirmed pneumonia within 3 months prior to screening; requiring long-term maintenance systemic corticosteroids (prednisone equivalent ≥5 mg/d and ≥30 days); acute coronary syndrome or decompensated heart failure within the past 3 months; end-stage renal disease requiring dialysis; Child–Pugh C liver dysfunction; pregnancy or lactation; investigator judged unable to use a metered-dose inhaler device correctly or unable to complete 52-week follow-up.

***Enrollment procedure***: during the screening period, pulmonary function testing, complete blood count (including absolute eosinophil count), verification of prior exacerbations and baseline questionnaire assessments were completed; eligible patients were randomized and started study medication.

### *Blood eosinophil measurement and stratification strategy*

Blood eosinophils were measured from peripheral venous blood, and the absolute eosinophil count (cells/μL) was determined with an automated hematology analyzer. To reduce the impact of recent infection and corticosteroid exposure on blood eosinophils, this study separately verified the history of systemic corticosteroid and antibiotic use within the past 4 weeks before screening and before randomization and used the absolute eosinophil count on the day of randomization as the basis for stratification. The stratification threshold was predefined as 300 cells/μL: <300 cells/μL was the low-eosinophil stratum; ≥300 cells/μL was the high-eosinophil stratum (Sharma *et al.*, 2024). Randomization was implemented separately within each stratum to ensure balance between the two groups on the stratification variable. A post-hoc sensitivity analysis using the average of two measurements (screening and randomization day) in 422 patients confirmed the primary interaction finding.

### *Sample size estimation and randomization design*

In this study, participants were randomized 1:1 to the ICS reduction group or the maintenance group, stratified by blood eosinophils (the assumed annualized acute exacerbation rate in the low-eosinophil stratum was 0.8 events/person-year; in the high-eosinophil stratum, 1.0 events/person-year in the maintenance group and 1.7 events/person-year in the ICS reduction group, with a prespecified stratum proportion of 25%). The interaction between treatment and blood eosinophil stratification was the key effect and a negative binomial distribution model

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with Monte Carlo simulation (10,000 simulations) was used to estimate the sample size, with the dispersion parameter set to 0.7. With a two-sided α=0.05 and 80% power, the minimum required sample size was calculated as 540 participants; considering 10% loss to follow-up and treatment discontinuation, 600 participants were planned for enrollment.

The randomization sequence was generated by an independent statistician using a computer, with permuted blocks of sizes 4 and 6; the study pharmacy implemented allocation concealment according to the randomization sequence and dispensed study drugs with identical appearance; the drug codes were held only by the study pharmacy and the independent statistician. Both the high-dose (budesonide 160 μg) and low-dose (budesonide 80 μg) BGF inhalers were manufactured with identical external appearance—same color, shape, size and dose counter mechanism. The study pharmacy applied identical labels bearing only the participant ID and randomization number. The glycopyrrolate and formoterol doses were identical between the two devices. Neither investigators nor participants could distinguish the devices. Investigators and participants remained blinded throughout the study period; unblinding was permitted only when a serious adverse event occurred that required clarification of drug information to guide emergency treatment and the reason and time of unblinding were recorded and reviewed; outcome event adjudication was based on prespecified definitions and medical records and was completed under blinding.

***Intervention measures and concomitant treatment management***

All participants used budesonide/glycopyrrolate/formoterol (BGF) as the only long-term maintenance inhaled therapy, with a unified dosing frequency of twice daily, two inhalations per dose, via oral inhalation. The maintenance group used high-ICS-dose BGF (each actuation contained budesonide 160 μg, glycopyrrolate 7.2 μg and formoterol 4.8 μg); the ICS reduction group used low-ICS-dose BGF (each actuation contained budesonide 80 μg, glycopyrrolate 7.2 μg and formoterol 4.8 μg) (Khan *et al.*, 2025). The doses of glycopyrrolate and formoterol were kept consistent between the two groups and ICS reduction was achieved by a 50% reduction in the budesonide dose. Study medication started on the day of randomization and continued for 52 weeks, with no planned escalation or step-down of maintenance therapy during the study period.

Rescue medication was uniformly an inhaled short-acting β2-agonist, used as needed and with the dose recorded. During the study period, other ICS-containing inhaled preparations and other long-acting bronchodilators were prohibited as maintenance therapy to avoid systematic interference with the primary outcome. Concomitant medications for underlying diseases that had been stably used before screening were continued under the original regimen; if medical indications requiring adjustment occurred during the study period, they were recorded as such and included in the protocol deviation assessment. After an acute exacerbation occurred, the study center managed it according to a unified diagnostic and treatment pathway: moderate acute exacerbations were treated with a short course of systemic corticosteroids in outpatient clinics or the emergency department; antibiotics were added for those meeting at least two of the following three criteria: worsened dyspnea, increased sputum volume and sputum becoming purulent; severe acute exacerbations were treated according to emergency department or hospitalization pathways. All medications for acute exacerbation treatment and the visit settings were completely recorded in the study database.

***Follow-up schedule and data collection***

Participants were followed up at prespecified time points after randomization: on-site visits were conducted at weeks 4, 12, 24, 36, and 52; telephone follow-up was conducted every 4 weeks between visits to reduce the risk of underreporting acute exacerbations. At each follow-up, adherence to study medication (based on device dose counts and medication records), rescue medication use, acute exacerbations, adverse events, and changes in concomitant medications were collected.

Pulmonary function testing was performed at baseline, week 24 and week 52 and post-bronchodilator pulmonary function parameters were used as the basis for analysis; tests were completed according to a standardized procedure using the same device and FEV1% predicted was calculated according to reference equations for Chinese adults (Huang *et al.*, 2024). Symptoms and health status were assessed at baseline and at each on-site follow-up visit using CAT and mMRC questionnaires (Jones *et al.*, 2009, Sunjaya *et al.*, 2022). Acute exacerbation events were captured through three approaches: patient self-report, telephone follow-up inquiry and verification against hospital information system records; each event was entered into the database after investigators verified medical records and prescription information and severity grading was adjudicated under blinding according to prespecified definitions.

***Outcome measures and operational definitions***

The primary outcome was the annualized rate of moderate or severe COPD acute exacerbations within 52 weeks after randomization. An acute exacerbation was defined as an event of sustained worsening of respiratory symptoms (dyspnea, cough, sputum production) compared with the stable period that required additional treatment; a moderate acute exacerbation was defined as an event requiring systemic corticosteroids and/or antibiotics but

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without hospitalization; a severe acute exacerbation was defined as an event leading to emergency department visit or hospitalization. For consecutive acute exacerbation events in the same participant, if the interval between events was less than 14 days and the participant had not returned to a stable period, the events were combined as a single event.

Secondary outcomes included: time to first moderate or severe acute exacerbation; annualized rate of severe acute exacerbations within 52 weeks; change from baseline in post-bronchodilator FEV1 at week 52; change from baseline in CAT score at week 52; change from baseline in mMRC grade at week 52; mean daily number of rescue medication uses within 52 weeks.

Safety outcomes included: incidence of pneumonia during the study period; incidence of oral candidiasis; incidence of hoarseness; incidence of serious adverse events; and all-cause death. Pneumonia was defined as the presence of one or more of the following: fever, worsening cough, purulent sputum, worsening dyspnea, new infiltrates on chest imaging, and receipt of antibiotic treatment.

***Statistical analysis***

Statistical analyses were performed according to the intention-to-treat (ITT) principle. The primary analysis set comprised all randomized participants; the safety analysis set comprised participants who received at least one dose of study medication; the per-protocol analysis set was used for sensitivity analyses, excluding participants with major protocol deviations. Continuous variables were described as mean ± standard deviation or median (interquartile range) and categorical variables were described as counts and percentages.

The primary outcome was analyzed using a negative binomial regression model, with the log of follow-up time as an offset. Independent variables included treatment group, eosinophil stratification and the treatment × stratification interaction term and baseline number of acute exacerbations and baseline FEV1% predicted were included as covariates to improve estimation precision. The primary effect measure was the incidence rate ratio (IRR), along with its 95% confidence interval. Interaction was assessed using the two-sided P value of the interaction term. Stratified treatment effects (IRR in the low-eosinophil stratum and IRR in the high-eosinophil stratum) were calculated based on the same model.

Time to first moderate or severe acute exacerbation was analyzed using a Cox proportional hazards model, with independent variables set consistently with those for the primary outcome, and hazard ratios (HRs) and 95% confidence intervals were reported. Repeated measures of FEV1, CAT and mMRC were analyzed using linear mixed-effects models. Fixed effects included treatment group, follow-up time point, treatment × time interaction term, eosinophil stratification and its interaction with treatment and the corresponding baseline values were included; participant was included as a random effect. Safety outcomes were primarily described as incidence rates, with between-group comparisons using chi-square tests or Fisher's exact tests; time to first pneumonia was analyzed using a Cox model as a supplementary analysis.

For count outcomes and time-to-event outcomes, participants who discontinued study medication early or were lost to follow-up were censored at their last valid follow-up time point and contributed their actual follow-up time. For continuous outcomes, the mixed-effects model used maximum likelihood estimation when missing data met the missing-at-random assumption. All tests were two-sided, with the significance level set at 0.05; P values for secondary outcomes were used for descriptive inference and were not used to replace conclusions for the primary outcome. Statistical analyses were performed using R and SAS, with version numbers fixed and recorded in the statistical analysis scripts.

***Safety monitoring, treatment discontinuation and withdrawal management***

An independent Data and Safety Monitoring Board (DSMB) was established, consisting of three members: a pulmonologist, a clinical trialist and a biostatistician, none of whom were involved in trial conduct. The DSMB reviewed unblinded safety data (pneumonia, serious adverse events, deaths) at 12-week intervals and after every 200 participants enrolled. No prespecified stopping boundaries were crossed and the DSMB did not recommend early termination. Study medication was discontinued in the event of a serious adverse event related to study medication, participant request to discontinue, pregnancy, or a non-COPD indication requiring long-term systemic corticosteroid treatment. After discontinuation, follow-up was still completed as planned to ensure ITT analysis. All reasons for discontinuation and withdrawal were prespecified, categorized and recorded truthfully.

***Data management and quality control***

Study data were entered and managed through an EDC system, with logic/range checks and audit trails. Double-checking and source data verification were implemented for key variables, including acute exacerbations, pulmonary function, CAT/mMRC, adherence, and pneumonia adjudication. Uniformly trained technicians administered and checked on-site questionnaires and pulmonary function testing performed by designated research staff. Acute exacerbations and pneumonia were entered after cross-verification based on prescriptions, laboratory/imaging findings and visit records. Anonymous data review, query resolution and determination of analysis sets were completed before the database lock.

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## RESULTS

***Study population, enrollment and baseline characteristics***

A total of 893 patients were screened. After excluding 293 patients, 600 patients were randomized to the ICS reduction group and the maintenance group (300 patients each). The safety analysis included 296 and 298 patients, respectively. The 52-week follow-up was completed by 286 and 288 patients, respectively. The per-protocol analysis included 268 and 272 patients (Fig. 1). Baseline characteristics at randomization were balanced between the two groups, with similar age, sex, smoking history and pulmonary function indices and consistent distributions of symptom scores and the number of acute exacerbations in the past year; the proportions of blood eosinophils ≥300 cells/μL were 25.67% and 25.33%, respectively (Table 1).

***Primary outcome: Annualized rate of moderate-to-severe acute exacerbations over 52 weeks***

In the ITT analysis set, the annualized rate of moderate-to-severe acute exacerbations was 1.05 and 0.89 events/person-year in the ICS reduction and maintenance groups, respectively, with an adjusted IRR of 1.17 (95% CI 0.99–1.38, P = 0.064). Stratified analyses showed that, at blood eosinophils ≥300 cells/μL, the rate was higher in the ICS reduction group (IRR = 1.57, 95% CI 1.18–2.09, P = 0.002), whereas at <300 cells/μL, the two groups were similar (IRR = 1.03, 95% CI 0.86–1.23); P_interaction = 0.006. Results of the per-protocol analysis were consistent with the ITT analysis (Table 2). A post-hoc sensitivity analysis using the average of two eosinophil measurements (screening and randomization) in 422 patients confirmed the primary interaction finding (P_interaction = 0.009).

***Secondary outcomes: Exacerbation-related outcomes (time and severe exacerbations)***

In the blood eosinophils ≥300 cells/μL subgroup, the risk of first moderate/severe acute exacerbation was higher in the ICS reduction group (HR=1.69, P=0.002); in the blood eosinophils <300 cells/μL subgroup, the two groups were similar (HR=1.04, P=0.687); the interaction was significant (P_interaction=0.006) (Fig 2). In the overall population, there was no significant difference in the annualized rate of severe acute exacerbations between the ICS reduction group and the maintenance group (IRR=1.21, P=0.154); however, in the blood eosinophils ≥300 cells/μL subgroup, the risk increased significantly after reduction (IRR=1.49, P=0.045), while no clear difference was observed in the blood eosinophils <300 cells/μL subgroup (IRR=1.07, P=0.688); the interaction was significant (P_interaction=0.032) (Table 3).

***Secondary outcomes: Pulmonary function, symptoms and rescue medication***

No statistical evidence of between-group differences was observed between the ICS reduction group and the maintenance group in changes in FEV1 at weeks 24 and 52, mMRC at week 52, or changes in rescue SABA use (all P > 0.05); the decrease in CAT score at week 52 was smaller in the ICS reduction group than in the maintenance group (Δ = 0.71 points, P = 0.040). The smaller CAT score improvement in the ICS reduction group (Δ = 0.71 points, P = 0.040) approached the minimal clinically important difference of 1.0 point, suggesting that some patients experienced perceptible worsening of symptoms despite stable lung function (Table 4).

***Safety and treatment exposure/adherence***

The incidences of pneumonia, oral candidiasis and hoarseness were all lower in the ICS reduction group than in the maintenance group (all P<0.05), whereas SAE and all-cause death were similar between the two groups (all P>0.05) (Table 5). Study medication exposure duration and adherence were generally similar between the two groups: median exposure was >51 weeks in both groups, the proportions with complete exposure were 85.14% and 88.26% and the proportions with adherence ≥80% were 78.38% and 81.88%; the proportions with permanent discontinuation were 9.12% and 7.72% and rescue SABA record completeness was >92% in both groups (Table 6).

## DISCUSSION

Among stable patients receiving maintenance triple inhaled therapy with budesonide/ glycopyrrolate/ formoterol (BGF), after down-titrating the budesonide dose within BGF, changes in moderate-to-severe acute exacerbations showed clear heterogeneity: at the overall level, only a shift of risk toward an unfavorable direction was observed, whereas in patients with higher blood eosinophils, the exacerbation burden was more clearly associated with dose reduction; patients with low blood eosinophils maintained a similar level. The interaction test supported modification of the treatment effect by blood eosinophils and this pattern was consistent in the per-protocol analysis. The significant treatment-by-eosinophil interaction (P = 0.006) is the central finding of this trial, demonstrating that the effect of ICS dose reduction differs qualitatively based on blood eosinophil count.

The discrepancy between ITT (P = 0.064) and per-protocol (P = 0.041) analyses for the primary outcome warrants discussion. In the ITT analysis, participants who discontinued study medication or had poor adherence were still analyzed according to their randomized assignment. These participants contributed less exposure to the assigned ICS dose, biasing the ITT estimate toward the null.

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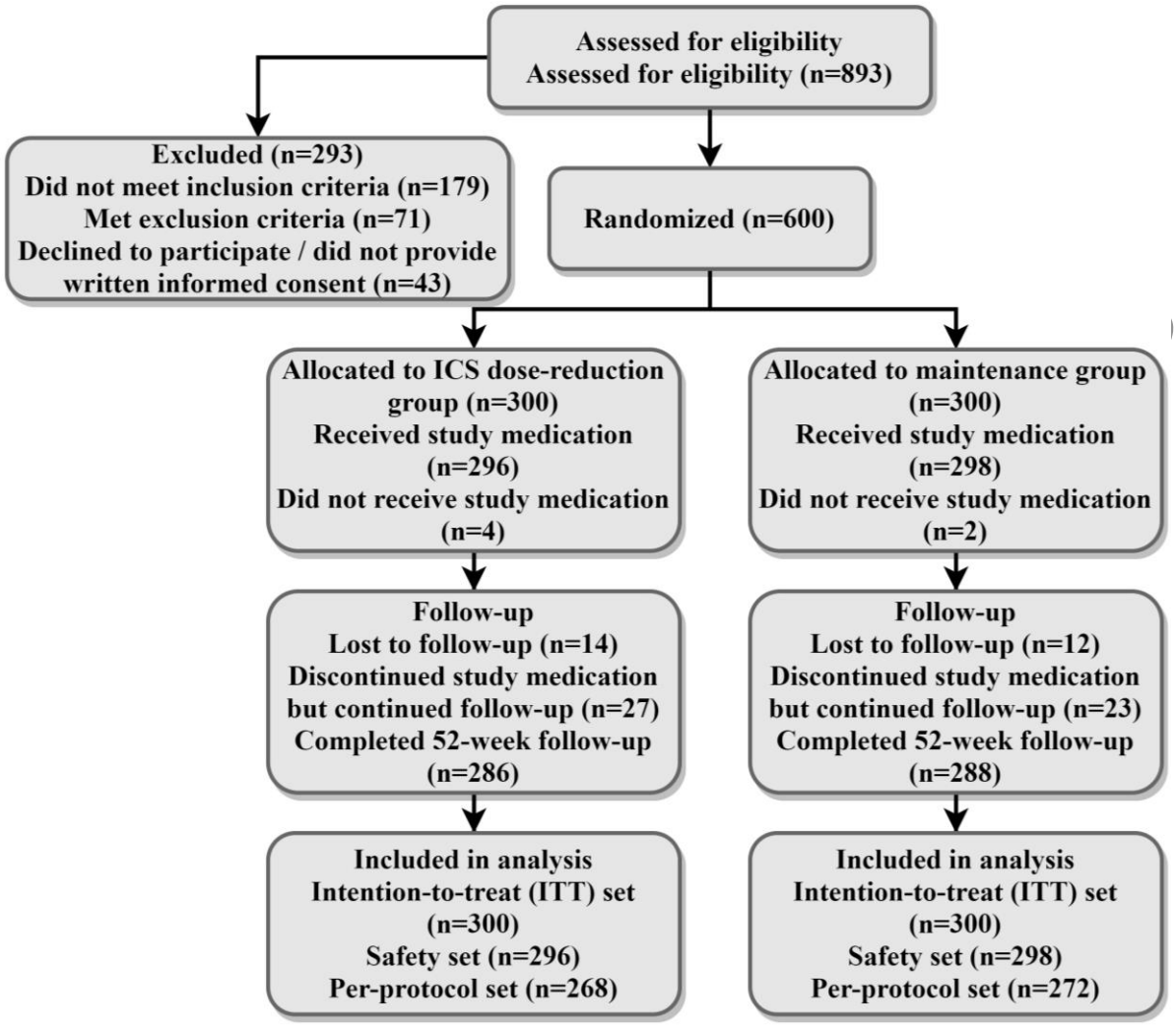



**Fig. 1**: CONSORT flow diagram of participants

In the per-protocol analysis, which excluded participants with major protocol deviations (including <80% adherence or early discontinuation), the treatment effect was larger and reached statistical significance. This pattern suggests that the true biological effect of ICS dose reduction may exceed the ITT estimate, and that real-world effectiveness may depend on adherence. Clinically, this implies that dose reduction decisions should be accompanied by adherence monitoring.

Elevated eosinophils suggest a more corticosteroid-responsive inflammatory phenotype and ICS reduce the tendency for exacerbations by inhibiting type 2 inflammation-related signals and reducing eosinophil activation and airway inflammatory fluctuations (Lea *et al.*, 2023). Because the bronchodilator components remained unchanged, reduced anti-inflammatory intensity became the main change; patients with high eosinophils were more likely to experience a lowered threshold of inflammatory control, reducing the threshold for triggering exacerbations and thereby presenting as exacerbations occurring more easily or earlier (Pascoe *et al.*, 2019). Exacerbations in patients with low eosinophils are more often driven by infection and dominated by neutrophilic inflammation; the marginal benefit of ICS is limited and the lack of an evident change in risk after dose reduction is consistent with their pathophysiology (Fricker & Lokwani, 2025). Previous step-down studies and clinical guidelines have regarded blood eosinophils as a key indicator for evaluating the benefit of ICS and the risk of withdrawal and have indicated that the risk of exacerbations increases after withdrawal or dose reduction in populations with high eosinophils (Ferguson *et al.*, 2020). The evidence from double-blind, stratified randomization with prespecified interaction testing strengthened the causal direction of this pattern, suggesting that dose-reduction decisions in stable patients receiving triple inhaled therapy should be based on blood eosinophil counts, with patients with high eosinophils requiring more cautious dose reduction strategies and more intensive follow-up monitoring.

**Table 1**: Baseline characteristics of participants at randomization

| Variable | ICS reduction group (n=300) | Maintenance group (n=300) |
|---|---|---|
| Age (years) | 66.28 ± 7.41 | 66.07 ± 7.58 |
| Male , n (%) | 229 (76.33%) | 232 (77.33%) |
| Smoking pack-years (pack-years) | 41.63 ± 19.27 | 40.88 ± 18.94 |
| Post-bronchodilator FEV1 (mL) | 1184.62 ± 386.15 | 1176.93 ± 392.48 |
| Post-bronchodilator FEV1% predicted (%) | 45.72 ± 13.86 | 45.39 ± 14.12 |
| Post-bronchodilator FEV1/FVC (%) | 51.38 ± 8.67 | 51.12 ± 8.94 |
| CAT score (0–40) | 18.42 ± 6.21 | 18.35 ± 6.09 |
| mMRC grade (0–4) | 2.16 ± 0.88 | 2.14 ± 0.86 |
| Number of moderate/severe acute exacerbations in the 12 months prior to randomization, median [IQR] | 2 [1, 3] | 2 [1, 3] |
| Number of severe acute exacerbations in the 12 months prior to randomization, median [IQR] | 0 [0, 1] | 0 [0, 1] |
| Absolute blood eosinophil count (cells/μL), median [IQR] | 212 [125, 310] | 216 [123, 308] |
| Eosinophil stratification: <300 cells/μL, n (%) | 223 (74.33%) | 224 (74.67%) |
| Eosinophil stratification: ≥300 cells/μL, n (%) | 77 (25.67%) | 76 (25.33%) |

Note: Descriptive statistics only; no between-group significance testing performed. Continuous variables: mean ± SD or median [IQR]; categorical: n (%). FEV1 and FVC are post-bronchodilator values.

**Table 2**: Primary outcome: annualized rate of moderate-to-severe acute exacerbations and treatment effect

| Analysis set / population (n) | ICS reduction group, annualized rate (E/PY) | Maintenance group, annualized rate (E/PY) | IRR (95% CI) | P |
|---|---|---|---|---|
| ITT analysis | | | | |
| Overall (300 vs 300) | 1.05 (307/292.91) | 0.89 (260/293.33) | 1.17 (0.99–1.38) | 0.064 |
| Eosinophils <300 cells/μL (n=223 vs 224) | 0.88 (192/218.63) | 0.85 (186/219.42) | 1.03 (0.86–1.23) | 0.753 |
| Eosinophils ≥300 cells/μL (n=77 vs 76) | 1.55 (115/74.28) | 1.00 (74/73.91) | 1.57 (1.18–2.09) | 0.002 |
| P_interaction (ITT) | — | — | — | 0.006 |
| Per-protocol | | | | |
| Overall (268 vs 272) | 1.02 (272/266.84) | 0.86 (233/270.92) | 1.19 (1.01–1.41) | 0.041 |
| Eosinophils <300 cells/μL (n=198 vs 203) | 0.84 (166/197.11) | 0.83 (167/201.74) | 1.02 (0.84–1.24) | 0.823 |
| Eosinophils ≥300 cells/μL (n=70 vs 69) | 1.52 (106/69.73) | 0.95 (66/69.18) | 1.60 (1.18–2.17) | 0.003 |
| P_interaction (per-protocol) | — | — | — | 0.004 |

Note: Annualized rate = total number of events (E) / actual person-years of follow-up (PY). IRR was estimated by negative binomial regression (with log[PY] as the offset), adjusted for the number of moderate/severe acute exacerbations in the 12 months prior to randomization and baseline FEV1% predicted; P_interaction refers to treatment group × eosinophil stratification (<300 vs ≥300). Participants lost to follow-up/discontinued were censored at the last follow-up; two exacerbations with an interval <14 days were combined as one event.

In the time dimension, in the high blood eosinophils population, the first moderate-to-severe acute exacerbation occurred earlier after ICS dose reduction, whereas the curves were similar between the two groups in the low blood eosinophils population. The interaction suggests that blood eosinophils affect not only the total number of exacerbations but also the timing of exacerbation occurrence. Severe acute exacerbations are more closely related to healthcare resource utilization and prognosis. No clear overall difference was observed, but unfavorable changes and an interaction were present in the high blood eosinophils subgroup, suggesting that risk may extend from frequency to severity. This is consistent with the anti-inflammatory threshold theory: under the background of stable triple inhaled therapy-induced bronchodilation, short-term fluctuations during acute exacerbations depend more on the homeostasis of inflammatory control (Bakakos *et al.*, 2025). After corticosteroid dose reduction, airway eosinophilic inflammation in high-eosinophil patients is prone to rebound, and the mucosal barrier and airway hyperresponsiveness are prone to imbalance under minor triggers, leading to an earlier susceptible period (Polverino & Sin, 2024).

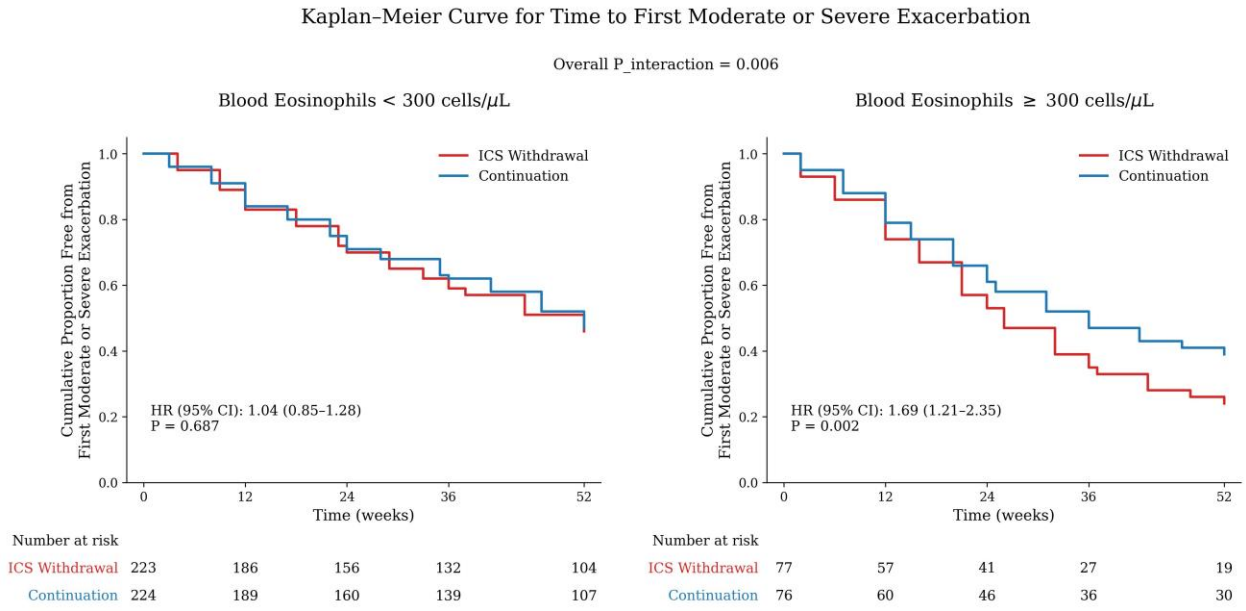



**Fig 2**: Kaplan–Meier Curve for Time to First Moderate or Severe Exacerbation. HR is the hazard ratio of the ICS reduction group relative to the maintenance group (adjusted for the number of moderate/severe acute exacerbations in the 12 months prior to randomization and baseline FEV1% predicted); P_interaction is the P value for the treatment × eosinophil stratification interaction term. Participants without a first exacerbation were censored at the last valid follow-up or week 52.

**Table 3**: Secondary outcome: annualized rate of severe acute exacerbations and treatment effect

| Analysis set (ITT) | ICS reduction group, annualized rate (E/PY) | Maintenance group, annualized rate (E/PY) | IRR (95% CI) | P |
|---|---|---|---|---|
| Overall (300 vs 300) | 0.33 (97/292.91) | 0.29 (84/293.33) | 1.21 (0.93–1.57) | 0.154 |
| Eosinophils <300 cells/μL (n=223 vs 224) | 0.26 (56/218.63) | 0.24 (53/219.42) | 1.07 (0.77–1.49) | 0.688 |
| Eosinophils ≥300 cells/μL (n=77 vs 76) | 0.55 (41/74.28) | 0.42 (31/73.91) | 1.49 (1.01–2.21) | 0.045 |
| P_interaction (ITT) | — | — | — | 0.032 |

Note: Annualized rate = total number of events (E) / actual person-years of follow-up (PY). IRR was estimated by negative binomial regression (with log[PY] as the offset), adjusted for the number of moderate/severe acute exacerbations in the 12 months prior to randomization and baseline FEV1% predicted; P_interaction refers to the P value for the treatment group × eosinophil stratification (<300 vs ≥300) interaction term. A severe acute exacerbation was defined as an event leading to emergency department visit or hospitalization. Participants lost to follow-up/discontinued were censored at the last follow-up; two exacerbations with an interval <14 days were combined as one event.

Early-onset exacerbations initiate the inflammatory cascade earlier; when accompanied by aggravated airflow limitation, viscous sputum, and superimposed infection, they are more likely to cross the outpatient or emergency department management threshold and evolve into emergency department visits or hospitalization (Bhatt *et al.*, 2023). In contrast, exacerbations in low-eosinophil patients are mostly driven by infection burden, mucus secretion, and neutrophilic inflammation, with limited corticosteroid effects; after dose reduction, they remain relatively stable over time and are associated with fewer severe outcomes, showing biological consistency (Keir *et al.*, 2021). Previous withdrawal studies generally showed neutral severe outcomes overall, but high blood eosinophils repeatedly showed signals of earlier or more exacerbations (Pirera *et al.*, 2024). With continued maintenance of long-acting bronchodilators, similar stratified effects persisted after only down-titrating the corticosteroid dose, suggesting that this risk is not due to insufficient bronchodilation but is more consistent with reduced corticosteroid-related anti-inflammatory effects.

Pulmonary function indices and dyspnea scores changed similarly between the two groups during follow-up and no clear difference was observed in rescue medication use, suggesting that airway dilation effects were maintained under constant doses of glycopyrrolate and formoterol and that ICS dose reduction did not incur a detectable ventilatory functional cost.

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**Table 4**: Secondary outcomes: changes in pulmonary function and symptom outcomes

| Outcome | ICS reduction group: LS mean change (95% CI) | Maintenance group: LS mean change (95% CI) | Δ (95% CI) | P |
|---|---|---|---|---|
| FEV1 change (mL) (week 24) | −6.84 (−26.92–13.24) | −1.27 (−21.41–18.87) | −5.57 (−34.11–22.97) | 0.702 |
| FEV1 change (mL) (week 52) | −27.63 (−52.89–−2.37) | −12.41 (−37.78–12.96) | −15.22 (−51.11–20.67) | 0.406 |
| CAT change (points) (week 52) | −0.98 (−1.54–−0.42) | −1.69 (−2.25–−1.13) | 0.71 (0.03–1.39) | 0.040 |
| mMRC change (grade) (week 52) | −0.13 (−0.21–−0.05) | −0.18 (−0.26–−0.10) | 0.05 (−0.06–0.16) | 0.379 |
| Change in mean daily rescue SABA use (times/day) (week 52) | −0.17 (−0.24–−0.10) | −0.25 (−0.32–−0.18) | 0.08 (−0.02–0.18) | 0.120 |

Note: LS mean change is the change from baseline; Δ=change in the ICS reduction group−change in the maintenance group. Estimates were obtained from linear mixed-effects models (including baseline values, with participant-specific random intercepts); P values correspond to Δ. Reductions in CAT, mMRC, and rescue SABA indicate improvement (Δ<0 indicates greater improvement in the ICS reduction group).

**Table 5**: Safety outcomes

| Adverse event category | ICS reduction group (n=296) | Maintenance group (n=298) | P |
|---|---|---|---|
| Pneumonia (≥1 event), n (%) | 17 (5.74%) | 31 (10.40%) | 0.049 |
| Oral candidiasis (≥1 event), n (%) | 10 (3.38%) | 22 (7.38%) | 0.044 |
| Hoarseness (≥1 event), n (%) | 12 (4.05%) | 30 (10.07%) | 0.006 |
| Serious adverse events (≥1 event), n (%) | 34 (11.49%) | 36 (12.08%) | 0.899 |
| All-cause death, n (%) | 3 (1.01%) | 4 (1.34%) | 1.000 |

Note: Between-group comparisons were performed using Fisher's exact test (two-sided); the safety analysis set comprised participants who received at least one dose of study medication. Pneumonia adjudication required both worsening clinical symptoms, new infiltrates on imaging, and receipt of antibiotic treatment; SAE was defined according to GCP.

**Table 6**: Actual study medication exposure and adherence

| Indicator | ICS reduction group | Maintenance group |
|---|---|---|
| Number of participants included in the safety analysis set | 296 | 298 |
| Study medication exposure duration (weeks) | 51.6 [49.2, 52.0] | 51.9 [49.8, 52.0] |
| Participants with complete exposure (≥48 weeks) | 252 (85.14%) | 263 (88.26%) |
| Adherence (%), mean ± SD | 86.72 ± 11.34 | 88.41 ± 10.96 |
| Participants with adherence ≥80%, n (%) | 232 (78.38%) | 244 (81.88%) |
| Participants who permanently discontinued study medication | 27 (9.12%) | 23 (7.72%) |
| ─ Discontinuation due to serious adverse events | 9 | 11 |
| ─ Participant-requested discontinuation | 11 | 7 |
| ─ Discontinuation due to pregnancy | 0 | 0 |
| ─ Discontinuation due to non-COPD medical indications requiring long-term systemic corticosteroid treatment | 7 | 5 |
| Participants with complete rescue SABA records | 275 (92.91%) | 279 (93.62%) |

Note: Adherence (%) =actual actuations/planned actuations×100 (planned=4 actuations/day×exposure days); exposure days were defined as from the first to the last dosing day. "Complete rescue SABA records" indicates that records were available for each follow-up interval (missing=0). This table presents descriptive statistics only.

In terms of health status, CAT improvement was smaller in the reduction group than in the maintenance group, suggesting that symptom and quality-of-life questionnaires are more sensitive than FEV1 in reflecting

changes in the intensity of inflammatory control and are directionally consistent with stratified differences in exacerbation outcomes. The 0.71-point difference in CAT improvement between groups did not reach the established minimal clinically important difference of 1.0 point for COPD. However, the directionally consistent worsening across multiple symptom measures (CAT, numerically worse mMRC and rescue use) suggests that a subset of patients may experience clinically meaningful deterioration. The lack of a difference in FEV1 indicates that symptom questionnaires capture aspects of disease control not reflected in spirometry, particularly inflammatory burden and day-to-day variability. Clinicians considering dose reduction should monitor symptoms closely even when lung function remains stable.

In terms of safety, after dose reduction, pneumonia and local oropharyngeal corticosteroid-related reactions were less frequent, while serious adverse events and mortality remained similar, consistent with the expected reduction in local immunosuppression (Mkorombindo & Dransfield, 2020). Considering stratified exacerbation risk and overall safety outcomes, dose reduction is more acceptable in patients with low blood eosinophils, whereas patients with high blood eosinophils should prioritize exacerbation control and cautiously assess pneumonia risk (Ashdown *et al*., 2022, Khan *et al.*, 2026). Previous randomized studies and meta-analyses have repeatedly observed an association between ICS and pneumonia risk with a dose relationship and step-down can reduce related adverse events; for populations with higher blood eosinophils, the relative benefit of ICS for exacerbation prevention is more prominent (Melani *et al*., 2024). Consistent with the interaction evidence, the main value of dose reduction lies in reducing the burden of infection and local adverse reactions, but the scope of applicability should be limited by the blood eosinophil phenotype, and safety benefits should not be used as a one-size-fits-all basis for dose reduction (Dalin *et al*., 2022). The similar exposure duration, adherence, and completeness of rescue SABA records between the two groups support the idea that the above differences mainly originate from treatment effects rather than follow-up or information bias.

***Limitations***

This study has several limitations. First, the single-center design limits generalizability to populations with different demographic characteristics, healthcare access patterns and exacerbation management protocols. Our findings are most directly applicable to specialty respiratory clinics in similar health systems. In primary care settings without routine eosinophil testing, implementation would require additional infrastructure. For patients without a recent exacerbation history (excluded from our trial), the risk-benefit balance of dose reduction may differ and our conclusions should not be extrapolated to that population. External validation in multi-center studies across diverse healthcare systems is needed. Second, the study population was limited to stable patients who had continuously used budesonide/glycopyrrolate/formoterol (BGF) and had a history of exacerbations, and the conclusions should not be directly generalized to populations without a history of exacerbations, with frequent recent infections, or to those initiating triple therapy. Third, eosinophils were stratified based on a single measurement on the day of randomization. Although recent infection and systemic corticosteroid exposure were excluded during screening, short-term fluctuations may still have led to stratification shifts. A post-hoc sensitivity analysis using the average of two measurements (screening and randomization) in 422 patients confirmed the primary interaction (P = 0.009), but repeated measurements over time would have been preferable.

Fourth, we did not collect sputum eosinophils, FeNO, or exacerbation-specific inflammatory biomarkers (e.g., serum C-reactive protein at exacerbation onset). Consequently, we could not definitively classify exacerbations as eosinophilic versus infection-driven. While the stratified treatment effect suggests that patients with high eosinophil counts experience more exacerbations after dose reduction, we cannot confirm that these exacerbations were indeed eosinophilic. Future studies should incorporate point-of-care inflammatory testing at exacerbation to validate the mechanistic pathway. Fifth, the numbers of secondary outcomes and safety events were limited, especially the small number of death events, making estimates of rare serious risks insufficiently precise. Sixth, although acute exacerbations were captured through multiple sources including active reporting, telephone follow-up and medical record verification and were adjudicated under blinding, underreporting due to mild events without medical visits or grading errors due to incomplete treatment records may still exist.

## CONCLUSION

The significant treatment-by-eosinophil interaction (P_interaction = 0.006) is the central finding of this trial, providing the statistical justification for a stratified approach. In stable COPD patients receiving maintenance triple inhaled therapy with budesonide/glycopyrrolate/formoterol (BGF), blood eosinophil count significantly modified the clinical effect of ICS dose reduction. In patients with blood eosinophils ≥300 cells/μL, dose reduction increased the risk of moderate-to-severe acute exacerbations (IRR = 1.57, P = 0.002) and led to earlier first exacerbation (HR = 1.69, P = 0.002); routine dose reduction is not recommended in this population. Maintaining anti-inflammatory intensity should be the primary goal, with strengthened follow-up monitoring. In

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patients with blood eosinophils <300 cells/μL, dose reduction did not increase the risk of exacerbations (IRR = 1.03) and may be considered in patients with unchanged maintenance bronchodilation to reduce pneumonia and local corticosteroid-related adverse events. Blood eosinophils are a useful but insufficient standalone biomarker for dose-reduction decisions. Clinical judgment should integrate eosinophil count with exacerbation history, pneumonia risk factors and symptom burden. Dose-reduction decisions should be based on eosinophil stratification to rebalance risks and benefits.

***Acknowledgments***
The authors thank the patients who participated in this study and the nursing staff at the Department of Respiratory and Critical Care Medicine for their assistance with patient follow-up and data collection. We also thank the Department of Laboratory Medicine for processing blood eosinophil counts.

***Authors' contributions***
Zhou Zheng: Conceptualization, study design, protocol development, funding acquisition, supervision, data interpretation, manuscript writing and revision Liu Chen: Patient recruitment, data collection, statistical analysis, manuscript drafting, literature review Both authors read and approved the final manuscript.

***Funding***
This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. The study was supported by institutional resources from The People's Hospital of Linshui.

***Data availability statement***
The data supporting the findings of this study are available from the corresponding author upon reasonable request. Individual participant data will not be shared publicly to protect participant privacy, but aggregated data and statistical code can be made available for academic purposes.

***Ethical approval***
This study was approved by the Ethics Committee of The People's Hospital of Linshui (approval number: LYLL2022009). All procedures performed were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments. This study was performed in adherence with the CONSORT guidelines. See supplementary file for the CONSORT checklist.

***Conflict of interest***
The authors declare that they have no competing interests. No pharmaceutical company funding or support was received for this study. The study medication was purchased through hospital research funds and the authors have no financial relationships with manufacturers of inhaled corticosteroids or combination therapies.

***Informed consent statement***
Written informed consent was obtained from all individual participants included in the study. Participants were informed about the purpose of the study, the intervention, potential risks and benefits and their right to withdraw at any time without affecting their medical care.

***Clinical trial registration***
This trial was registered with the China Clinical Trial Registration Center (https://www.chictr.org.cn/hvshowproject.html?id=156762) (Registration Number: ChiCTR2200058145; registered March 30, 2022).

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