ORIGINAL RESEARCH

Effect of Inhaled Corticosteroid Withdrawal on Chronic Obstructive Pulmonary Disease Exacerbations in Patients Taking Triple Therapy at Baseline

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Purpose: In the Withdrawal of Inhaled Steroids during Optimized Bronchodilator Management (WISDOM) trial, inhaled corticosteroid (ICS) withdrawal in patients with chronic obstructive pulmonary disease receiving triple therapy (long-acting β_2-agonist+long-acting muscarinic antagonist+ICS) did not change moderate/severe exacerbation risk. However, many patients were not taking triple therapy before study participation. This analysis was conducted to eliminate the impact of non-ICS users on WISDOM results by re-analyzing the data using only the subset of patients who were taking triple therapy at screening.

Patients and Methods: The effect of ICS withdrawal on moderate/severe exacerbation risk in the subgroup of WISDOM patients taking triple therapy before enrolling in the study was evaluated in this post hoc analysis. Additionally, the effect of ICS withdrawal in patients with a history of ≥2 exacerbations in the previous year and various blood eosinophil counts was assessed.

Results: Overall, 39.0% (n=970: ICS continuation, 479; ICS withdrawal, 491) of the WISDOM trial population were taking triple therapy at screening. Baseline characteristics were generally similar between groups. Moderate/severe exacerbation risk between the ICS withdrawal and continuation groups (hazard ratio [HR], 1.05; 95% confidence interval [CI]: 0.89–1.25) was not increased in patients taking triple therapy at screening versus the overall trial population (HR [95% CI]: 1.06 [0.94–1.19]). However, in patients with a history of ≥2 exacerbations, exacerbation risk (HR [95% CI]) increased nominally with blood eosinophil count from 1.07 [0.81–1.41] (≥100 cells/μL) to 1.45 [0.58–3.60] (≥400 cells/μL).

Conclusion: Consistent with results from the overall WISDOM trial population, ICS withdrawal did not increase exacerbation risk in patients taking triple therapy at screening. Patients with a history of frequent exacerbations and higher blood eosinophil counts could benefit from continuation of ICS-based therapy.

Keywords: COPD, dual bronchodilator, glucocorticoid, triple therapy

Introduction

A maintenance bronchodilator (long-acting β_2-agonist [LABA] or long-acting muscarinic antagonist [LAMA]) has long been recommended in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy report for patients with chronic obstructive pulmonary disease (COPD) and breathlessness or exercise limitation.[1] For patients with continued symptoms or an increased risk of COPD exacerbations, escalation to a LAMA+LABA combination is recommended.[1] De-escalation of

therapy for COPD is also proposed.[1] Criteria for bronchodilator de-escalation include lack of symptomatic or functional response after adding a second bronchodilator or the development of significant adverse events associated with the added medication.

Collectively, the role of inhaled corticosteroids (ICS) in the treatment of COPD was further revised in GOLD 2020, and ICS are now recommended for use only in certain circumstances, namely in patients with a history of hospitalizations for COPD exacerbations or with ≥2 moderate COPD exacerbations per year after failure with single or dual maintenance bronchodilator therapy or in patients with eosinophilia or a history of asthma.[1]

Unlike asthma, where ICS are a cornerstone of treatment,[2] ICS may not be as broadly beneficial in patients with COPD due to the involvement of non-eosinophilic inflammatory cells, which may not respond effectively to ICS treatment.[3,4] Moreover, long-term use of ICS in patients with COPD can be associated with the risk of adverse events.[4,5]

Despite GOLD recommendations, real-world evidence shows inappropriate prescribing and overuse of ICS-containing therapy in COPD patients, for whom ICS are not clinically indicated.[6–8] De-escalation or withdrawal of ICS therapy in COPD is now recommended if the original indication for starting an ICS was inappropriate or if an adverse outcome such as pneumonia occurs after adding an ICS or there is no clinical response to the added ICS.[1] An eosinophil count of <100 cells/μL has also been suggested as a potential indication for de-escalating from an ICS.[1]

Results of the Withdrawal of Inhaled Steroids during Optimized Bronchodilator Management (WISDOM) trial showed that stepwise withdrawal of ICS in patients with severe-to-very severe COPD and a history of or risk for COPD exacerbations after being placed on triple therapy for ≥6 weeks was noninferior to ICS continuation for the risk of moderate or severe exacerbations.[9] Some patients were receiving triple therapy at screening, but many were not. The reasons for medication choice for entry into the study were not determined. The SUNSET trial,[10] a trial requiring clinical prescription and use of triple therapy for ≥6 months prior to study entry, supports many of the findings of WISDOM. However, ICS withdrawal in a subset of patients on triple therapy with increased blood eosinophils resulted in an increased risk for exacerbations and deterioration of lung function.[10]

Prior analyses of WISDOM did not include the impact of ICS withdrawal on patients on triple therapy prior to the study. Consequently, the effect of ICS withdrawal in patients already taking triple therapy at screening was unknown. Identifying patients with COPD who are suitable for triple therapy and understanding whether or not and in which patients to de-escalate treatment from triple therapy to dual bronchodilator therapy is important. The objective of this post hoc analysis of data from the WISDOM trial was to evaluate the effect of ICS withdrawal on the risk of moderate or severe exacerbations in the subgroup of patients who were receiving triple therapy prior to study participation. Additionally, we assessed the effect of ICS withdrawal in those patients who had a history of ≥2 exacerbations in the year before the study and blood eosinophil counts above different thresholds.

Patients and Methods
Study Design

The design of the WISDOM trial (ClinicalTrials.gov number, NCT00975195) has been described previously.[9,11] Briefly, WISDOM was a 12-month, multinational, randomized, double-blind, parallel-group, active-controlled trial. Patients were selected on the basis of their heightened risk for COPD exacerbations based on severity of lung function and history of ≥1 documented exacerbation during the 12-month period before the initial screening visit. One week after screening, all patients entered a 6-week run-in period during which they received triple therapy with tiotropium (18 μg once daily) via HandiHaler® (a dry powder inhaler) and salmeterol (50 μg twice daily; 2 actuations of 25 μg) and fluticasone propionate (500 μg twice daily; 2 actuations of 250 μg) via a metered-dose inhaler. Patients were then randomized in a 1:1 ratio to either continue the same triple therapy as received in the run-in period (ICS continuation group) or continue tiotropium and salmeterol with a stepwise reduction of fluticasone for 12 weeks followed by stable therapy for 40 weeks (ICS withdrawal group) during the 52-week study period (Figure 1).[9,11]

The study was carried out in accordance with the Declaration of Helsinki, local regulations, and the International Conference on Harmonisation Harmonised Tripartite Guidelines for Good Clinical Practice. Local institutional review boards, independent ethics committees, and competent authorities approved the protocol (Supplementary Table 1). All patients provided written, informed consent.
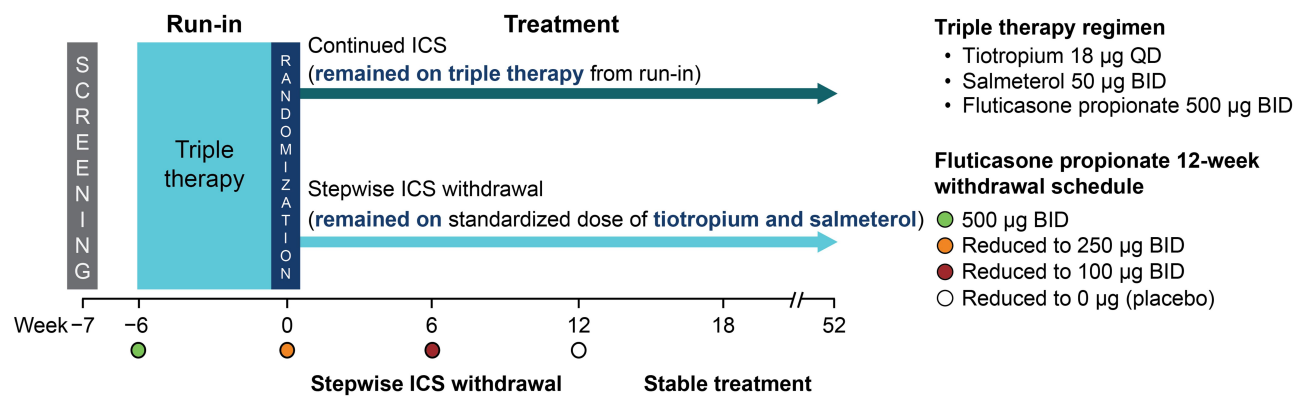
Figure 1 WISDOM trial design.
Abbreviations: BID, twice daily; ICS, inhaled corticosteroids; QD, once daily.

Patients

Patients who were aged ≥40 years, were diagnosed with severe or very severe COPD (defined by forced expiratory volume in 1 second [FEV_1] <50% of the predicted volume and FEV_1 <70% of forced vital capacity after bronchodilation), had a history of ≥1 documented exacerbation in the 12 months before screening, and were either former or current (≥10 pack-years) smokers were included. Patients with a clinical diagnosis of asthma were excluded. The full inclusion and exclusion criteria have been reported previously.[11]

In these subgroup analyses, patients taking triple therapy (LABA, LAMA, and ICS; with or without other pulmonary medication such as oral β-agonists, oral glucocorticoids, leukotriene receptor antagonists, mucolytic agents, oxygen, and xanthines) since the time of screening and irrespective of baseline blood eosinophil counts were included. Use of xanthines and mucolytic agents, but not maintenance oral glucocorticoid treatment, was allowed throughout the trial. All patients were provided with open-label salbutamol (albuterol) for use as needed. At the investigator's discretion, randomized treatment could be discontinued, and open-label fluticasone could be initiated for the remainder of the trial.[9,11]

Endpoints and Assessments

The primary endpoint was time to the first moderate or severe, on-treatment COPD exacerbation during the 52-week randomized treatment period. Moderate or severe COPD exacerbation was defined as worsening or onset of ≥2 lower respiratory symptoms related to COPD, such as shortness of breath, cough, wheezing, chest tightness,

and sputum production and purulence, with ≥1 symptom lasting for ≥3 days and requiring a change in treatment. Moderate exacerbations were treated with antibiotics and/or systemic steroids, whereas severe exacerbations required hospitalization or treatment in an urgent care unit. Exacerbations reported after discontinuation of randomized treatment were excluded in the primary endpoint analyses. The primary endpoint was additionally analyzed for the following subgroups: geographical region, age group, sex, smoking status, baseline values of body mass index (BMI), and 6-minute walk test. Secondary endpoints included the number of moderate or severe, on-treatment COPD exacerbations per year during the study period, and were additionally analyzed for subgroups with a history of ≥2 exacerbations and blood eosinophil counts above various thresholds (≥100 cells/µL to ≥400 cells/µL).

Statistical Analyses

Time to first exacerbation was analyzed using a Cox proportional hazards model with adjustment for baseline FEV_1. Annualized rates of exacerbations were obtained from a negative binomial regression adjusted for time at risk and compared by rate ratio (RR; ICS withdrawal versus continuation). This subgroup analysis was not formally powered.

Results
Study Population and Baseline Characteristics

Of the 2485 patients in the overall trial population who received tiotropium (18 µg once daily) and salmeterol+fluticasone propionate (50+500 µg twice daily) during the 6-

week run-in period, 970 (39.0%) were taking triple therapy at screening before the run-in period. These patients were roughly equally randomized to the ICS continuation (n=479) and ICS withdrawal (n=491) groups.

Baseline characteristics were generally similar between patients taking triple therapy at screening and the overall trial population (Table 1); most of the patients in both groups were male (79.1% and 82.5%, respectively), with a mean±standard deviation (SD) age of 64.3±8.1 and 63.8 ±8.5 years, mean±SD postbronchodilator $FEV_1\%$ predicted of 33.0±9.0 and 32.8±9.1, and mean±SD duration of COPD of 8.4±6.5 years and 7.9±6.2 years, respectively; in addition, most patients had GOLD grade 3 (63.0% and 61.2%, respectively) or 4 (36.3% and 38.1%, respectively) severity. Further, history of moderate-to-severe (mean±SD, 1.8±1.3 and 1.7±1.3, respectively) and severe (0.4±0.8 and 0.4±0.8, respectively) exacerbations in the previous year was comparable. Finally, fewer patients taking triple therapy at screening than those in the overall trial population had a baseline blood eosinophil count of ≥300 cells/μL (15.9% versus 19.7%, respectively).

COPD Exacerbations

The risk of moderate or severe COPD exacerbations was higher in the triple therapy group than in the overall population (Table 2), but the risk introduced by ICS withdrawal was not increased in patients receiving triple therapy at screening (hazard ratio [HR], 1.05; 95% confidence interval [CI]: 0.89, 1.25; Table 2, Figure 2A) compared with that in the overall trial population (HR [95% CI]: 1.06 [0.94, 1.19]; Table 2, Figure 2B). Although the annual exacerbation rate was higher among patients taking triple therapy at screening than in the overall trial population, the RR for exacerbations was not increased following ICS withdrawal (RR [95% CI]: 1.02 [0.86, 1.20] versus 1.05 [0.93, 1.18], respectively; Table 2). The risk of severe, on-treatment COPD exacerbations was increased in the subgroup of patients taking triple therapy at screening. However, the HRs and RRs for ICS withdrawal versus ICS continuation were similar for patients taking triple therapy at screening versus the overall trial population (HR [95% CI]: 1.23 [0.92, 1.64] versus 1.20 [0.98, 1.48]; RR [95% CI]: 1.12 [0.82, 1.53] versus 1.15 [0.92, 1.45], respectively) (Table 2, Figure 3A and B). Further, no obvious increase in the frequency of exacerbations following ICS withdrawal was observed within different time periods in the triple therapy group and the overall population (Supplementary Figure 1).

Across the different subgroups (geographical region, age group, sex, smoking status, baseline BMI, and baseline 6-minute walk test), HRs for time to first moderate or severe exacerbations were similar in the subgroup of patients taking triple therapy at screening (Figure 4A) and in the overall trial population (Figure 4B), suggesting the robustness of the results.

In patients taking triple therapy at screening with a history of ≥2 exacerbations, exacerbation risk (HR [95% CI]) increased nominally (Figure 5) with blood eosinophil count from 1.07 [0.81–1.41] (≥100 cells/μL) to 1.45 [0.58–3.60] (≥400 cells/μL).

Discussion

Results from these post hoc analyses of the WISDOM trial data show that patients taking triple therapy—a LAMA, a LABA, and an ICS—at screening and during the run-in period had a higher risk of moderate or severe COPD exacerbations than those in the overall trial population. This suggests that history of exacerbations may have partly influenced clinicians to prescribe triple therapy in these patients to a greater degree. Importantly, the risk of COPD exacerbations associated with stepwise ICS withdrawal over a 12-week period was not increased in this subgroup of patients receiving triple therapy at screening. These results are consistent with the main findings from the WISDOM trial, which showed that the risk of moderate or severe exacerbations was similar in patients receiving triple therapy who underwent ICS withdrawal and those who continued triple therapy.[9]

The main findings from the WISDOM trial[9] and these post hoc analyses are consistent with those from other ICS withdrawal studies. In the SUNSET trial, where subjects on triple therapy without clear indication for ICS therapy (≤1 moderate or severe exacerbation in the prior year) were abruptly discontinued from ICS by switching from open triple therapy to a LAMA+LABA combination, there was only a small decrease in lung function and no impact on COPD exacerbations in the overall treatment groups.[10] Similarly, a subgroup analysis of the real-life, Outpatient Care With Long-Acting Bronchodilators: COPD Registry in Germany (DACCORD) study revealed that ICS withdrawal during a 2-year follow-up period did not increase the risk of exacerbations in patients with COPD who continued treatment with a LAMA or a LABA.[12]

On the other hand, conflicting results on the impact of ICS withdrawal have also been reported in some studies. In the single-center, COPD Study of the Department of

Table 1 Disease and Patient Characteristics at Screening (Patients Taking Triple Therapy at Screening[a] and the Overall Trial Population)

	Triple Therapy at Screening			Overall Trial Population		
	ICS Continuation, n=479	ICS Withdrawal, n=491	Total, n=970	ICS Continuation, n=1243	ICS Withdrawal, n=1242	Total, n=2485
Age, years, mean±SD	64.5±8.0	64.1±8.2	64.3±8.1	63.6±8.6	64.0±8.4	63.8±8.5
Age groups, n (%)						
<55 years	55 (11.5)	62 (12.6)	117 (12.1)	194 (15.6)	164 (13.2)	358 (14.4)
≥55 to <65 years	185 (38.6)	192 (39.1)	377 (38.9)	473 (38.1)	490 (39.5)	963 (38.8)
≥65 to <75 years	179 (37.4)	186 (37.9)	365 (37.6)	437 (35.2)	455 (36.6)	892 (35.9)
≥75 years	60 (12.5)	51 (10.4)	111 (11.4)	139 (11.2)	133 (10.7)	272 (10.9)
Male, n (%)	376 (78.5)	391 (79.6)	767 (79.1)	1013 (81.5)	1036 (83.4)	2049 (82.5)
Body mass index, kg/m², mean±SD	25.7±5.0	25.6±5.1	25.7±5.0	25.3±5.1	25.2±5.1	25.2±5.1
Body mass index groups, n (%)						
<20 kg/m²	59 (12.3)	61 (12.4)	120 (12.4)	186 (15.0)	183 (14.7)	369 (14.8)
≥20 to <25 kg/m²	162 (33.8)	172 (35.0)	334 (34.4)	453 (36.4)	470 (37.8)	923 (37.1)
≥25 to <30 kg/m²	175 (36.5)	175 (35.6)	350 (36.1)	401 (32.3)	388 (31.2)	789 (31.8)
≥30 kg/m²	83 (17.3)	83 (16.9)	166 (17.1)	203 (16.3)	201 (16.2)	404 (16.3)
Current smoker, n (%)	145 (30.3)	141 (28.7)	286 (29.5)	432 (34.8)	399 (32.1)	831 (33.4)
Duration of COPD, years, mean±SD	8.3±6.4	8.5±6.6	8.4±6.5	7.8±6.0	8.0±6.5	7.9±6.2
6-minute walk test						
Patients with available data, n	472	486	958	1234	1233	2467
6-minute walk test, m, mean±SD	351.4±114.7	343.3±128.4	347.3±121.8	358.0±116.9	353.5±123.3	355.7±120.2
6-minute walk test groups, n (%)						
<350 m	231 (48.2)	228 (46.4)	459 (47.3)	574 (46.2)	562 (45.2)	1136 (45.7)
≥350 m	241 (50.3)	258 (52.5)	499 (51.4)	660 (53.1)	671 (54.0)	1331 (53.6)
Missing	7 (1.5)	5 (1.0)	12 (1.2)	9 (0.7)	9 (0.7)	18 (0.7)
Baseline lung function						
Patients with available data, n	479	489	968	1240	1240	2480
Postbronchodilator FEV$_1$ % predicted, %, mean±SD	33.0±8.7	33.0±9.4	33.0±9.0	32.7±8.9	32.8±9.2	32.8±9.1
Postbronchodilator FVC, L, mean±SD	2.5±0.8	2.5±0.7	2.5±0.7	2.4±0.7	2.4±0.7	2.4±0.7
Postbronchodilator FEV$_1$/FVC, %, mean±SD	41.4±12.4	41.6±11.7	41.5±12.1	42.4±11.9	42.0±11.4	42.2±11.6
Diagnosed with chronic bronchitis, n (%)	318 (66.4)	320 (65.2)	638 (65.8)	772 (62.1)	810 (65.2)	1582 (63.7)
Diagnosed with emphysema, n (%)	274 (57.2)	280 (57.0)	554 (57.1)	723 (58.2)	757 (61.0)	1480 (59.6)
GOLD disease severity, n (%)						
≥80% (GOLD 1)	0 (0.0)	1 (0.2)	1 (0.1)	1 (0.1)	2 (0.2)	3 (0.1)
50% to <80% (GOLD 2)	3 (0.6)	1 (0.2)	4 (0.4)	6 (0.5)	3 (0.2)	9 (0.4)
30% to <50% (GOLD 3)	300 (62.6)	311 (63.3)	611 (63.0)	760 (61.1)	761 (61.3)	1521 (61.2)
<30% (GOLD 4)	176 (36.7)	176 (35.8)	352 (36.3)	473 (38.1)	474 (38.2)	947 (38.1)
Missing	0 (0.0)	2 (0.4)	2 (0.2)	3 (0.2)	2 (0.2)	5 (0.2)
Blood eosinophil count, n (%)						
<300 cells/μL	383 (80.0)	399 (81.3)	782 (80.6)	959 (77.2)	971 (78.2)	1930 (77.7)
≥300 cells/μL	78 (16.3)	76 (15.5)	154 (15.9)	252 (20.3)	238 (19.2)	490 (19.7)
Missing	18 (3.8)	16 (3.3)	34 (3.5)	32 (2.6)	33 (2.7)	65 (2.6)

(Continued)

Table 1 (Continued).

	Triple Therapy at Screening			Overall Trial Population		
	ICS Continuation, n=479	ICS Withdrawal, n=491	Total, n=970	ICS Continuation, n=1243	ICS Withdrawal, n=1242	Total, n=2485
Exacerbation history						
Patients with exacerbations, n	479	490	969	1243	1241	2484
Moderate-to-severe exacerbations in the previous year, mean±SD	1.9±1.4	1.7±1.2	1.8±1.3	1.7±1.3	1.7±1.3	1.7±1.3
Severe exacerbations in the previous year, mean±SD	0.5±1.0	0.3±0.7	0.4±0.8	0.4±0.8	0.4±0.7	0.4±0.8

Note: [a]Before the run-in period where all patients took triple therapy.
Abbreviations: COPD, chronic obstructive pulmonary disease; FEV$_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroids; SD, standard deviation.

Table 2 Time to First COPD Exacerbation and Number of COPD Exacerbations (in Patients Taking Triple Therapy at Screening[a] and in the Overall Trial Population)

	Triple Therapy at Screening		Overall Trial Population	
	ICS Continuation, n=479	ICS Withdrawal, n=491	ICS Continuation, n=1243	ICS Withdrawal, n=1242
Time to first moderate or severe on-treatment COPD exacerbation				
Patients with exacerbations, n (%)	259 (54.1)	280 (57.0)	550 (44.2)	580 (46.7)
Hazard ratio, ICS withdrawal versus ICS continuation (95% CI)[b]	1.05 (0.89, 1.25)		1.06 (0.94, 1.19)	
Number of moderate or severe on-treatment COPD exacerbations				
Events, n[c]	495	494	953	972
Mean number of events per patient-year (95% CI)[d]	1.29 (1.14, 1.45)	1.31 (1.16, 1.48)	0.91 (0.83, 0.99)	0.95 (0.87, 1.04)
Rate ratio, ICS withdrawal versus ICS continuation (95% CI)[d]	1.02 (0.86, 1.20)		1.05 (0.93, 1.18)	
Time to first severe on-treatment COPD exacerbation				
Patients with exacerbations, n (%)	85 (17.7)	98 (20.0)	167 (13.4)	189 (15.2)
Hazard ratio, ICS withdrawal versus ICS continuation (95% CI)[b]	1.23 (0.92, 1.64)		1.20 (0.98, 1.48)	
Number of severe on-treatment COPD exacerbations				
Events, n[c]	107	118	205	230
Mean number of events per patient-year (95% CI)[d]	0.28 (0.22, 0.35)	0.31 (0.25, 0.39)	0.20 (0.17, 0.23)	0.23 (0.19, 0.27)
Rate ratio, ICS withdrawal versus ICS continuation (95% CI)[d]	1.12 (0.82, 1.53)		1.15 (0.92, 1.45)	

Notes: [a]Before the run-in period where all patients took triple therapy; [b]Hazard ratio from Cox proportional hazards model with terms for baseline FEV$_1$; [c]Total number of events with onset between the day of the first randomized dose and the day after the last randomized dose, both inclusive; [d]Negative binomial regression adjusted for time at risk.
Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEV$_1$, forced expiratory volume in 1 second; ICS, inhaled corticosteroids.
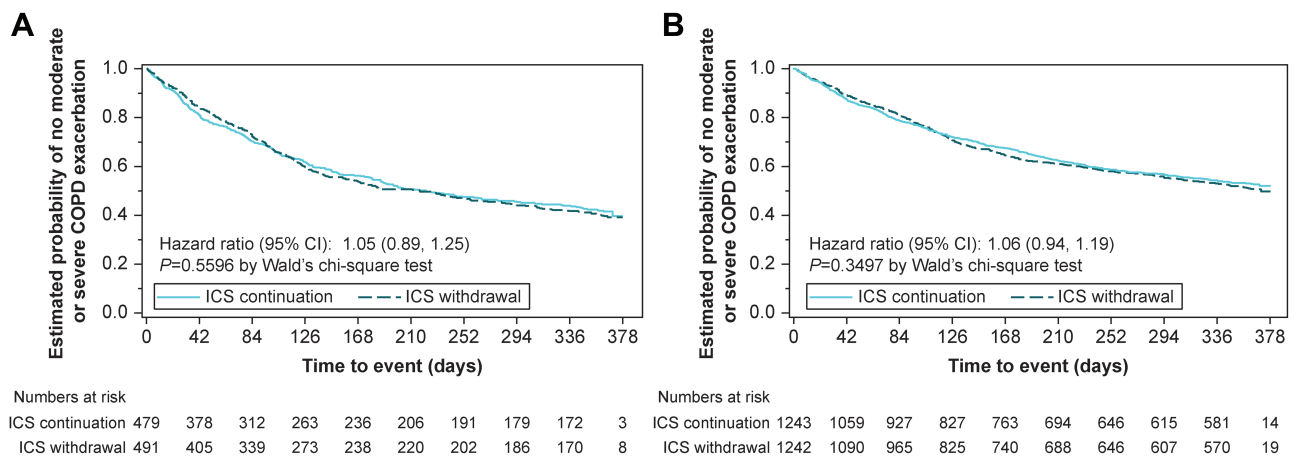
A

B

Figure 2 Kaplan–Meier estimates of the probability of no moderate or severe on-treatment COPD exacerbation in (**A**) patients taking triple therapy at screening and (**B**) overall trial population.
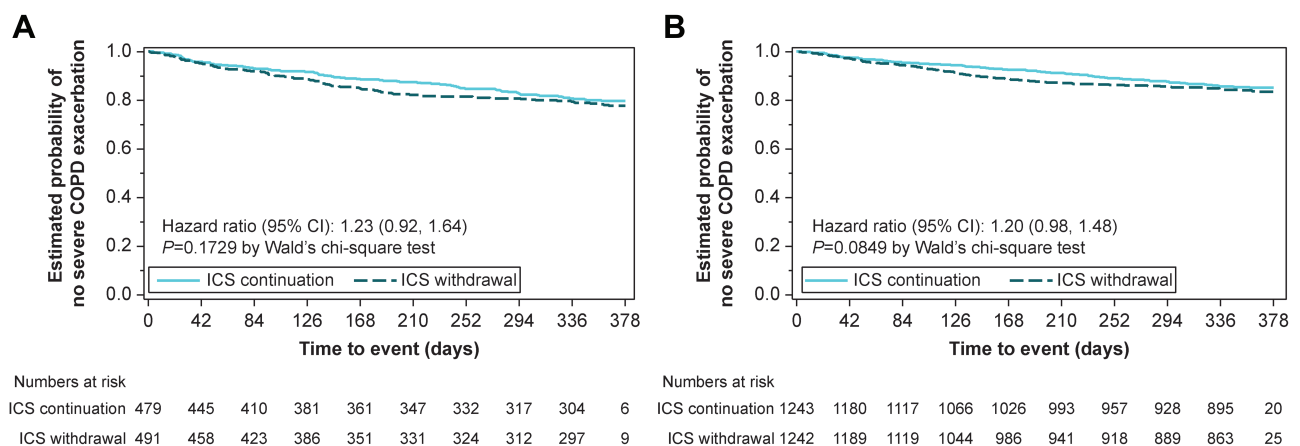**Abbreviations:** CI, confidence interval; COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroids.

A

B

Figure 3 Kaplan–Meier estimates of the probability of no severe on-treatment COPD exacerbation in (**A**) patients taking triple therapy at screening and (**B**) overall trial population.
Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroids.

Pulmonary Medicine, Enschede (COPE) study, ICS withdrawal was associated with rapid recurrent exacerbations.[13] The proportion of patients who developed ≥1 exacerbation was higher in the placebo group (57%) than in the ICS group (47.2%). Moreover, patients who discontinued ICS after 4 months of ICS treatment (placebo group) experienced rapid recurrent exacerbations compared with those who continued ICS (21.5% versus 4.9%, respectively). Health-related quality of life (QoL) also significantly deteriorated in patients who discontinued ICS.[13] Similarly, in the COPD and Seretide: a Multi-Center Intervention and Characterization (COSMIC) study, the rate of mild exacerbations significantly increased, lung function significantly decreased, and dyspnea worsened a year after ICS withdrawal in patients originally treated with LABA+ICS (salmeterol+fluticasone).[14] Finally,

in a 5-year observational follow-up of the Groningen and Leiden Universities Corticosteroids in Obstructive Lung Disease (GLUCOLD) study, ICS withdrawal in patients with moderate-to-severe COPD was associated with worsened airway hyperresponsiveness and QoL and deterioration of lung function.[15]

In light of the conflicting results, a meta-analysis of 4 randomized controlled trials, including the COPE and COSMIC studies, was performed.[16] No significant difference was observed between the ICS withdrawal and ICS continuation groups. Although the ICS withdrawal group had a 1.11-fold higher risk of exacerbations, the definition of exacerbation was not consistent across 3 of the 4 trials; therefore, the results should be interpreted with caution.[16] In another meta-analysis of 10 randomized controlled
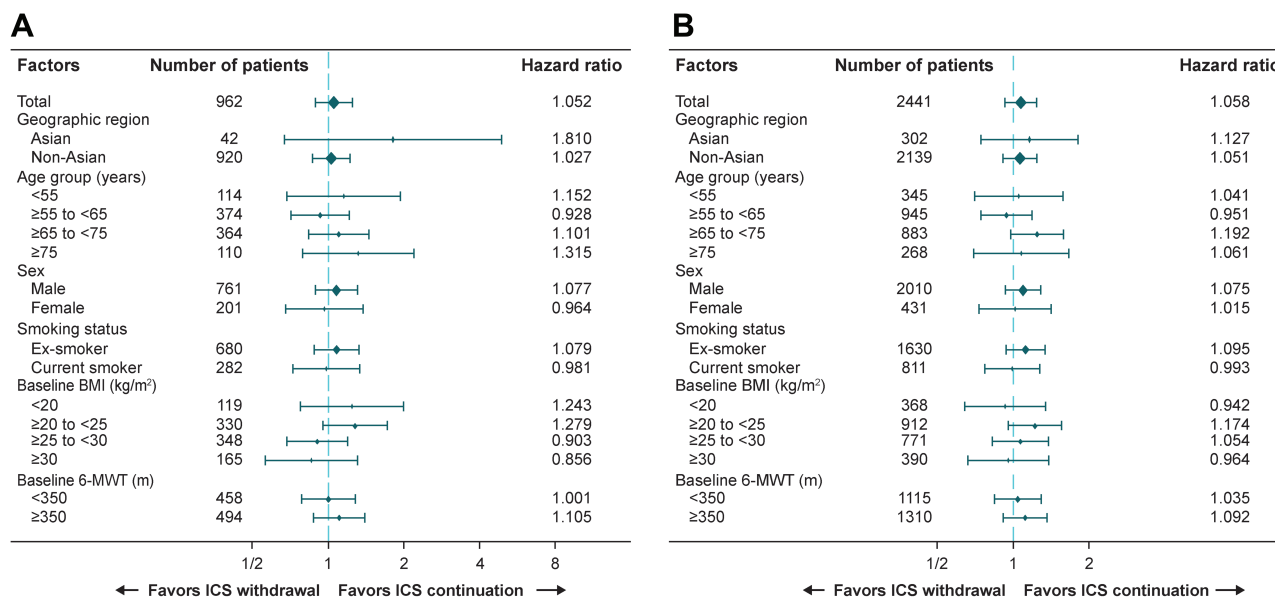
A

Factors	Number of patients		Hazard ratio
Total	962		1.052
Geographic region			
Asian	42		1.810
Non-Asian	920		1.027
Age group (years)			
<55	114		1.152
≥55 to <65	374		0.928
≥65 to <75	364		1.101
≥75	110		1.315
Sex			
Male	761		1.077
Female	201		0.964
Smoking status			
Ex-smoker	680		1.079
Current smoker	282		0.981
Baseline BMI (kg/m²)			
<20	119		1.243
≥20 to <25	330		1.279
≥25 to <30	348		0.903
≥30	165		0.856
Baseline 6-MWT (m)			
<350	458		1.001
≥350	494		1.105

1/2   1   2   4   8

← Favors ICS withdrawal   Favors ICS continuation →

B

Factors	Number of patients		Hazard ratio
Total	2441		1.058
Geographic region			
Asian	302		1.127
Non-Asian	2139		1.051
Age group (years)			
<55	345		1.041
≥55 to <65	945		0.951
≥65 to <75	883		1.192
≥75	268		1.061
Sex			
Male	2010		1.075
Female	431		1.015
Smoking status			
Ex-smoker	1630		1.095
Current smoker	811		0.993
Baseline BMI (kg/m²)			
<20	368		0.942
≥20 to <25	912		1.174
≥25 to <30	771		1.054
≥30	390		0.964
Baseline 6-MWT (m)			
<350	1115		1.035
≥350	1310		1.092

1/2   1   2

← Favors ICS withdrawal   Favors ICS continuation →

Figure 4 Forest plot of time to first moderate or severe COPD exacerbation in (**A**) patients taking triple therapy at screening and (**B**) overall trial population. **Abbreviations:** 6-MWT, 6-minute walk test; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroids.

Dark bars = ICS continuation   Light bars = ICS withdrawal

Triple Overall: *1.1× *1.1× | *1.0× *1.1× | *1.1× *1.2× | *1.1× *1.2× | *1.2× *1.2× | *1.4× *1.3× | *1.4× *1.6×

≥2 exc + eos ≥100: 68.4, 72.3, 54.1, 57.8
≥2 exc + eos ≥150: 71.2, 72.8, 54.7, 58.3
≥2 exc + eos ≥200: 65.8, 73.9, 50.6, 58.4
≥2 exc + eos ≥250: 67.9, 76, 51.2, 59.8
≥2 exc + eos ≥300: 63.9, 78.8, 48.4, 59.1
≥2 exc + eos ≥350: 57.9, 80, 44.3, 58.8
≥2 exc + eos ≥400: 58.3, 82.4, 38.3, 61.5

Subgroups of patients with a history of ≥2 exacerbations and blood eosinophil counts (cells/μL) at baseline
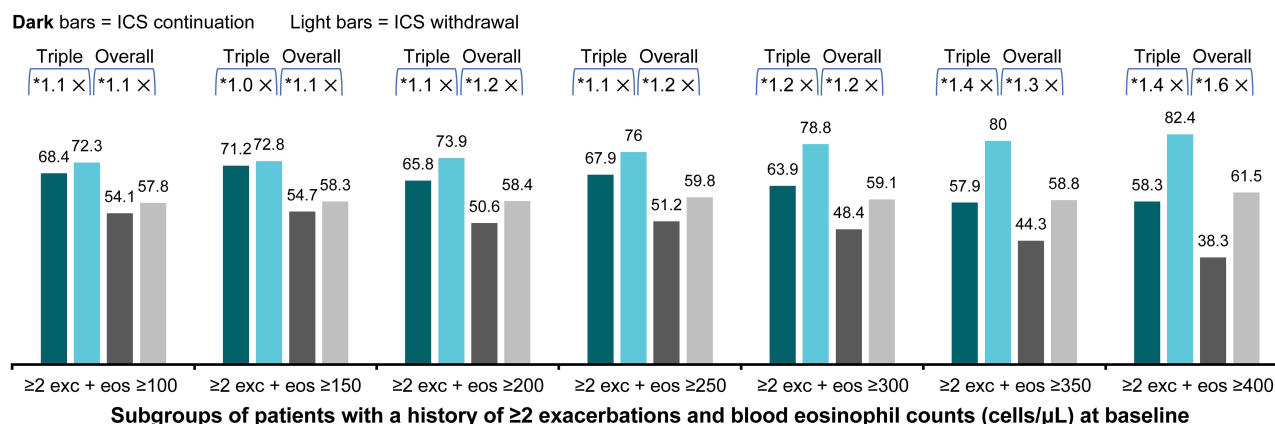
Figure 5 Percentage of patients with at least one moderate or severe COPD exacerbation (in patients taking triple therapy at screening[a] and in the overall trial population). **Notes:** [a]Before the run-in period where all patients took triple therapy; The numbers above the bars indicate percentages of patients with at least one exacerbation during the study; *Indicates the ratio of the percentages of patients with at least one exacerbation within the ICS continuation and ICS withdrawal groups. **Abbreviations:** COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 second; eos, blood eosinophil counts; exc, exacerbations; ICS, inhaled corticosteroids.

trials and real-world studies, ICS withdrawal did not significantly increase the rate of exacerbations; however, a significant decrease in lung function and impaired QoL was observed.[17] Collectively, these results imply that, although ICS withdrawal may not negatively impact all patients, understanding which patients are likely to benefit from ICS and, therefore, which patients should continue taking triple therapy is important.

The results of the present analyses confirmed that frequent exacerbators (≥2 exacerbations in the previous year) with high blood eosinophil counts could benefit from continuing ICS treatment, as the risk of exacerbation increased nominally with increasing blood eosinophil levels. However, there was high variability due to small sample sizes in this subgroup analysis. Our results are consistent with those of previous post hoc analyses of the WISDOM trial which showed that the rate of moderate or severe exacerbations increased after ICS withdrawal in patients with blood eosinophil counts of ≥2% (of the total white blood cell count) or ≥300 cells/μL, suggesting that these patients benefited from ICS-based therapy.[18,19] In the SUNSET study, only patients with blood eosinophil counts

≥300 cells/µL had an increased risk of exacerbations and greater decline in lung function compared with patients with counts <300 cells/µL.[10]

Based on cumulative results from ICS withdrawal studies, use of peripheral blood eosinophil counts as a biomarker to guide ICS-based therapy is recommended in GOLD for reducing COPD exacerbations.[1] Clinicians should consider the long-term risks as well as benefits associated with ICS before prescribing an ICS.[20] As mentioned, escalation to triple therapy is recommended if patients experience exacerbations despite optimal LAMA+LABA therapy and have blood eosinophil counts of ≥100 cells/µL.[1] Furthermore, patients with blood eosinophil counts of ≥300 cells/µL have a greater likelihood of experiencing exacerbations following ICS withdrawal; therefore, they should be monitored closely if de-escalation is attempted. Overall, findings from the present analyses suggest that physicians choosing to prescribe triple therapy are doing so, in part, because of the increased exacerbation risk. Additionally, even though many patients would be categorized as GOLD B, clinicians may be better at identifying an appropriate therapy for patients with COPD.

A limitation of these subgroup analyses was that the number of patients with frequent exacerbations and high eosinophil counts was low. Therefore, these analyses were exploratory in nature, and the results need to be confirmed in subsequent robust studies.

Conclusion

The risk of first moderate or severe COPD exacerbation was increased in patients taking triple therapy at screening versus the overall WISDOM trial population. Furthermore, ICS withdrawal did not increase the risk of exacerbations in patients taking triple therapy at screening compared with the overall trial population. Patients with a history of frequent exacerbations (≥2 exacerbations in the previous year) and higher blood eosinophil counts could benefit from ICS-based therapy. The findings suggest that stepwise ICS withdrawal could be considered in particular in patients with lower blood eosinophil counts and without a history of frequent exacerbations.

Abbreviations

BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HR, hazard ratio; FEV$_1$, forced expiratory volume in 1 second; ICS, inhaled corticosteroids; LABA, long-acting β$_2$-agonist; LAMA, long-acting muscarinic antagonist; QoL, quality of life; RR, rate ratio; SD, standard deviation.

Data Sharing Statement

Results of the WISDOM trial and subgroup analysis of patients with blood eosinophil count of ≥300 cells/µL and history of ≥2 exacerbations have been published previously: https://www.ncbi.nlm.nih.gov/pubmed/25196117 and https://www.ncbi.nlm.nih.gov/pubmed/27066739. Individual patient data are not publicly accessible but are available on request via the transparency platform https://clinicalstudydatarequest.com/Study-Sponsors.aspx.

Ethics Approval and Informed Consent

The study was carried out in accordance with the Declaration of Helsinki, local regulations, and the ICH Harmonised Tripartite Guideline for Good Clinical Practice. Local institutional review boards, independent ethics committees, and competent authorities approved the protocol. All patients provided written, informed consent.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Disclosure

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