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Withdrawal of Inhaled Glucocorticoids and Exacerbations of COPD

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ABSTRACT

BACKGROUND

Treatment with inhaled glucocorticoids in combination with long-acting bronchodilators is recommended in patients with frequent exacerbations of severe chronic obstructive pulmonary disease (COPD). However, the benefit of inhaled glucocorticoids in addition to two long-acting bronchodilators has not been fully explored.

METHODS

In this 12-month, double-blind, parallel-group study, 2485 patients with a history of exacerbation of COPD received triple therapy consisting of tiotropium (at a dose of 18 μg once daily), salmeterol (50 μg twice daily), and the inhaled glucocorticoid fluticasone propionate (500 μg twice daily) during a 6-week run-in period. Patients were then randomly assigned to continued triple therapy or withdrawal of fluticasone in three steps over a 12-week period. The primary end point was the time to the first moderate or severe COPD exacerbation. Spirometric findings, health status, and dyspnea were also monitored.

RESULTS

As compared with continued glucocorticoid use, glucocorticoid withdrawal met the prespecified noninferiority criterion of 1.20 for the upper limit of the 95% confidence interval (CI) with respect to the first moderate or severe COPD exacerbation (hazard ratio, 1.06; 95% CI, 0.94 to 1.19). At week 18, when glucocorticoid withdrawal was complete, the adjusted mean reduction from baseline in the trough forced expiratory volume in 1 second was 38 ml greater in the glucocorticoid-withdrawal group than in the glucocorticoid-continuation group ($P<0.001$); a similar between-group difference (43 ml) was seen at week 52 ($P=0.001$). No change in dyspnea and minor changes in health status occurred in the glucocorticoid-withdrawal group.

CONCLUSIONS

In patients with severe COPD receiving tiotropium plus salmeterol, the risk of moderate or severe exacerbations was similar among those who discontinued inhaled glucocorticoids and those who continued glucocorticoid therapy. However, there was a greater decrease in lung function during the final step of glucocorticoid withdrawal. (Funded by Boehringer Ingelheim Pharma; WISDOM ClinicalTrials.gov number, NCT00975195.)

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*Investigators in the Withdrawal of Inhaled Steroids during Optimized Bronchodilator Management (WISDOM) study are listed in the Supplementary Appendix, available at NEJM.org.

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Exacerbations of chronic obstructive pulmonary disease (COPD) are symptomatically defined, acute events that lead to a change in treatment[1,2] and are associated with an accelerated decline in lung function and health status.[3] Treatment with inhaled glucocorticoids reduces the exacerbation rate, especially when the drugs are used in combination with a long-acting β-agonist (LABA).[4,5] Consequently, combination therapy with an inhaled glucocorticoid and a LABA is recommended in patients with severe COPD or a history of frequent exacerbations.[2] Long-acting muscarinic antagonists (LAMAs) have also been shown to prevent exacerbations.[6-8] However, in patients with severe or very severe COPD and a history of exacerbations, the benefit of inhaled glucocorticoids in a regimen that includes these two classes of long-acting bronchodilators has not yet been determined in an adequately powered study.

We hypothesized that with a controlled, stepwise withdrawal of inhaled glucocorticoids, the risk of exacerbation would be similar to that with continued use of inhaled glucocorticoids in patients with severe or very severe COPD who were receiving a combination of a LAMA (tiotropium) and a LABA (salmeterol). To test this hypothesis, we conducted the Withdrawal of Inhaled Steroids during Optimized Bronchodilator Management (WISDOM) trial, which was designed to determine whether patients with COPD who were receiving both LAMA and LABA therapy with inhaled glucocorticoids would have similar outcomes regardless of whether the glucocorticoids were withdrawn or continued.

Methods

Study Design

From February 2009 through July 2013, we performed this multinational, randomized, double-blind, parallel-group, active-control study. All patients entered a 6-week run-in period during which they received 18 μg of tiotropium once daily (delivered by a HandiHaler), 50 μg of salmeterol xinafoate twice daily (two actuations of 25 μg; a dose of 21 μg is designated on the U.S. product label), and 500 μg of fluticasone propionate (an inhaled glucocorticoid) twice daily (two actuations of 250 μg [U.S. designated dose, 230 μg] delivered by a metered-dose inhaler). In this study, we refer to the European Union designation of doses for consistency.

During the double-blind phase of the trial, patients underwent randomization in a 1:1 ratio to the two study groups. The first group continued to receive tiotropium, salmeterol, and fluticasone at the same doses as those used during the run-in period for the duration of the 52-week study period. The second group continued to receive tiotropium and salmeterol over the 52-week period but with a stepwise reduction in the fluticasone dose every 6 weeks, from a total daily dose of 1000 μg to 500 μg, then to 200 μg, and finally to 0 μg (placebo)[9] (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Patients who prematurely discontinued therapy were followed for vital status from the time of discontinuation until the completion of the trial at 52 weeks.

Patients

We recruited patients who were at least 40 years of age and who were either current smokers (≥10 pack-years) or former smokers and had received a diagnosis of severe or very severe COPD, which was defined as a forced expiratory volume in 1 second (FEV_1) that was less than 50% of the predicted volume and less than 70% of the forced vital capacity after bronchodilation and a history of at least one documented exacerbation in the 12 months before screening. Full inclusion and exclusion criteria have been reported previously[9] and are provided in the trial protocol, which is available at NEJM.org. All patients provided written informed consent.

The 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 (also known as 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. Any exacerbations that were reported after the discontinuation of randomized treatment were not included in the primary end point. Included in a prespecified sensitivity analysis were exacerbations that were reported in patients who were receiving open-label fluticasone therapy and in those who had discontinued treatment.

End Points and Assessments

The primary end point was the time to the first moderate or severe COPD exacerbation during the 12-month study period. We used a standard-

ized, structured questionnaire to collect data regarding exacerbations, with documentation at each study visit. In addition, we provided patients with a simple diary, to be completed on a daily basis, for noting changes in symptoms and the use of medications between visits. A moderate exacerbation was defined as an increase in lower respiratory tract symptoms related to COPD or the new onset of two or more such symptoms, with at least one symptom lasting 3 or more days and for which the treating physician prescribed antibiotics, systemic glucocorticoids, or both. A severe exacerbation was defined as an exacerbation requiring hospitalization in an urgent care unit. The start date of an exacerbation was defined as the onset date of the first recorded COPD symptom.

Secondary end points included the time to the first severe COPD exacerbation, the number of moderate or severe COPD exacerbations, the change from baseline in lung function (including the trough FEV_1, forced vital capacity, and peak expiratory flow rate), health status, and dyspnea. To assess health status, we used the total score on the St. George's Respiratory Questionnaire (SGRQ), on a scale of 0 to 100, with higher scores indicating worse function and a minimum clinically important difference of 4 points.[10] To assess dyspnea, we used the modified Medical Research Council (mMRC) scale of 0 to 4, with higher scores indicating more severe dyspnea; the absence of breathlessness was given a score of –1. No minimum clinically important difference has been identified.[11] All secondary end points were assessed over the 12-month study period.

We performed all spirometric measurements according to the recommendations of the American Thoracic Society and the European Respiratory Society[12] at baseline and at weeks 6, 12, 18, and 52. We used values after bronchodilation in qualifying tests of pulmonary function. Before performing spirometric testing, we obtained scores on the SGRQ at baseline and at weeks 27 and 52 and obtained scores on the mMRC scale at baseline and at weeks 18 and 52. (Additional details regarding the end points are provided in the protocol and in Table S1 in the Supplementary Appendix.)

SAFETY

We performed physical examinations at the time of screening and at week 52 and measured and recorded vital signs at baseline and at weeks 6, 12, 18, and 52. Chest radiography was requested when pneumonia was suspected during the trial. Adverse events and serious adverse events, regardless of causality, were recorded throughout the study, and results are reported descriptively. If patients did not spontaneously report adverse events, they were asked open-ended questions, such as "How have you felt since the last visit?"

STUDY OVERSIGHT

The study protocol was approved by the ethics review board at each institution. The first draft of the manuscript and subsequent revisions were written by the academic authors, and all the authors worked collaboratively to prepare the final content; all the authors made the decision to submit the manuscript for publication. Editorial assistance was provided by a medical writer employed by a company that was paid by the study sponsor, Boehringer Ingelheim Pharma. Statistical analyses were performed by the sponsor. All study drugs were supplied by the sponsor. All the authors vouch for the accuracy and completeness of the data and the fidelity of the study to the protocol.

STATISTICAL ANALYSIS

We estimated that 2456 patients would need to undergo randomization at the 200 study centers to ensure a minimum of 2234 patients who could be evaluated in order to provide the study with a power of 90% to determine the noninferiority of the hazard ratio for exacerbation among patients in the glucocorticoid-withdrawal group, as compared with the glucocorticoid-continuation group, with a one-sided alpha level of 0.025 and an expected dropout rate of 15% per year. The assumed median time to the first primary event was 9 months. The prespecified noninferiority margin of 1.20 was defined as the upper limit of the 95% confidence interval for the hazard ratio for the first moderate or severe exacerbation in the glucocorticoid-withdrawal group, as compared with the glucocorticoid-continuation group. Both efficacy and safety were evaluated in the modified intention-to-treat population, which was defined as all patients who received at least one dose of a study drug.

We used a Cox proportional-hazards regression model with adjustment for the baseline FEV_1 in the primary analysis, in the prespecified sensitivity analysis, and in the analysis of the time to the first severe COPD exacerbation. In the sensitivity analysis, we included exacerbations in pa-

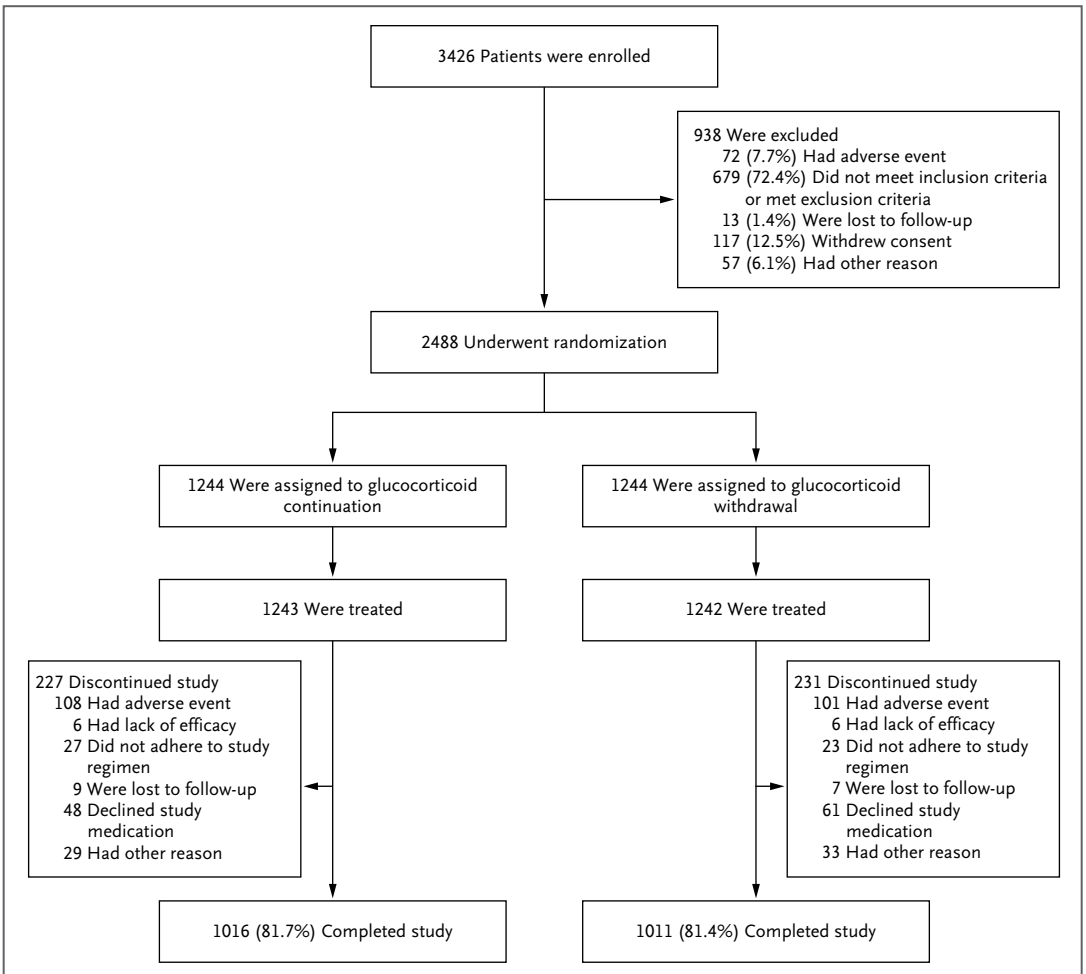

Figure 1. Enrollment and Outcomes.

tients who were switched to open-label fluticasone. In a post hoc sensitivity analysis of the primary end point, we removed the covariate from the model in order to include treated patients with missing data regarding the baseline FEV_1. In addition, we used the Kaplan–Meier method to estimate the probability of a moderate or severe COPD exacerbation. This procedure was repeated for determining the probability of a severe COPD exacerbation. Additional details regarding the statistical analysis are provided in the protocol and in Section 4 in the Supplementary Appendix.

RESULTS

PATIENTS

A total of 2485 patients underwent randomization at 200 centers in 23 countries. A total of 82.5% of the patients were men; the mean age was 63.8 years, and the mean FEV_1 after bronchodilation was 0.93 liters, which was 32.8% of the predicted value. Of the 2485 patients, 2027 completed the 52-week study, including those who received open-label fluticasone.

Characteristics of the patients at baseline and dropout rates were similar in the two study groups (Fig. 1 and Table 1, and Table S2 in the Supplementary Appendix). According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria, 61.2% of the patients had an FEV_1 that was 30 to 49% of the predicted value (GOLD 3), and 38.1% of the patients had an FEV_1 that was less than 30% of the predicted value (GOLD 4). The percentages of patients receiving inhaled glucocorticoids, LABAs, or LAMAs at baseline were 69.9%, 64.6%, and 46.9%, respectively, with 39.0% receiving the three treatments in combination.

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Glucocorticoid Continuation (N=1243)	Glucocorticoid Withdrawal (N=1242)	All Patients (N=2485)
Male sex — no. (%)	1013 (81.5)	1036 (83.4)	2049 (82.5)
Age — yr	63.6±8.6	64.0±8.4	63.8±8.5
Former smoker — no. (%)†	811 (65.2)	843 (67.9)	1654 (66.6)
Duration of COPD — yr	7.75±5.99	8.00±6.47	7.87±6.23
Percentage of predicted FEV_1 after bronchodilation — no. (%)			
30–49%: GOLD 3	760 (61.1)	761 (61.3)	1521 (61.2)
<30%: GOLD 4	473 (38.1)	474 (38.2)	947 (38.1)
Other category‡	10 (0.8)	7 (0.6)	17 (0.7)
Baseline lung function§			
Patients with available data — no.	1223	1218	2441
FEV_1			
Value — liters	0.97±0.36	0.98±0.36	0.98±0.36
Percentage of predicted value	34.2±11.2	34.3±10.8	34.2±11.0
Score on mMRC scale¶			
Patients with available data — no.	1238	1237	2475
Mean score	1.8±0.9	1.9±0.9	1.8±0.9
SGRQ score‖			
Patients with available data — no.	1136	1126	2262
Mean score	46.35±17.89	45.91±18.19	46.13±18.04
Medication use — no. (%)			
LAMA	588 (47.3)	578 (46.5)	1166 (46.9)
LABA	807 (64.9)	798 (64.3)	1605 (64.6)
Inhaled glucocorticoid	876 (70.5)	862 (69.4)	1738 (69.9)
Triple therapy with LAMA, LABA, and inhaled glucocorticoid, with or without other pulmonary medication — no. (%)**	479 (38.5)	491 (39.5)	970 (39.0)

* Plus–minus values are means ±SD. There were no significant differences between the two groups at baseline on the basis of t-tests for continuous variables and chi-square tests or Fisher's exact test, as appropriate, for categorical variables. COPD denotes chronic obstructive pulmonary disease, FEV_1 forced expiratory volume in 1 second, GOLD Global Initiative for Chronic Obstructive Lung Disease, LABA long-acting β-agonist, and LAMA long-acting muscarinic antagonist.

† All patients in the study were either current smokers (≥10 pack-years) or former smokers.

‡ Of the 17 patients in this category, 3 had mild COPD (FEV_1, ≥80% of predicted value, or GOLD 1), 9 had moderate COPD (FEV_1, 50 to 79% of predicted value, or GOLD 2), and 5 had missing values.

§ Patients for whom baseline lung-function data were available were evaluated after receiving triple therapy during the run-in period. Usable data regarding lung function were missing for 44 patients at baseline.

¶ Scores on the modified Medical Research Council (mMRC) scale range from 0 to 4, with higher scores indicating more severe dyspnea; the absence of breathlessness was given a score of –1. No minimum clinically important difference has been identified.

‖ Scores on St. George's Respiratory Questionnaire (SGRQ) range from 0 to 100, with higher scores indicating worse function and a minimum clinically important difference of 4 points.

** Other respiratory medications included oral β-agonists, oral glucocorticoids, leukotriene-receptor antagonists, mucolytic agents, oxygen, and xanthines.

Overall, 28.2% of patients had cardiac disorders at baseline, and 45.8% had vascular disorders (Table S3 in the Supplementary Appendix).

PRIMARY END POINT

The hazard ratio for a first moderate or severe COPD exacerbation was 1.06 (95% confidence in-

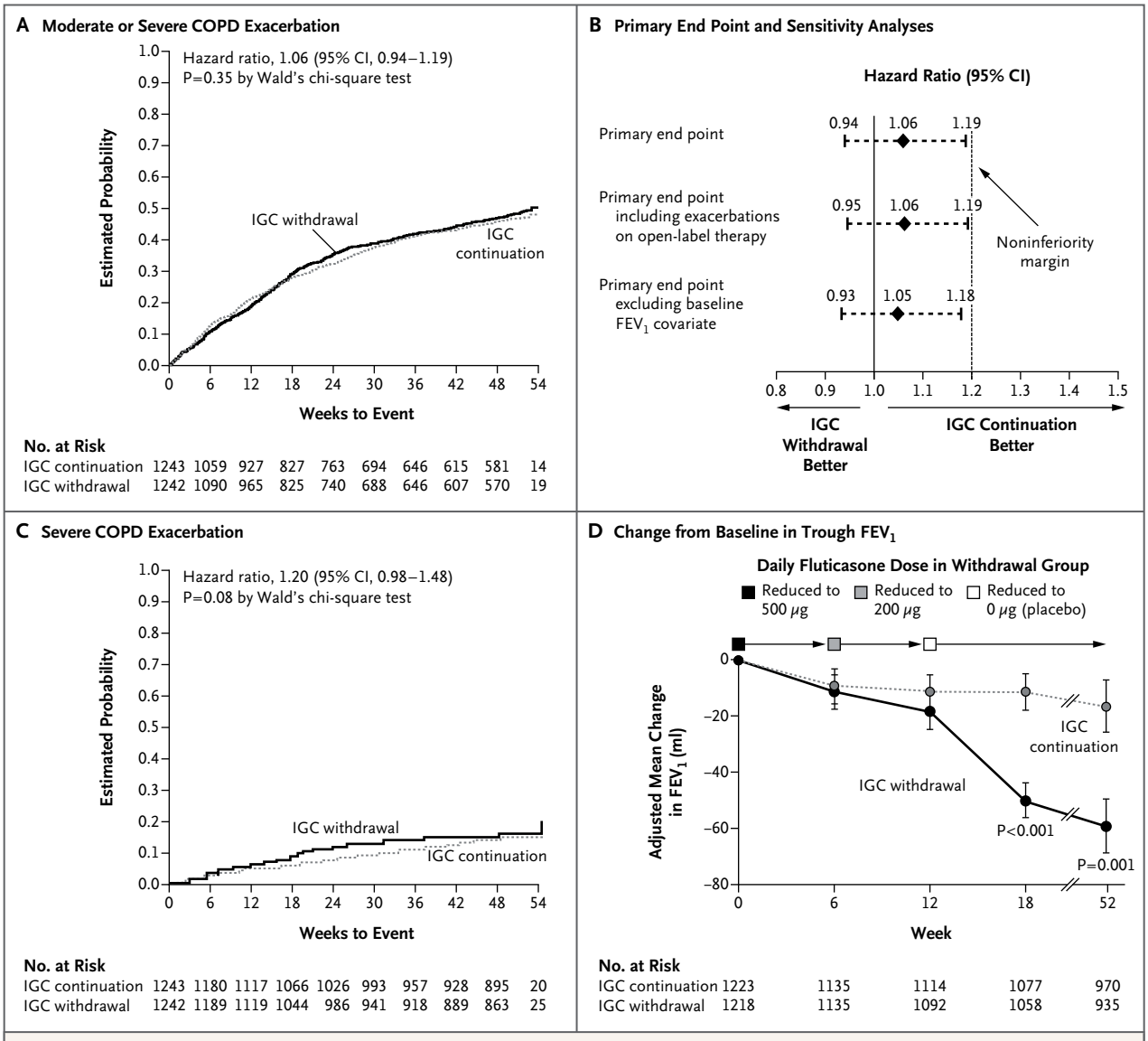

Figure 2. COPD Exacerbations and Lung Function.

Panel A shows Kaplan–Meier curves for the estimated probability of moderate or severe exacerbations of chronic obstructive pulmonary disease (COPD) during the study, with no significant difference between the group assigned to withdrawal of inhaled glucocorticoids (IGC) and the group assigned to continued IGC treatment. Panel B shows a forest plot of hazard ratios for the first COPD exacerbation (the primary end point), the primary end point including exacerbations during open-label therapy (sensitivity analysis), and the primary end point excluding the covariate of the baseline forced expiratory volume in 1 second (FEV_1) (sensitivity analysis). All three categories fall within the prespecified noninferiority margin of 1.20 (the upper limit of the 95% confidence interval for the hazard ratio in the glucocorticoid-withdrawal group as compared with the glucocorticoid-continuation group). Horizontal dashed lines indicate 95% confidence intervals. Panel C shows Kaplan–Meier curves for the estimated probability of severe COPD exacerbations, with no significant between-group difference. Panel D shows the adjusted mean change from baseline in the FEV_1, as measured during clinic visits. In the glucocorticoid-withdrawal group, there was a significant decline in lung function at weeks 18 and 52, as compared with the change from baseline in the glucocorticoid-continuation group. I bars indicate standard errors. In Panels A and C, the study period ends at 54 weeks because some visits could not be scheduled at 52 weeks.

terval [CI], 0.94 to 1.19) with glucocorticoid withdrawal as compared with glucocorticoid continuation, which indicated noninferiority, since the upper limit of the confidence interval was below the predefined noninferiority margin of 1.20 (Fig. 2A and 2B). The results were similar in a sensitivity analysis that included exacerbations occurring after patients had discontinued random-

ized treatment and in a post hoc analysis that excluded the FEV_1 from the model (Fig. 2B, and Fig. S2 in the Supplementary Appendix). The time by which 25% of patients had a first moderate or severe exacerbation (first quartile) was 110 days in the glucocorticoid-withdrawal group and 107 days in the glucocorticoid-continuation group.

SECONDARY END POINTS

The adjusted event rate for moderate or severe exacerbations was 0.95 per patient-year (95% CI, 0.87 to 1.04) in the glucocorticoid-withdrawal group and 0.91 per patient-year (95% CI, 0.83 to 0.99) in the glucocorticoid-continuation group. Analysis of the time to the first severe COPD exacerbation showed a hazard ratio of 1.20 (95% CI, 0.98 to 1.48) for glucocorticoid withdrawal as compared with glucocorticoid continuation (Fig. 2C). The majority of patients with one or more exacerbations had one or two moderate or severe exacerbations during the study (Fig. S3 and S4 in the Supplementary Appendix). There were no significant between-group differences in hazard ratios in any of the subgroup analyses (Fig. 3).

FEV_1

At week 18, when glucocorticoid withdrawal was complete, the adjusted mean reduction from baseline in the trough FEV_1 was 38 ml greater in the glucocorticoid-withdrawal group than in the glucocorticoid-continuation group ($P<0.001$). A similar between-group difference (43 ml) was seen at week 52 (Fig. 2D). No significant between-group differences were observed at weeks 6 and 12.

HEALTH STATUS

The change from baseline in the mMRC score did not differ significantly between the glucocorticoid-withdrawal group and the glucocorticoid-continuation group at week 18 (−0.001 and −0.030 points, respectively; $P=0.36$) or at week 52 (0.035 and −0.028 points, respectively; $P=0.06$). The changes from baseline in the total SGRQ scores were an increase of 0.55 points in the glucocorticoid-withdrawal group and a reduction of 0.42 points in the glucocorticoid-continuation group at week 27 ($P=0.08$) and an increase of 1.15 and a decrease of 0.07, respectively, at week 52 ($P=0.047$).

SAFETY

The overall proportion of patients who had one or more adverse events while receiving the study treatment was 71.2%, and the proportions were similar in the two groups (Table 2, and Table S4 in the Supplementary Appendix). Serious adverse events were reported in 24.2% of the patients in the glucocorticoid-withdrawal group and 23.5% of the patients in the glucocorticoid-continuation group. Rates of fatal adverse events were 3.2% in the glucocorticoid-withdrawal group and 2.7% in the glucocorticoid-continuation group.

The incidence of pneumonia was 5.5% in the glucocorticoid-withdrawal group and 5.8% in the glucocorticoid-continuation group. The incidence of cardiac adverse events of interest was similarly balanced between the groups, with major adverse cardiac events reported in 2.2% of the patients in the glucocorticoid-withdrawal group and 2.0% of patients in the glucocorticoid-continuation group. Major adverse cardiac events that were fatal were reported in 1.5% and 1.1% of the patients, respectively, and stroke was reported in 0.5% and 0.7% of the patients, respectively (Table 2).

DISCUSSION

In our study, in which patients with severe or very severe COPD received triple therapy with a LAMA, a LABA, and an inhaled glucocorticoid during a run-in period, followed by withdrawal of the inhaled glucocorticoid over a 3-month period or continued triple therapy, the upper limit of the 95% confidence interval for an increase in the risk of a moderate or severe acute exacerbation was below the prespecified noninferiority margin of 1.20 in the glucocorticoid-withdrawal group. Differences in FEV_1 and health status emerged in the 18-week analysis after inhaled glucocorticoid treatment was completely withdrawn. We did not identify any subgroup of patients that had an increased likelihood of an exacerbation after glucocorticoid withdrawal. Since a history of exacerbation and substantial impairment in lung function were entry criteria, our study population was representative of patients for whom inhaled glucocorticoids are recommended on the basis of GOLD guidance.[1]

Most clinical trials involving patients with COPD have established the benefit of treatment by comparing a new therapy with placebo or a relevant active control. Few trials have considered the question of whether such therapy should be continued after clinical stability has been achieved, an approach that is commonly adopted for pa-

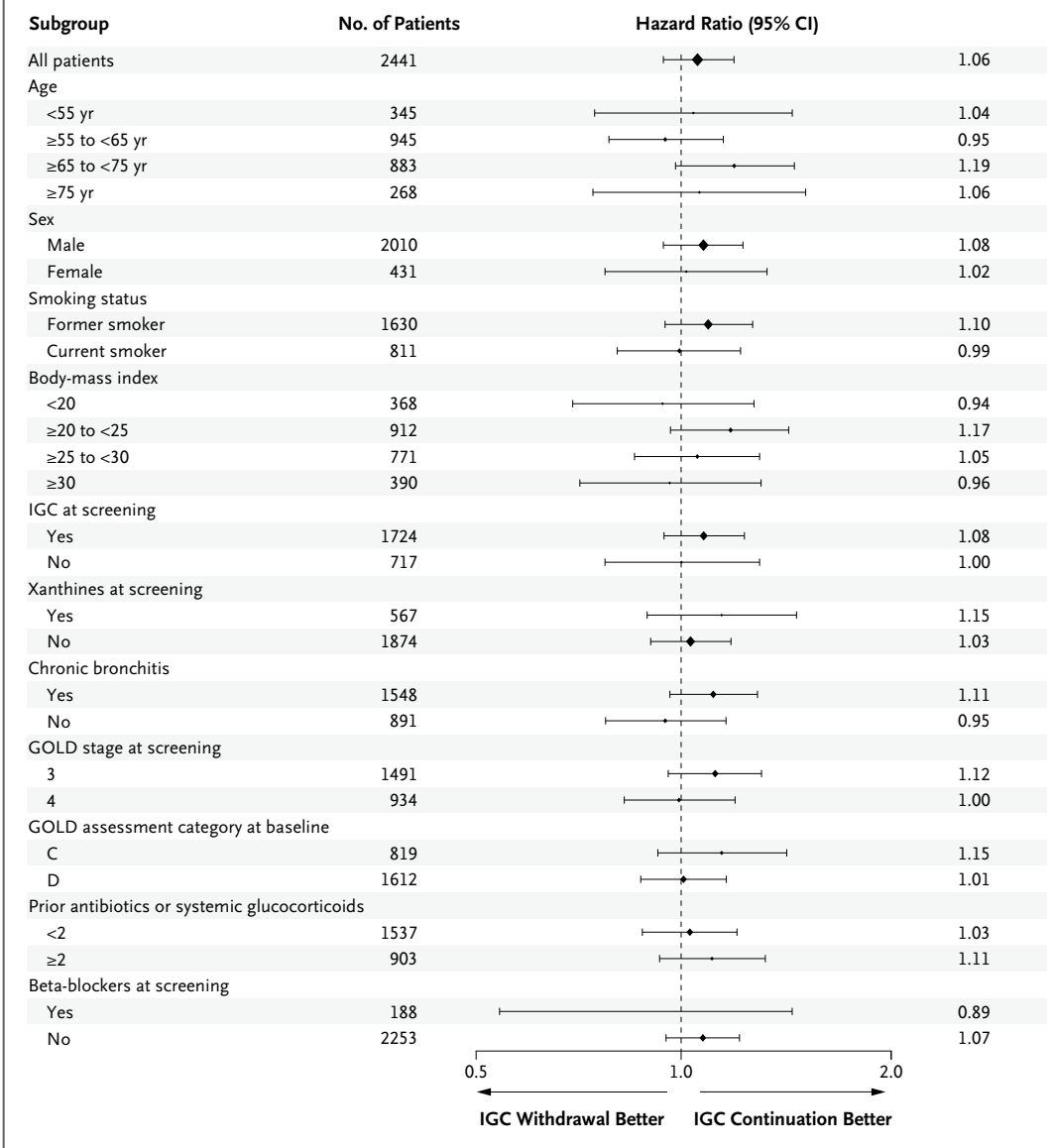

Figure 3. Subgroup Analyses of the First Moderate or Severe COPD Exacerbation in All Study Patients.

All categories were evaluated in post hoc analyses except for age, sex, smoking status, and baseline body-mass index. Data with respect to chronic bronchitis were obtained from electronic case-report forms. The size of the diamonds is proportional to the number of patients in the subgroup. The horizontal lines indicate 95% confidence intervals. Usable data regarding lung function were missing for 44 patients at baseline. GOLD denotes Global Initiative for Chronic Obstructive Lung Disease.

tients with asthma.[13] Initial studies showed that abrupt withdrawal of inhaled glucocorticoids in patients with a range of COPD severities led to more exacerbations and some worsening of lung function, at least when patients used short-acting bronchodilators as maintenance treatment.[14-17] In our study, we used dual bronchodilation with salmeterol and tiotropium, which has proved to be more effective than salmeterol alone in the prevention of exacerbations.[6] Moreover, we withdrew glucocorticoid treatment gradually from a common baseline of maximized therapy.

In our study, we saw no significant between-group difference in the rate of dropout, which typically occurs more frequently in the placebo groups in clinical trials.[18,19] There was a tran-

sient increase in the number of severe exacerbations soon after the complete withdrawal of glucocorticoids, but this increase was not significant and was not sustained during the study period. We considered a number of subgroups in which a greater degree of dependence on glucocorticoids might be expected, but we did not find notable differences in outcomes between inhaled glucocorticoid withdrawal and continued triple therapy in any of these subgroups.

After complete withdrawal of glucocorticoids, we observed a small but significant and persistent between-group difference in the FEV_1, with a larger reduction from the baseline value in the glucocorticoid-withdrawal group. This change was similar to that observed in previous trials of glucocorticoid withdrawal[14-17] and in a study of roflumilast, an oral nonglucocorticoid antiinflammatory drug, in a patient population that was similar to the one in our study.[20] The change in the FEV_1 may represent the spirometric signal associated with antiinflammatory therapy but does not seem to be associated with exacerbations, as reported in recent studies of combination therapy with once-daily inhaled glucocorticoids plus LABAs.[21] In our study, the between-group difference in FEV_1 became apparent only after the final step of inhaled glucocorticoid withdrawal (from 200 μg to 0 μg of fluticasone per day).

We saw no significant effect of glucocorticoid withdrawal on the mMRC score, but there was a difference in the total SGRQ score that was noted during the study period and that favored continued glucocorticoid therapy. However, the importance of this finding is unclear, since the between-group difference was smaller than the frequently used minimum clinically important difference[22] and was not related to differences in the number of exacerbations. We saw no significant between-group difference in the safety profile, including the number of cases of pneumonia. In contrast, other studies have shown an increase in cases of pneumonia among patients with COPD who received fluticasone.[5,8,21] On the basis of our study data, we cannot determine whether our findings with respect to pneumonia reflect differences in our patient population or a sustained effect on pneumonia risk in our glucocorticoid-withdrawal group, since patients in that group received inhaled glucocorticoids for 4 months (including the run-in period); this question merits future study.

Our study has both strengths and limitations. We enrolled substantially more patients than were enrolled in all previous trials of glucocorticoid withdrawal combined, which allowed for further examination of the response in various subgroups. We had 9 months of observation of patients who were not receiving glucocorticoids, with no suggestion that exacerbations were occurring more frequently. It is unlikely that a longer follow-up period would have changed this conclusion. Our study population consisted mainly of white men; we believe that the proportionally smaller enrollment of women was the result of a combination of disease prevalence in the study countries and the severity of disease within our population. However, we observed no significant difference in outcome on the basis of sex (Fig. 3).

Table 2. Adverse Events.*

Variable	Glucocorticoid Continuation (N=1243)	Glucocorticoid Withdrawal (N=1242)
	no. of patients (%)	
Adverse events		
Any	880 (70.8)	890 (71.7)
Leading to discontinuation of study drug	115 (9.3)	127 (10.2)
Serious adverse events		
Any	292 (23.5)	300 (24.2)
Death		
During study period	34 (2.7)	40 (3.2)
Including vital-status follow-up	38 (3.1)	43 (3.5)
Requiring hospitalization	273 (22.0)	271 (21.8)
Adverse events of special interest†		
Pneumonia	72 (5.8)	68 (5.5)
Major adverse cardiac event		
Any	25 (2.0)	27 (2.2)
Fatal	14 (1.1)	19 (1.5)
Stroke	9 (0.7)	6 (0.5)

* A more detailed list of adverse events is provided in Table S4 in the Supplementary Appendix.

† The preferred terms in the *Medical Dictionary for Regulatory Activities* (MedDRA) that were included in the category of pneumonia were bronchopneumonia, lobar pneumonia, pneumonia, pneumonia klebsiella, pneumonia pneumococcal, and pneumonia streptococcal; the system organ classes that were included in the category of major adverse cardiac events were cardiac disorders (fatal) and vascular disorders (fatal); the preferred terms were sudden death, cardiac death, and sudden cardiac death; the Standardized MedDRA query (SMQ) was ischemic heart disease, and the sub-SMQs were myocardial infarction (broad) and myocardial infarction (fatal); and those that were included in the category of stroke were cerebellar infarction, cerebral infarction, cerebrovascular accident, embolic cerebral infarction, ischemic cerebral infarction, ischemic stroke, and transient ischemic attack.

In conclusion, we found that in patients with severe but stable COPD who were receiving combination therapy with tiotropium, salmeterol, and glucocorticoids, the stepwise withdrawal of glucocorticoids was noninferior to the continuation of such therapy, with respect to the risk of moderate or severe exacerbations. The effect of withdrawal on symptoms and lung function also needs to be considered when making decisions regarding maintenance therapy in patients with severe but stable COPD.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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APPENDIX

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REFERENCES

1. Rabe KF, Hurd S, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 2007;176:532-55.
2. Vestbo J, Hurd SS, Agustí AG, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 2013;187:347-65.
3. Wedzicha JA, Brill SE, Allinson JP, Donaldson GC. Mechanisms and impact of the frequent exacerbator phenotype in chronic obstructive pulmonary disease. BMC Med 2013;11:181.
4. Burge PS, Calverley PMA, Jones PW, Spencer S, Anderson JA, Maslen TK. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. BMJ 2000;320:1297-303.
5. Calverley PMA, Anderson JA, Celli B, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med 2007;356:775-89.
6. Vogelmeier C, Hederer B, Glaab T, et al. Tiotropium versus salmeterol for the prevention of exacerbations of COPD. N Engl J Med 2011;364:1093-103.
7. Tashkin DP, Celli B, Senn S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. N Engl J Med 2008;359:1543-54.
8. Wedzicha JA, Calverley PMA, Seemungal TA, Hagan G, Ansari Z, Stockley RA. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. Am J Respir Crit Care Med 2008;177:19-26.
9. Magnussen H, Watz H, Kirsten A, et al. Stepwise withdrawal of inhaled corticosteroids in COPD patients receiving dual bronchodilation: WISDOM study design and rationale. Respir Med 2014;108:593-9.
10. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation: the St. George's Respiratory Questionnaire. Am Rev Respir Dis 1992;145:1321-7.
11. de Torres JP, Pinto-Plata V, Ingenito E, et al. Power of outcome measurements to detect clinically significant changes in pulmonary rehabilitation of patients with COPD. Chest 2002;121:1092-8.
12. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur Respir J 2005;26:319-38.
13. Global Initiative for Asthma. Global strategy for asthma management and prevention, revised 2014 (http://www.ginasthma.org/local/uploads/files/GINA_Report_2014_Jun11.pdf).
14. Jarad NA, Wedzicha JA, Burge PS, Calverley PMA. An observational study of inhaled corticosteroid withdrawal in stable chronic obstructive pulmonary disease. Respir Med 1999;93:161-6.
15. van der Valk P, Monninkhof E, van der Palen J, Zielhuis G, van Herwaarden C. Effect of discontinuation of inhaled corticosteroids in patients with chronic obstructive pulmonary disease: the COPE study. Am J Respir Crit Care Med 2002;166:1358-63.
16. Choudhury AB, Dawson CM, Kilvington HE, et al. Withdrawal of inhaled corticosteroids in people with COPD in primary care: a randomised controlled trial. Respir Res 2007;8:93.
17. Wouters EFM, Postma DS, Fokkens B, et al. Withdrawal of fluticasone propionate from combined salmeterol/fluticasone treatment in patients with COPD causes immediate and sustained disease deterioration: a randomised controlled trial. Thorax 2005;60:480-7.
18. Vestbo J, Anderson JA, Calverley PM, et al. Bias due to withdrawal in long-term randomised trials in COPD: evidence from the TORCH study. Clin Respir J 2011;5:44-9.
19. Calverley PMA, Spencer S, Willits L, Burge PS, Jones PW. Withdrawal from treatment as an outcome in the ISOLDE study of COPD. Chest 2003;124:1350-6.
20. Calverley PMA, Rabe KF, Goehring U-M, Kristiansen S, Fabbri LM, Martinez FJ. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. Lancet 2009;374:685-94. [Erratum, Lancet 2010;376:1146.]
21. Dransfield MT, Bourbeau J, Jones PW, et al. Once-daily inhaled fluticasone furoate and vilanterol versus vilanterol only for prevention of exacerbations of COPD: two replicate double-blind, parallel-group, randomised controlled trials. Lancet Respir Med 2013;1:210-23.
22. Jones PW. Estimation and application of the minimum clinically important difference in COPD. Lancet Respir Med 2014;2:167-9.