Effect of Discontinuation of Inhaled Corticosteroids in Patients with Chronic Obstructive Pulmonary Disease

The COPE Study

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The aim of this double-blind single center study (the COPE study) was to investigate the effect of discontinuation of the inhaled corticosteroid fluticasone propionate (FP) on exacerbations and health-related quality of life in patients with chronic obstructive pulmonary disease. After 4 months of treatment with FP (1,000 μg/day), 244 patients were randomized to either continue FP or to receive placebo for 6 months: 123 patients continued FP (FP group), and 121 received placebo (placebo group). In the FP group, 58 (47%) patients developed at least one exacerbation compared with 69 (57%) in the placebo group. The hazard ratio of a first exacerbation in the placebo group compared with the FP group was 1.5 (95% confidence interval [CI] 1.1–2.1). In the placebo group 26 patients (21.5%) experienced rapid recurrent exacerbations and were subsequently unblinded and prescribed FP compared with 6 patients (4.9%) in the FP group (relative risk = 4.4; 95% CI 1.9–10.3). Over a 6-month period, a significant difference in favor of the FP group was observed in the total score (+2.48 95% CI 0.37–4.58), activity domain (+4.64 95% CI 1.60–7.68), and symptom domain (+4.58 95% CI 1.05–8.10) of the St. George's Respiratory Questionnaire. This study indicates that discontinuation of FP in patients with chronic obstructive pulmonary disease is associated with a more rapid onset and higher recurrence-risk of exacerbations and a significant deterioration in aspects of Health-Related Quality of Life.

Keywords: COPD; inhaled corticosteroids; exacerbations; health-related quality of life

Chronic obstructive pulmonary disease (COPD) constitutes a major public health burden worldwide (1). The World Health Organization (2) estimates COPD to be the world's fifth most common disease and fourth leading cause of death. Both prevalence and mortality are expected to increase in the coming decades (3, 4).

Smoking cessation (5) and bronchodilator therapy (5, 6) are the mainstay of the management of COPD. Born from the idea that both asthma and COPD result from chronic inflammation and that inhaled corticosteroids (ICS) are remarkably effective in controlling inflammation in asthma, there is an intense discussion whether or not ICS are beneficial in COPD (7, 8). Inevitably, clinicians have prescribed ICS in COPD. However, the inflammatory pattern in COPD differs markedly from that in asthma (9, 10), and the safety of long-term, high-dose ICS has not been well established (11).

Beneficial clinical effects of ICS were observed in recent randomized controlled trials: amelioration of respiratory symptoms (12), persistent improvement in airways reactivity (12), decreased frequency (13) or severity (14) of exacerbations, diminished use of healthcare resources (12), and improved health-related quality of life (HRQL) (13). One observational study (15) suggested that ICS therapy is associated with reduced COPD-related morbidity and mortality in elderly patients. Of the previously mentioned outcome parameters in COPD, exacerbations are most relevant for HRQL, but in all reported studies these were only measured as secondary outcomes that were poorly defined.

Inhaled corticosteroids have been shown to be ineffective in arresting long-term decline in FEV_1 as recently reported in five major studies (12, 13, 16–18). A remarkable finding reported in two of these studies (13, 17) was that treatment with ICS improves FEV_1 slightly in the first 3 to 6 months, an effect that is maintained during follow-up treatment. This led to the idea that this initial improvement in lung function due to ICS is worth pursuing, but the overall effect of prolonged ICS treatment is not yet clear. Only two studies have investigated the effect of withdrawal of ICS: one observational, nonrandomized, study (19) as part of the run-in phase of the ISOLDE study (13) and a small, underpowered cross-over study with a short follow-up and no wash-out period (20). As most of the newly diagnosed patients with COPD receive initial trial treatment for several months, and many of them will show the initial improvement in FEV_1, they will be prescribed ICS for life. Therefore, there is an urgent need for large randomized controlled studies on discontinuation of ICS treatment.

We investigated the effect of discontinuing maintenance therapy with high doses (1,000 μg/day) of inhaled fluticasone propionate (FP) in a randomized, double-blind, placebo controlled study (COPE study) on time to first exacerbation and rapid recurrence of well-defined exacerbations in patients with moderate to severe COPD.

METHODS

Patients

All patients were recruited from one outpatient pulmonary clinic, from May 1999 till March 2000. To be eligible for the study the patients had to meet the following criteria: (*1*) a clinical diagnosis of stable COPD, as defined by American Thoracic Society criteria (21); (*2*) no history of asthma; (*3*) no exacerbation in the month before enrollment; (*4*) current or former smoker; (*5*) age between 40 and 75 years; (*6*) baseline prebronchodilator FEV_1 value of 25 to 80% of predicted; (*7*) prebronchodilator ratio FEV_1 inspiratory vital capacity (IVC) value of 60% or less; (*8*) reversibility of FEV_1 postinhalation of 80 μg of ipratropium bromide via a metered dose inhalator with Aerochamber 12% of predicted value or less (22); (*9*) thin layer chromatography greater than

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the thin layer chromatography predicted minus 1.64 SD; (*10*) no maintenance treatment of oral steroids or antibiotics; (*11*) no medical condition with low survival or serious psychiatric morbidity (e.g., cardiac insufficiency, alcoholism); (*12*) absence of any other active lung disease (e.g., sarcoidosis); and (*13*) use of medication such as nasal corticosteroids, theophyllines, chronic use of acetylcysteine, and all other bronchodilators was allowed.

The hospital's medical ethical committee approved this study. All patients provided written informed consent.

Trial Design

This study was a randomized, double-blind, parallel-group single center study that comprised 4 months run-in, 6 months active treatment or placebo, with follow-up visits at 3 and 6 months. In the run-in phase all patients were prescribed FP via Diskus/Accuhaler 500 μg twice daily and ipratropiumbromide 40 μg four times daily to optimize lung function. All patients were prescribed short-acting β2-agonists (salbutamol) as rescue medication. Patients using rescue medication more than twice daily were offered a long-acting β2-agonist. All patients received inhalation instruction in small group sessions at the start of the study. Current smokers were offered an individual smoking cessation program (23).

After 4 months, eligible patients were randomly assigned to continue 500 μg of FP twice daily or to receive placebo administered via the Diskus inhalation device for 6 months. Randomization was performed in blocks of six by computer-generated allocation. Follow-up visits were scheduled 3 and 6 months post randomization. Spirometry at regular follow-up visits was measured under postbronchodilation medication and only when the patient was in a stable condition. If the patient was using a short course of oral steroids or antibiotics or was experiencing an exacerbation at the time of the follow-up visit, this visit was postponed 4 weeks.

If patients experienced any worsening of their respiratory symptoms they were instructed to contact the COPE study personnel by telephone. They were subsequently invited to attend the hospital within 12 hours for spirometry measurements and consultation by one of the study physicians who subsequently decided either to continue the trial or to prescribe 500 μg of FP twice daily unblinded. The latter was allowed according to the benefit of the doubt principle in case patients experienced rapid recurrent exacerbations. This was defined as either twice an objective increase in respiratory symptoms within a 3-month period, defined as more than 20% or 300 ml decrease in FEV_1, compared with stable lung function at randomization, or three times a subjective increase of respiratory symptoms in a 3-month period as experienced by the patient regardless of the criteria mentioned previously.

Outcome Measurements

Primary outcome measures were first and second exacerbation and the occurrence of rapid recurrent exacerbations, as well as HRQL. Exacerbations were defined as worsening of respiratory symptoms that required treatment with a short course of oral corticosteroids or antibiotics as judged by the study physician. A short course of oral corticosteroids was defined as 30 mg prednisolon for a period of 10 days. The first choice of antibiotics was amoxicillin/clavulanic acid 625 mg four times daily for a period of 10 days. The second choice was doxycycline 100 mg daily for a period of 10 days. Exacerbations were followed actively as described in Trial Design.

Patients with rapid recurrence of exacerbations were those who had to be prescribed FP unblinded due to safety reasons as mentioned previously. HRQL was measured immediately before randomization and after 3 and 6 months follow-up by means of the Dutch version of the St. George's Respiratory Questionnaire and the Euroqol 5D including a visual analogue scale. The St. George's Respiratory Questionnaire is a disease-specific instrument composed of 76 items that are weighted to produce domain scores: "symptoms," "activity," and "impact." The total score is calculated from all items and provides a global view of the patient's respiratory health. The scores range from 0 to 100, with a score of 100 indicating maximum disability (24). A difference of four units indicates a small clinically relevant effect. The Euroqol 5D visual analogue scale records the respondent's self-rated health status from 0 (worst imaginable health state) to 100 (best imaginable health state).

Secondary outcome measures were lung function parameters and exercise tolerance. Spirometry was assessed immediately before randomization and after 3 and 6 months follow-up. Well-trained lung function technicians performed spirometry on water sealed spirometers according to standardized guidelines (25) and FEV_1 and IVC were measured until three reproducible recordings (less than 5% difference) were obtained. Highest values were used for analyses. Exercise tolerance was measured at randomization and after 6 months follow-up by the standardized 6-minute walking test. Oxygen saturation, heart rate, and the Borg scale of breathlessness by means of a 11-point scale were recorded pretest and after every minute (26). The performance of the test was standardized: patients performed a practice walk, were instructed pretest, and no encouragement was used during the test (27). A change of 54 m in walking distance is considered clinically important (28).

Use of health care facilities was registered during the study: hospitalizations, emergency room visits, scheduled and emergency outpatient visits, and exacerbations treated by the patient's general practitioner. Pharmacists reported all drugs used during the study period.

Patients were asked to complete a 2-week diary before each follow-up visit and during periods of increased respiratory symptoms. In the diary, data on breathlessness, cough, sputum volume, sputum color, and use of rescue β2-agonists was collected. Every week patients graded their health status from 1 to 10. At each visit patients were questioned about possible adverse events.

Statistical Analyses

We calculated that 192 patients (96 per treatment group) were required to detect a hazard ratio of a first exacerbation of 1.50 (FP compared with placebo) with 80% power and a two-sided 0.05 α–level test (29).

Baseline characteristics are reported as means ± SD or as percentages within groups. Analyses were performed according to the intention-to-treat principle. The effect of discontinuing FP on the subsequent exacerbation risk (the primary outcome) was assessed using Cox proportional hazard analyses. Between-group differences in the proportion of patients with rapid recurrences of exacerbations were assessed by means of chi-square tests.

Between-group differences in continuous variables (Quality-of-Life-scores, lung function parameters) were assessed by analyses of repeated measurements using Proc Mixed (mixed models approach) from SAS (30). Linear regression analysis was used to assess between-group differences for the distance walked in 6 minutes.

Within-patient comparisons were done by the paired *t* test (normal distribution) or the Wilcoxon Signed Rank Test (non-normal distribution). We adjusted the analyses for potential confounding variables if these variables were not equally distributed at randomization.

We performed subgroup analyses for the patients with a FEV_1 value less than 50% predicted according to the GOLD recommendations for ICS prescription (1).

Except for the repeated measurements analyses, all statistical analyses were performed using SPSS version 10 (31).

RESULTS

Baseline Characteristics

Of the 509 eligible patients, a total of 269 were enrolled (Figure 1). The mean age of the participants was 64.0 ± 7.2 years. Table 1 shows the baseline characteristics of the study population stratified by treatment group. Except for smoking the two treatment groups were similar with respect to the known prognostic variables. Eighty-three percent (203/244) of the patients had used ICS at least 6 months before entering the study. In the year preceding the study, patients experienced a mean number of 1.3 exacerbations per year (median = 1). Long-acting β-agonists were used by 48% of the patients in the fluticasone group and 44% of the patients in the placebo group. This difference is not statistically significant.

During the 4-months run-in phase 263 patients received 500 μg of FP twice daily. Of these, 244 patients were randomized; 123 received 500 μg of FP twice a day and 121 received placebo during a period of 6 months. In the run-in phase, 19 patients (7%) had to be withdrawn (Figure 1), 6 because of intolerance to FP. During the double-blind phase, two patients died; one in

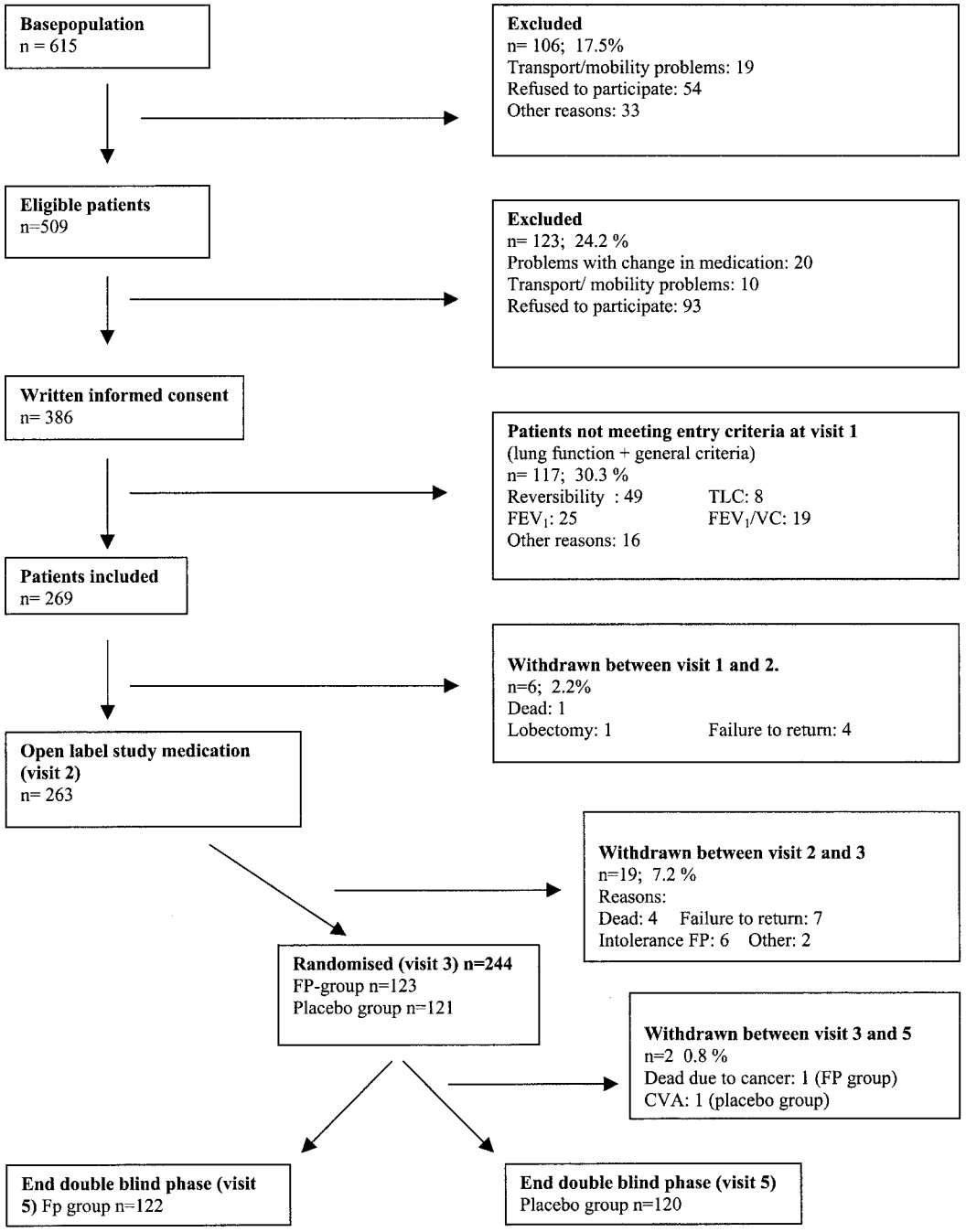

Figure 1. Flow diagram of subject progress through the COPE study.

the FP group (from cancer) and the other in the placebo group from a cerebrovascular accident (Figure 1).

Exacerbations

Of the 244 patients, 117 (48%) did not have any exacerbation. A total of 127 patients (52%) developed at least one exacerbation: 58 (47.2%) in the FP group and 69 (57.0%) in the placebo group. The hazard ratio of a first exacerbation in the placebo group (adjusted for smoking status) was 1.5 (95% confidence interval [CI] 1.05–2.1) compared with the FP group (Figure 2). Mean difference in time to first exacerbation, adjusted for smoking status, between the FP group (75.2 days) and the placebo group (42.7 days) was 34.6 days (95% CI 15.4–53.8) in favor of the FP group. The hazard ratio of a second exacerbation adjusted for smoking status in the placebo group compared with the FP group was 2.4 (95% CI 1.5–3.9).

In the placebo group, 26 patients (21.5%) experienced rapid recurrent exacerbations and were thus prescribed FP in an open way in contrast to 6 patients (4.9%) in the FP group (relative risk = 4.4; 95% CI 1.9–10.3).

Five of the six patients (83%) in the FP group who were prescribed FP in an open way continued to have exacerbations over the remaining trial period in contrast to 38% (10/26) in the placebo group.

Subgroup Analysis

Analysis of the prognostic variables at the baseline indicated that the placebo subgroup with recurrent exacerbations had a

TABLE 1. BASELINE CHARACTERISTICS OF THE TWO TREATMENT GROUPS

	Fluticasone Propionate	Placebo
Number of patients	123	121
Age, yr (mean ± SD)	64.1 ± 6.8	64.0 ± 7.7
Male, %	85.4	83.5
Body mass index, kg/m² (mean ± SD)	26.9 ± 4.0	26.9 ± 4.1
Number of exacerbations in preceding year (mean ± SD)	1.31 ± 1.50	1.36 ± 1.66
Smoking status (%)		
Former smokers	78.0	66.9
Current smokers	22.0	33.3
Pack years	38.2 ± 26.6	37.3 ± 21.7
Previous use of inhaled corticosteroids, %	86.2	80.2
Use of long-acting β-agonists, %	59 (48)	53 (44)
Lung function postbronchodilation (mean ± SD)		
FEV_1, L	1.78 ± 0.53	1.69 ± 0.53
FEV_1, % predicted of normal	57.5 ± 14.1	56.1 ± 14.8
IVC, L	3.89 ± 0.85	3.77 ± 0.84
Total score SGRQ (mean ± SD)	34.3 ± 15.5	38.2 ± 16.7
Six-minute walk, m (mean ± SD)	458 ± 77	435 ± 87

Definition of abbreviations: IVC = inspiratory vital capacity; SGRQ = St. George's Respiratory Questionaire.

slightly higher exacerbation rate pretrial, a worse health status, and walked less in 6 minutes. The lung function of this subgroup did not differ from the overall study population. Analysis of the subgroup of patients with a FEV_1 value less than 50% predicted (low FEV_1 group) suggests that the difference in time to first exacerbation between groups is driven by this subset. The hazard ratio was 2.1 (95% CI 1.1–3.6) and 1.2 (95% CI 0.8–2.0) in the low- and high-FEV_1 group, respectively.

Health-related Quality of Life

Adjusted for baseline scores, smoking status, and time effects, a statistically significant difference was observed between both groups in the total score (+2.48, 95% CI 0.37–4.58), in the activity domain (+4.64, 95% CI: 1.60–7.68) and the symptom domain (+4.58, 95% CI: 1.05–8.10) over 6 months. No difference was seen in the impact domain. The results are summarized in Figure 3. Adjusted for baseline differences, smoking status, and time effects, a small but statistically significant difference in mean Euroqol-5D visual analogue scale-score of 3.1 points (95% CI 0.8–5.3) in favor of the FP group was observed.

Lung Function and Exercise Capacity

During the 4-month run-in period, FEV_1 did not change. Adjusted for baseline values, smoking status, and time effects, an almost statistically significant difference of 38 ml in postbronchodilation FEV_1 was observed in favor of the FP group. Mean distance walked in 6 minutes and mean Borg score of breathlessness remained unchanged (Table 2).

Safety

In concordance with the primary outcome results, the frequency of serious adverse respiratory events (mainly hospital admissions for exacerbations of COPD) was higher in the placebo group (Table 3). There was no indication that FP caused serious or nonserious adverse events.

DISCUSSION

This randomized placebo-controlled study demonstrated that discontinuation of FP (1,000 μg/day) after 4 months of maintenance therapy induced a more rapid onset and higher recurrence-risk of exacerbations in patients with moderate to severe COPD.

The study was motivated by the observation in two earlier

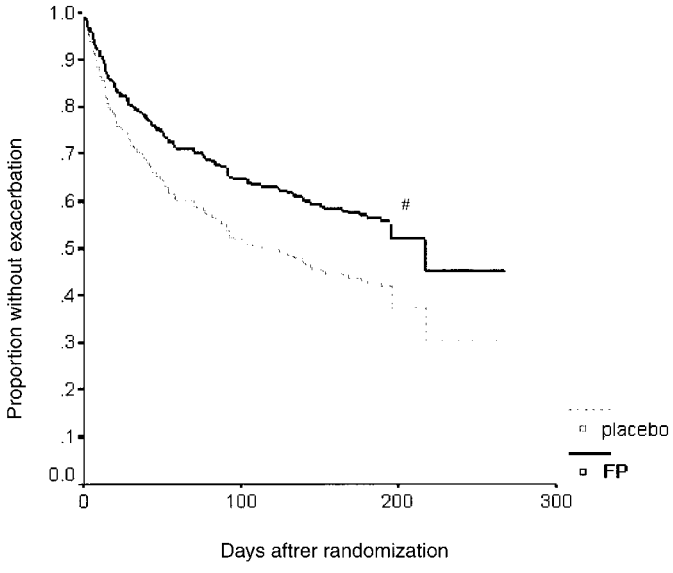

Figure 2. Time to first exacerbation curve (Cox regression) adjusted for smoking status for patients assigned to FP and placebo. #In order to measure outcome variables in a stable condition, 20 patients had a 6 month follow-up visit postponed to a date exceeding 200 days.

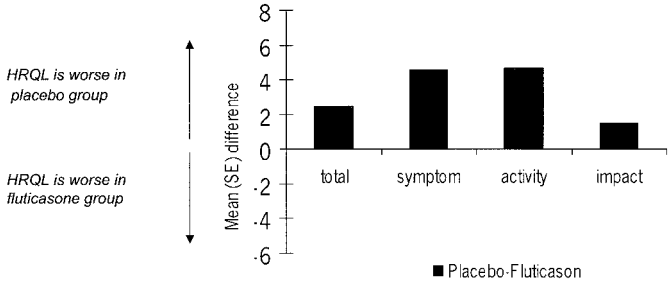

Figure 3. Difference between placebo and FP groups in St. George's Respiratory Questionnaire-scores over 6 months adjusted for time-effects, smoking status, and baseline value.

TABLE 2. EFFECT OF TREATMENT BY PLACEBO RELATIVE TO FLUTICASONE PROPIONATE ON FEV_1, 6 MINUTE WALK, AND BORG SCORE OF BREATHLESSNESS

Outcome Parameter	FP (*Mean ± SE*)	Placebo (*Mean ± SE*)	Difference* (*95% CI*)	p Value
Change in FEV_1 after bronchodilator, ml	−4.6 ± 1.6 (n = 122)	−22.9 ± 1.7 (n = 120)	38 (−79.5; 1.6)†	0.056
Six minute walk, m	−11.0 ± 4.8 (n = 87)‡	−0.2 ± 5.2 (n = 85)‡	9.37 (−4.47; 23.21)§	0.18
Change in Borg score, units	−0.07 ± 0.2 (n = 88)‡	−0.29 ± 0.2 (n = 85)‡	0.29 (−0.13; 0.71)§	0.17

Definition of abbreviations: CI = confidence interval; FP = fluticasone propionate.

* Analysis of treatment differences were adjusted for smoking status and baseline values.

† Based on repeated measurements analyses with Proc Mixed.

‡ Numbers are smaller than randomized population for 6-minute walk distance and Borg score because of practical problems not all patients performed a 6-minute walk. Patients were randomly assigned to a do a 6-minute walk.

§ Based on linear regression analysis.

studies (13, 17) showing that ICS produces a small, initial improvement in FEV_1 without additional reduction in lung function loss in subsequent years. Before enrollment in the present study, 85% of patients with COPD were receiving ICS, which may explain the lack of the improvement in FEV_1 during the run-in period.

The increased risk of exacerbations after withdrawal of ICS is in accordance with the limited evidence available (19, 20). In the run-in phase of the ISOLDE study (19), ICS were withheld from patients already using these medications. In the first 7 weeks post withdrawal, 38% of patients previously treated with ICS experienced an exacerbation compared with 6% of those who had not received ICS previously. Although the patients in the ISOLDE study were more severe, the higher frequency of exacerbations seen in the COPE study after withdrawal of ICS might be explained by a prospective and complete registration of exacerbations. In agreement with the ISOLDE study, the majority of exacerbations in our study occurred in the first 7 weeks. The study by O'Brien and colleagues (20) demonstrated that withdrawal of ICS in elderly patients with COPD led to deterioration in ventilatory function and increased exercise-induced dyspnea and showed a trend toward an increased frequency of exacerbations. However, results of this small crossover study should be viewed with caution as only 15 of the 24 patients completed the study, and follow-up was only 12 weeks. Moreover, lung function varied considerably (range of FEV_1 between 0.73 and 2.42 L), and the only three patients with exacerbations were withdrawn. Also our own results regarding the larger decline in FEV_1 in the placebo group should be viewed with caution. The difference of 38 ml seems relevant but is based only on three measurements in a period of 6 months.

It should further be stressed that in most studies on effects of ICS in COPD (including the two studies dealing with effects of ICS withdrawal), exacerbations were only considered a secondary outcome and hence were poorly defined, described, or measured (13, 14). By contrast, the COPE study was designed to investigate the effect of discontinuing ICS on first and second exacerbation and occurrence of rapid recurrence of well-defined exacerbations. The exacerbation data of our study can be considered very reliable because all patients were instructed to call and visit the COPE center as soon as they experienced any serious worsening of their respiratory condition, to clinically verify the suspicion of an exacerbation. In all these instances lung function tests were performed within 12 hours. In addition, all diaries, week reports, hospital records (hospitalizations and emergency department visits), and records from the patient's general practitioner and pharmacists were searched for additional information on exacerbations.

Assessment of the HRQL, which is an important outcome in COPD studies (10), provided us with a comprehensive picture of the overall impact of FP treatment withdrawal in COPD (32). This study showed a significant deterioration in the total score, symptoms, and activity domains of the St. George's Respiratory Questionnaire in the placebo group. This suggests that discontinuation of FP affects distress, due to respiratory symptoms, and disturbance of physical activity but does not affect the impact on daily living. These findings are in line with the study by Spencer and colleagues (33). Their results suggest that FP has greatest influence on deterioration in physical aspects of health rather than psychosocial functions. Another study assessing the effect of exacerbations on HRQL in COPD, however, showed a worse St. George's Respiratory Questionnaire total and domain scores in patients with frequent exacerbations (34). Based on this study, one expects worse health status in our patients in the placebo group because of their higher rate of exacerbations. However, it should be noted that the patients with frequent exacerbations in the COPE study received open FP treatment for safety reasons most times already before the first follow-up visit, and this may have lead to dilution of the effect on HRQL.

We did not find relevant differences in the Eurol-5D visual analogue scale score within and between treatment groups, a finding concordant with the view that a global assessment of patients' health underestimates the impact of airways disease on patients' perceived health (32).

Further research is needed to analyze the clinical intangible factors of sensitivity to ICS as it is still not well understood why patients with COPD would benefit from ICS. In addition it should be stressed that patients treated at a chest clinic in the Netherlands may have another manifestation of COPD compared with those treated by the general practitioner. This should lead to caution in extrapolating the results of this study to the group of patients with COPD treated in primary care.

A hypothetical explanation for ICS sensitivity could be the inclusion of patients with COPD who also have asthma features. Although patients with a history of asthma or reversible bron-

TABLE 3. ADVERSE EVENTS DURING DOUBLE-BLIND PERIOD

	Fluticasone Proprionate (*n = 123*)	Placebo (*n = 121*)
No. of serious adverse events		
Total (no. of points)	14 (12)	24 (13)
Lower respiratory	10	15
Cardiovascular	1	2
Gastrointestinal	2	2
Other	1	5
No. of patients with throat irritation		
At randomization	7	7
At 3 months follow-up	4	7
At end of study	2	1

chial obstruction were excluded, some patients might have hidden asthma-like characteristics and thus were probably prone to develop an exacerbation after discontinuation of FP. In this context it might be relevant that the subgroup experiencing rapid recurrent exacerbations had slightly more advanced disease before enrollment.

Our study demonstrated that discontinuation of high doses of FP in patients with moderate to severe COPD induced a more rapid onset and higher recurrence-risk of exacerbations. However, as 40% of the patients have no untoward effect from the withdrawal of ICS there is an urgent need to identify which subgroup of patients with COPD patients responds well to prolonged ICS therapy. Moreover, there is need for further studies to investigate the efficacy and safety of long-term use of ICS for the management of COPD.

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References

1. Pauwels RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. *Am J Respir Crit Care Med* 2001;163:1256–1276.
2. World Health Organization. The World Health Report. Life in the 21st century. A vision for all. Geneva: World Health Organization; 1998.
3. Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990–2020. Global Burden of Disease Study. *Lancet* 1997;349: 1498–1504.
4. World Health Organization. World Health Report. Geneva: World Health Organization; 2000. Available at: http://www.who.int/whr/2000/en/statistics.htm
5. Anthonisen NR, Connett JE, Kiley JP, Altose MD, Bailey WC, Buist AS, Conway WA Jr, Enright PL, Kanner RE, O'Hara P, *et al.* Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV_1. The Lung Health Study. *JAMA* 1994;272:1497–1505.
6. Barnes PJ. New therapies for chronic obstructive pulmonary disease. *Thorax* 1998;53:137–147.
7. Calverley PM. Inhaled corticosteroids are beneficial in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000;161:341–342.
8. Barnes PJ. Inhaled corticosteroids are not beneficial in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000;161:342–344.
9. Keatings VM, Jatakanon A, Worsdell YM, Barnes PJ. Effects of inhaled and oral glucocorticoids on inflammatory indices in asthma and COPD. *Am J Respir Crit Care Med* 1997;155:542–548.
10. Barnes PJ. Chronic obstructive pulmonary disease. *N Engl J Med* 2000; 343:269–280.
11. Lipworth BJ. Systemic adverse effects of inhaled corticosteroid therapy: a systematic review and meta-analysis. *Arch Intern Med* 1999;159:941–955.
12. The Lung Health Study Research Group. Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease. *N Engl J Med* 2000;343:1902–1909.
13. Burge PS, Calverley PM, 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;320:1297–1303.
14. Paggiaro PL, Dahle R, Bakran I, Frith L, Hollingworth K, Efthimiou J. Multicentre randomised placebo-controlled trial of inhaled fluticasone propionate in patients with chronic obstructive pulmonary disease: International COPD Study Group. *Lancet* 1998;351:773–780.
15. Sin DD, Tu JV. Inhaled corticosteroids and the risk of mortality and readmission in elderly patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001;164:580–584.
16. Bourbeau J, Rouleau MY, Boucher S. Randomised controlled trial of inhaled corticosteroids in patients with chronic obstructive pulmonary disease. *Thorax* 1998;53:477–482.
17. Pauwels RA, Lofdahl CG, Laitinen LA, Schouten JP, Postma DS, Pride NB, Ohlsson SV. Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. European Respiratory Society Study on Chronic Obstructive Pulmonary Disease. *N Engl J Med* 1999;340:1948–1953.
18. Vestbo J. Long-term effect of inhaled budesonide in mild and moderate chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 1999;353:1819–1823.
19. Jarad NA, Wedzicha JA, Burge PS, Calverley PM. An observational study of inhaled corticosteroid withdrawal in stable chronic obstructive pulmonary disease. ISOLDE Study Group. *Respir Med* 1999;93:161–166.
20. O'Brien A, Russo-Magno P, Karki A, Hiranniramol S, Hardin M, Kaszuba M, Sherman C, Rounds S. Effects of withdrawal of inhaled steroids in men with severe irreversible airflow obstruction. *Am J Respir Crit Care Med* 2001;164:365–371.
21. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1995;152:s77–s120.
22. Brand PL, Quanjer PH, Postma DS, Kerstjens HA, Koeter GH, Dekhuijzen PN, Sluiter HJ. Interpretation of bronchodilator response in patients with obstructive airways disease: The Dutch Chronic Non-Specific Lung Disease (CNSLD) Study Group. *Thorax* 1992;47:429–436.
23. Pieterse ME, Seydel ER, DeVries H, Mudde AN, Kok GJ. Effectiveness of a minimal contact smoking cessation program for Dutch general practitioners: a randomized controlled trial. *Prev Med* 2001;32:182–190.
24. 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: 1321–1327.
25. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows: official statement of the European Respiratory Society. *Eur Respir J* 1993;6:5–40.
26. Wilson RC, Jones PW. A comparison of the visual analogue scale and modified Borg scale for the measurement of dyspnoea during exercise. *Clin Sci* 1989;76:277–282.
27. Sciurba FC, Slivka WA. Six-minute walk testing. *Semin Resp Crit Care Med* 1998;19:383–392.
28. Redelmeier DA, Bayoumi AM, Goldstein RS, Guyatt GH. Interpreting small differences in functional status: the Six Minute Walk test in chronic lung disease patients. *Am J Respir Crit Care Med* 1997;155: 1278–1282.
29. Piantadosi P. Sample size and power. In: Piantadosi S, editor. Clinical trials. New York: John Wiley & Sons, Inc.; 1997. p. 148–185.
30. SAS Institute. Release 6.12. Cary, NC: SAS In.; 1996.
31. SPSS for Windows. Release 10. Chicago IL: SPSS In.; 2001.
32. Jones PW. Issues concerning health-related quality of life in COPD. *Chest* 1995;107:187S–193S.
33. Spencer S, Calverley PM, Sherwood BP, Jones PW. Health status deterioration in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001;163:122–128.
34. Seemungal TA, Donaldson GC, Paul EA, Bestall JC, Jeffries DJ, Wedzicha JA. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;157:1418–1422.