

ONLINE FIRST

Short-term vs Conventional Glucocorticoid Therapy in Acute Exacerbations of Chronic Obstructive Pulmonary Disease

The REDUCE Randomized Clinical Trial

Jörg D. Leuppi, MD, PhD

Philipp Schuetz, MD

Roland Bingisser, MD

Michael Bodmer, MD

Matthias Briel, MD

Tilman Drescher, MD

Ursula Duerring, RN

Christoph Henzen, MD

Yolanda Leibbrandt, RN

Sabrina Maier, RN

David Miedinger, MD, PhD

Beat Müller, MD

Andreas Scherr, MD

Christian Schindler, PhD

Rolf Stoeckli, MD

Sebastien Viatte, MD, PhD

Christophe von Garnier, MD

Michael Tamm, MD

Jonas Rutishauser, MD

ACUTE EXACERBATIONS OF chronic obstructive pulmonary disease (COPD) are a risk factor for disease deterioration,¹ and patients with frequent exacerbations have increased mortality.² In the general practitioner-based Swiss COPD cohort, approximately 23% to 25% of patients with COPD experienced exacerbations requiring pharmacological treatment within 1 year.^{3,4} International guidelines and systematic reviews advocate systemic glucocorticoid therapy in the management

Importance International guidelines advocate a 7- to 14-day course of systemic glucocorticoid therapy in acute exacerbations of chronic obstructive pulmonary disease (COPD). However, the optimal dose and duration are unknown.

Objective To investigate whether a short-term (5 days) systemic glucocorticoid treatment in patients with COPD exacerbation is noninferior to conventional (14 days) treatment in clinical outcome and whether it decreases the exposure to steroids.

Design, Setting, and Patients REDUCE (Reduction in the Use of Corticosteroids in Exacerbated COPD), a randomized, noninferiority multicenter trial in 5 Swiss teaching hospitals, enrolling 314 patients presenting to the emergency department with acute COPD exacerbation, past or present smokers (≥ 20 pack-years) without a history of asthma, from March 2006 through February 2011.

Interventions Treatment with 40 mg of prednisone daily for either 5 or 14 days in a placebo-controlled, double-blind fashion. The predefined noninferiority criterion was an absolute increase in exacerbations of at most 15%, translating to a critical hazard ratio of 1.515 for a reference event rate of 50%.

Main Outcome and Measure Time to next exacerbation within 180 days.

Results Of 314 randomized patients, 289 (92%) of whom were admitted to the hospital, 311 were included in the intention-to-treat analysis and 296 in the per-protocol analysis. Hazard ratios for the short-term vs conventional treatment group were 0.95 (90% CI, 0.70 to 1.29; $P = .006$ for noninferiority) in the intention-to-treat analysis and 0.93 (90% CI, 0.68 to 1.26; $P = .005$ for noninferiority) in the per-protocol analysis, meeting our noninferiority criterion. In the short-term group, 56 patients (35.9%) reached the primary end point; 57 (36.8%) in the conventional group. Estimates of reexacerbation rates within 180 days were 37.2% (95% CI, 29.5% to 44.9%) in the short-term; 38.4% (95% CI, 30.6% to 46.3%) in the conventional, with a difference of -1.2% (95% CI, -12.2% to 9.8%) between the short-term and the conventional. Among patients with a reexacerbation, the median time to event was 43.5 days (interquartile range [IQR], 13 to 118) in the short-term and 29 days (IQR, 16 to 85) in the conventional. There was no difference between groups in time to death, the combined end point of exacerbation, death, or both and recovery of lung function. In the conventional group, mean cumulative prednisone dose was significantly higher (793 mg [95% CI, 710 to 876 mg] vs 379 mg [95% CI, 311 to 446 mg], $P < .001$), but treatment-associated adverse reactions, including hyperglycemia and hypertension, did not occur more frequently.

Conclusions and Relevance In patients presenting to the emergency department with acute exacerbations of COPD, 5-day treatment with systemic glucocorticoids was noninferior to 14-day treatment with regard to reexacerbation within 6 months of follow-up but significantly reduced glucocorticoid exposure. These findings support the use of a 5-day glucocorticoid treatment in acute exacerbations of COPD.

Trial Registration isrctn.org Identifier: ISRCTN19646069

JAMA. 2013;309(21):2223-2231

Published online May 21, 2013. doi:10.1001/jama.2013.5023

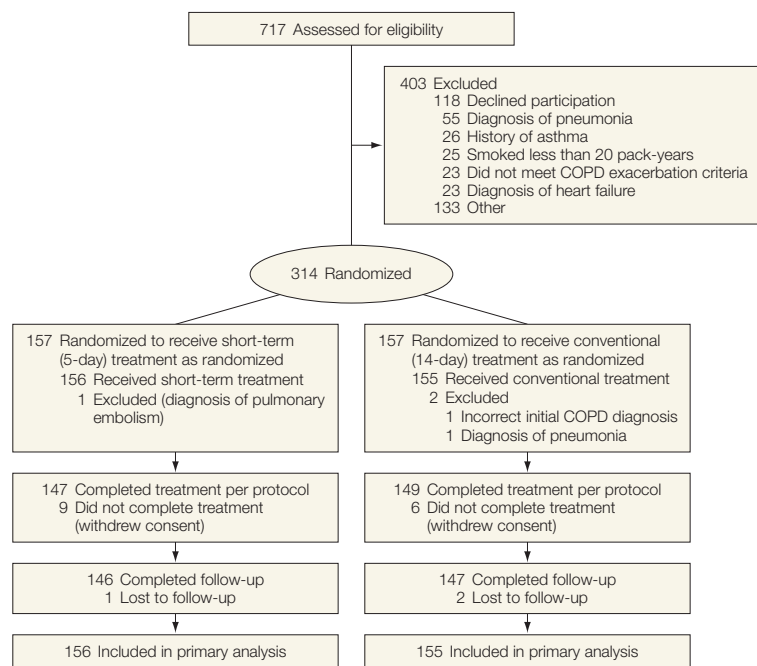
www.jama.com

For editorial comment see p 2272.

Author Audio Interview available at www.jama.com.

of acute exacerbations of COPD (eg, 30-40 mg of oral prednisolone for 10-14 days).⁵⁻⁷ Randomized clinical

Author Affiliations are listed at the end of this article. **Corresponding Author:** Jonas Rutishauser, MD, Department of Medicine, Clinic of Internal Medicine, Hospital Center, Vogelsang 84, CH-2501 Biel-Bienne, Switzerland (j.rutishauser@unibas.ch).

Figure 1. Flow of Patients Through the REDUCE Trial

Patients who were lost to follow-up between the end of intervention (day 14) and end of the study (day 180) were included in both the intention-to-treat and the per-protocol analyses and censored at the time of last study visit.

trials have shown that glucocorticoid therapy benefits clinical outcome,⁸⁻¹¹ reduces the length of hospital stay,^{9,10} and accelerates recovery of FEV₁ (forced expiratory volume in the first second).⁸⁻¹⁰ However, the optimal dose and duration of systemic glucocorticoids are not known. Observational data suggest that low-dose oral regimens are not associated with worse outcomes than high-dose intravenous treatment.¹² A recent Cochrane⁶ review of 7 studies including a total of 281 patients with exacerbated COPD found no significant differences in clinical outcome between short duration (≤ 7 days) and longer duration (> 7 days) of glucocorticoid treatment.

Long-term use of systemic glucocorticoids is an independent risk factor for increased mortality in COPD.¹³ Given the adverse effects of glucocorticoids and the potentially large number of exacerbations occurring in patients with COPD, glucocorticoid exposure should be minimized.¹⁰

Although it has become quite common clinical practice to administer glucocorticoids in COPD exacerbations for shorter periods, an adequately powered randomized clinical trial comparing reduced with recommended treatment duration has not been published. The REDUCE trial tested the hypothesis that in patients presenting to the emergency department with acute exacerbation of COPD, a 5-day course of systemic glucocorticoid treatment would not result in an inferior clinical outcome compared with conventional 14-day treatment, but would significantly decrease glucocorticoid exposure and reduce untoward effects.

METHODS

Study Design and Patients

The trial was approved by the institutional review boards of participating hospitals. All patients provided written informed consent. This study report adheres to the consolidated standards for the reporting of noninferiority

trials.¹⁷ The design of this investigator-initiated noninferiority trial has been published in detail.¹⁴ From March 2006 through February 2011, consecutive patients with exacerbated COPD were screened for eligibility at the emergency departments of 5 Swiss teaching hospitals. Inclusion criteria were exacerbation of COPD as defined by the presence of at least 2 of the following: change in baseline dyspnea, cough, or sputum quantity or purulence,^{15,16} age older than 40 years, and a smoking history of 20 pack-years or more. Exclusion criteria were a history of asthma, ratio of FEV₁ to forced vital capacity (FVC) greater than 70% as evaluated by bedside postbronchodilator spirometry prior to randomization, radiological diagnosis of pneumonia, estimated survival of less than 6 months due to severe comorbidity, pregnancy or lactation, and inability to give written informed consent.

Study Drugs, Randomization, and Masking

Eligible patients were randomly assigned either 5 or 14 days of systemic glucocorticoids using a centralized, secured study website in order to ensure allocation concealment (FIGURE 1). Allocation according to a computer-generated randomization list (nQuery Advisor, version 6.0; Statistical Solutions Ltd) was based on age-stratified blocks of 6, presence or absence of systemic glucocorticoid treatment prior to study entry (defined as daily therapy over 2 days or more directly before the day of inclusion), severity of COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification,¹⁸ and trial site. All patients received 40 mg of intravenous methylprednisolone on day 1, followed by 40 mg of oral prednisone daily from day 2 through 5. Patients received study glucocorticoid dose irrespective of possible pretreatment. The first dose was given intravenously to facilitate administration to patients in distress. From day 6 through 14, patients received 40 mg of oral prednisone or matching placebo once daily. Patients, caregivers, outcome assessors,

data collectors, the biostatistician, and all other investigators remained blinded to group allocation until the primary analysis was completed.

Procedures

In addition to the study medication, all patients received a broad-spectrum antibiotic for 7 days and an inhaled, nebulized, short-acting bronchodilator 4 to 6 times daily as needed while hospitalized. Inhaled glucocorticoids twice daily combined with inhaled β_2 -agonist twice daily plus tiotropium 18 μ g once daily were given throughout the study. Physiotherapy, supplemental oxygen, and ventilatory support were administered according to American Thoracic Society/European Respiratory Society guidelines.¹⁶ Additional glucocorticoids could be administered at the discretion of the treating physicians. End points were assessed daily during hospitalization, as well as on days 6, 15, 30, 90, and 180. On days 15 and 90, assessment was by telephone interview only.

End Points

The primary end point of this trial was time to next COPD exacerbation during a follow-up of 6 months, defined as an acute clinical deterioration beyond usual day-to-day variation, requiring interaction with a clinician.¹⁹ This could occur during the index exacerbation (ie, requiring open-label systemic glucocorticoids or other intensified treatment while patients were still hospitalized), or during follow-up.

Secondary end points were all-cause mortality, change in FEV₁, cumulative glucocorticoid dose, and clinical performance (assessed using questionnaires for the Medical Research Council dyspnea scale,²⁰ a bronchitis-associated quality-of-life score,²¹ and patient-reported overall performance using a visual analog scale), all assessed at the index exacerbation and during 6 months of follow-up. We assessed duration of hospital stay, time to open-label glucocorticoid therapy, and need for mechanical ventilation (intubation or noninvasive ventilation)

during the index exacerbation. We also assessed glucocorticoid-associated adverse effects (including new or worsening hyperglycemia), defined as fasting plasma glucose of 100 mg/dL (to convert to millimoles per liter, multiply by 0.0555) or greater, random plasma glucose of 140 mg/dL or greater, an increase of 20% or more in daily doses of insulin, any increase in oral antidiabetic drugs, initiation of 1 or more antidiabetic therapeutic principles, new or worsening hypertension (defined as blood pressure \geq 140 mm Hg systolic, \geq 90 mm Hg diastolic, or both) or the addition of 1 or more antihypertensive drugs to previous treatment regimens (all assessed during the index exacerbation), newly diagnosed infection, and other potentially glucocorticoid-related adverse events (assessed during the index exacerbation and during follow-up of 6 months).

Statistical Analysis

We used a modified Delphi technique to define noninferiority regarding the primary end point. Based on the judgment of 11 board-certified specialists, we defined a 15% absolute difference in the percentage of patients with a re-exacerbation during the 6 months of follow-up as the clinically tolerable upper limit. Based on previously published data,^{10,22} we assumed that approximately 50% of patients would experience an exacerbation during follow-up. Therefore, according to our noninferiority definition, the true proportion of patients under experimental (5 days) treatment experiencing a COPD exacerbation must not exceed 65%, which translates to a critical hazard ratio (HR) of 1.515 based on an exponential proportional hazards survival model.¹⁴

During the study, observed loss to follow-up was much lower (<4%) than expected (20%). Assuming 5% loss to follow-up, an α error of 5%, and a power of 85%, we needed to recruit 150 patients in each study group.

Statistical analyses were done with SAS (SAS Institute, version 9.3) and

Stata (StataCorp, version 12). Categorical variables are summarized by absolute numbers and percentages of total. Differences in time to next exacerbation or time to death were assessed using the Kaplan-Meier method in combination with the log-rank test and Cox proportional hazards models. The proportional hazard assumption was tested using Schoenfeld residuals. Noninferiority was concluded if the 2-sided, 90% confidence interval for the HR between the short-term and the conventional treatment group in an intention-to-treat and per-protocol analysis was below 1.515, which corresponds to an α level of 5%. Because differences between the 2 survival curves might appear mainly at the beginning of follow-up (which would be in contradiction to the proportional hazard assumption), we also estimated the difference in average event-free survival time over 180 days between short-term and conventional therapy by first determining the area under each of the 2 survival curves up to 180 days and then taking their difference. Patients lost to follow-up were censored at the time of last contact. Differences in categorical variables were assessed with the χ^2 test or Fisher exact test. Differences in cumulative dose of steroids were analyzed with the Mann-Whitney *U* test and bootstrap *t* tests. To compare length of hospital stay, we used the log-rank test, excluding individuals who were discharged from the emergency department, died, or withdrew consent during hospitalization. The time course of clinical parameters (FEV₁, dyspnea scale, quality-of-life score, self-assessed performance) was analyzed using mixed linear models. Time and group were treated as categorical variables. Their interaction was also included in the model and served to test the null hypothesis of parallel time course patterns. An unstructured covariance matrix was used to model correlations of residuals within participants. Conventional null hypotheses on single parameters were tested using 2-tailed tests. For the main outcome, noninferiority

was additionally assessed by a 1-tailed Wald test of the difference between the observed HR and 1.515. Potential interactions between treatment and other factors, also used to assess heterogeneity of results across subgroups, were tested using likelihood ratio tests for time-to-event outcomes and *F* tests for quantitative outcomes. Statistical significance was defined at the level of 5%. After approximately half of the intended number of patients had completed the study, an independent data and

safety monitoring board performed a preplanned interim safety analysis. Based on their findings, they advocated completion of the study without safety concerns.

RESULTS

Baseline characteristics of participants are summarized in TABLE 1, and results for the primary and secondary end points in TABLE 2 and TABLE 3. eTable 1 (available at <http://www.jama.com>) shows estimates of the risks of reexacerbation, death, and the com-

bined end point reexacerbation or death. eTable 2A and eTable 2B show the results of sensitivity analyses for the primary end point adjusted for baseline variables.

Baseline Characteristics

Of 717 patients evaluated for eligibility, 314 underwent randomization (Figure 1). Three patients were excluded after randomization in a blinded fashion because of erroneous initial COPD diagnoses. The data from the remaining 311 patients were used for all intention-to-treat analyses. A total of 296 patients completed the 14-day treatment period according to study protocol and were included in the per-protocol analysis. Twelve patients (7.7%) in the short-term group and 13 patients (8.4%) in the conventional treatment group were discharged directly from the emergency department and treated as outpatients ($P = .84$).

The 2 treatment groups were well balanced in terms of age, severity of airway obstruction, and pretreatment with glucocorticoids (Table 1). There were more women in the conventional group than in the short-term treatment group (46.5% vs 32.7%; $P = .02$); the other baseline variables did not differ significantly between groups.

Primary End Point

The median number of days of follow-up in the conventional group was 180 (10th percentile, 179; 90th percentile, 181 days) and 180 in the short-term group (10th percentile, 178; 90th percentile, 181 days). A total of 56 patients (35.9%) reached the primary end point of COPD exacerbation in the short-term treatment group compared with 57 patients (36.8%) in the conventional treatment group. Time to reexacerbation did not differ between groups as demonstrated in the Kaplan-Meier plots (FIGURE 2). In a Cox regression analysis, the HR of reexacerbation between the short-term and conventional treatment group was 0.95 (90% CI, 0.70 to 1.29; $P = .006$) in the intention-to-treat and 0.93 (90% CI, 0.68 to 1.26; $P = .005$) in the per-

Table 1. Baseline Characteristics of Study Participants

	Conventional Treatment (n = 155)	Short-term Treatment (n = 156)
Age, mean (SD), y	69.8 (10.6)	69.8 (11.3)
Women, No. (%) ^a	72 (46.5)	51 (32.7)
Smokers, No. (%)		
Current	62 (40)	77 (49.4)
Past	93 (60)	79 (50.6)
Pack-years smoked, median (IQR), y	45 (30-60)	50 (40-60)
FEV ₁ mean (SD), % predicted	31.3 (13.2)	31.7 (15.4)
GOLD COPD grade, No. (%) ^b		
1	0	1 (0.6)
2	18 (12.1)	22 (14.5)
3	53 (35.6)	45 (29.6)
4	78 (52.3)	84 (55.3)
Medical Research Council dyspnea scale, No. (%) ^c		
1	4 (2.8)	4 (2.7)
2	14 (9.8)	13 (8.8)
3	15 (10.5)	23 (15.5)
4	43 (30.1)	45 (30.4)
5	67 (46.9)	63 (42.6)
Home oxygen therapy, No. (%)	16 (10.6)	24 (15.5)
Pretreatment with systemic glucocorticoids, No. (%) ^d	28 (18.5)	35 (22.6)
Pretreatment daily prednisone dose, median (IQR), mg	15 (5-45)	20 (10-50)
Pretreatment with antibiotics, No. (%) ^e	21 (14.0)	32 (21.9)
Clinical variables, median (IQR)		
Blood pressure, mm Hg		
Systolic blood pressure	138 (124-158)	139 (124-160)
Diastolic blood pressure	80 (70-87.5)	80 (71-91)
Heart rate, beats/min	90 (79-105)	92 (80-106)
Oxygen saturation with nasal oxygen, %	95 (92-97)	95 (92-96)
Oxygen saturation without nasal oxygen, %	90 (85-93)	90 (86-94)
Leukocyte count, 10 ³ /μL	10.1 (7.5-13.6)	10.3 (8.3-13.3)

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in the first second; GOLD, Global Initiative for Chronic Obstructive Lung Disease; IQR, interquartile range.

^a $P = .02$.

^bAirflow limitation according to GOLD COPD grading: 1, mild; 2, moderate; 3, severe; 4, very severe.

^cGrading for severity of breathlessness according to the Medical Research Council questionnaire: 1, breathless only with strenuous exercise; 2, short of breath when hurrying on the level or up a slight hill; 3, walking slower than people of the same age on the level because of breathlessness, or stop for breath when walking at own pace on the level; 4, stop for breath after walking 100 yards or after a few minutes on the level; 5, too breathless to leave the house.

^dData refer to treatment prior to index acute COPD exacerbation, defined as daily therapy over 2 days or more directly before the day of inclusion.

^eData refer to treatment for the index acute COPD exacerbation.

protocol analysis, meeting our noninferiority criterion (Table 2). Among patients who experienced a reexacerbation during follow-up, the median time to event was 43.5 days (interquartile range [IQR], 13-118) in the short-term and 29 days (IQR, 16-85) in the conventional treatment group. Estimates of re-exacerbation rates were 37.2% (95% CI, 29.5% to 44.9%) in the short-term and 38.4% (95% CI, 30.6% to 46.3%) in the conventional treatment group, with a difference of -1.2% (95% CI, -12.2% to 9.8%) (eTable 1). Sensitivity analyses adjusting for baseline variables, including sex, provided similar results (eTable 2).

In a prespecified subgroup analysis, we also investigated differences in the primary

Table 2. Results for the Primary End Point

Primary End Point	Event Frequencies, No. (%)		Hazard Ratio (90% CI)	P Value ^a
	Conventional Treatment (n = 155)	Short-term Treatment (n = 156)		
Reexacerbations				
Intention to treat	57 (36.8)	56 (35.9)	0.95 (0.70-1.29)	.006
Per protocol	57 (38.3)	54 (36.7)	0.93 (0.68-1.26)	.005
Subgroup analyses ^b				
GOLD grade				
1 and 2 ^c	6 (33.3)	6 (26.1)	0.73 (0.28-1.88)	.10
3 ^c	19 (35.9)	15 (33.3)	0.93 (0.52-1.67)	.08
4 ^c	31 (39.7)	34 (40.5)	0.99 (0.66-1.49)	.04
Glucocorticoid pretreatment				
Yes	13 (46.4)	16 (45.7)	0.93 (0.50-1.72)	.09
No	44 (35.8)	40 (33.3)	0.88 (0.61-1.26)	.006

Abbreviation: GOLD, Global Initiative for Chronic Obstructive Lung Disease.

^aP value for noninferiority.

^bAnalyses were intention to treat. There was no evidence of heterogeneity in hazard ratios across subgroups (for GOLD grade, *P* = .82; for glucocorticoid pre treatment status, *P* = .93).

^cAirflow limitation according to GOLD chronic obstructive pulmonary disease grading: 1, mild; 2, moderate; 3, severe; 4, very severe.

Table 3. Results for Secondary End Points^a

Secondary End Point	No. (%) of Patients		Comparison Measure (95% CI) ^b	P Value
	Conventional Treatment (n = 155)	Short-term Treatment (n = 156)		
Deaths during follow-up	13 (8.4)	12 (7.7)	HR, 0.93 (0.40 to 2.20)	.87 ^c
Need for mechanical ventilation	21 (13.6)	17 (11.0)	OR, 0.78 (0.37 to 1.63)	.49 ^d
Time to open-label glucocorticoid therapy during index exacerbation, median (IQR), d	9 (5 to 15)	6 (5 to 10)		.52 ^e
Mean, d	10	7.8	Difference in means, -2.2 (-7.9 to 3.5)	.43 ^f
Patients receiving open-label glucocorticoids during index exacerbation	13 (8.4)	9 (5.8)	OR, 0.67 (0.28 to 1.61)	.39 ^d
Cumulative prednisone dose, median (IQR), mg ^{g,h}	560 (560 to 773)	200 (200 to 310)		<.001 ^e
Mean, mg	793	379	Difference in means, -414 (-521 to -307)	<.001 ^f
Patients receiving additional glucocorticoids during follow-up ^g	64 (44.4)	54 (36.5)	OR, 0.72 (0.45 to 1.15)	.19 ^d
Additional prednisone dose during follow-up, median (IQR), mg ^{g,h}	250 (77.5 to 707.5)	258 (100 to 640)		.85 ^e
Mean, mg	524	490	Difference in means, -34 (-264 to 196)	.77 ^f
Diagnoses of infection	44 (28.4)	44 (28.2)	OR, 0.99 (0.59 to 1.67)	>.99 ^d
New or worsening hyperglycemia at discharge	74 (57.4)	74 (56.9)	OR, 0.98 (0.58 to 1.66)	>.99 ^d
New or worsening hypertension at discharge	23 (17.8)	15 (11.6)	OR, 0.61 (0.28 to 1.29)	.22 ^d
Occurrence of other potential glucocorticoid adverse effects ⁱ	18 (11.6)	18 (11.5)	OR, 0.99 (0.47 to 2.12)	>.99 ^d
Duration of hospital stay, median (IQR), d ^j	9 (6 to 14)	8 (5 to 11)	HR, 1.25 (0.99 to 1.59)	.04 ^c
Mean, d	10.8	9.3		

Abbreviations: HR, hazard ratio; IQR, interquartile range; OR, odds ratio.

^aAnalyses are intention to treat, unless specified otherwise.

^bComparison between conventional and short-term treatment with 95% CI.

^cLog-rank test.

^dFisher exact test.

^eMann-Whitney *U* test.

^fBootstrap *t* test for difference in means.

^gOnly patients with complete follow-up data were included in these analyses (conventional treatment group, 144; short-term treatment group, 148).

^hAmong patients having received additional glucocorticoids during follow-up.

ⁱGastrointestinal tract bleeding, symptomatic gastrointestinal reflux, symptoms of congestive heart failure or ischemic heart disease, sleep disturbance, fractures, and depression were considered as potentially related to glucocorticoid treatment.

^jPatients discharged from the emergency department and patients who died or withdrew consent during hospitalization were excluded from these analyses.

outcome between patients with and without previous systemic glucocorticoid use and with different severities of COPD according to GOLD grade. All subgroup HRs were also smaller than 1 (Table 2), and we found no evidence of heterogeneity across subgroups (for GOLD grade, $P = .82$; for glucocorticoid pretreatment status, $P = .93$).

We calculated the areas under the survival curves (AUC) to quantify the difference in average event-free survival. In the intention-to-treat analysis, estimates of AUC were 135.5 days (95% CI, 125.2-145.8) in the short-term group and 130.7

days (95% CI, 119.2-141.7) in the conventional treatment group. If analyzed per protocol, the AUCs were 135.8 days (95% CI, 125.3-146.3) for the short-term group and 129.7 days (95% CI, 118.5-140.9) for the conventional group.

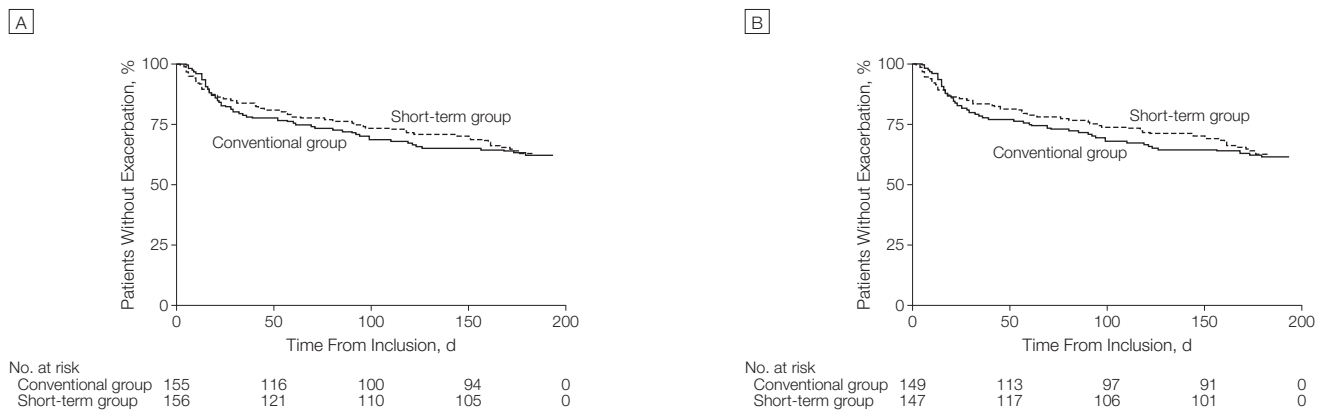
Secondary End Points

Overall survival did not differ between the treatment groups, as evidenced by Kaplan-Meier plots (FIGURE 3). The HRs for death for short-term compared with standard treatment were 0.93 (95% CI, 0.40-2.20, $P = .87$) in the intention-to-treat and

0.95 (95% CI, 0.40-2.25, $P = .91$) in the per-protocol analysis (Table 3, eTable 1).

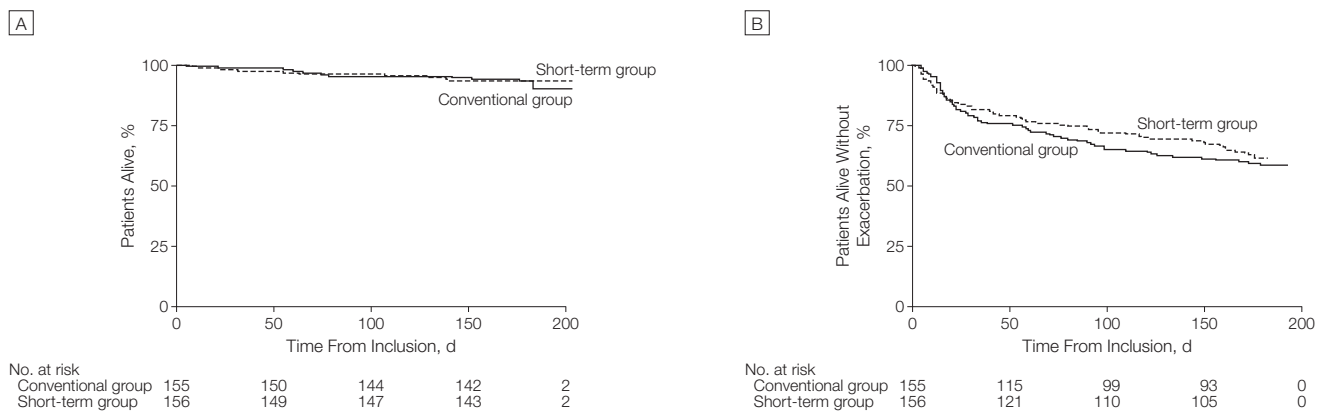
During hospital stay, there was no increase in the requirement for mechanical ventilation with the short-term treatment regimen. Patients under short-term treatment had a shorter hospital stay with a median of 8 days (IQR, 5-11; 95% CI, 7-9), compared with 9 days (IQR, 6-14; 95%-CI, 8-10) in the conventional treatment group ($P = .04$). The FEV₁ improved significantly in both groups between baseline and day 6 ($P < .001$ for difference) and re-

Figure 2. Time to Reexacerbation of Chronic Obstructive Pulmonary Disease



A, Proportions of patients without reexacerbation in the intention-to-treat analysis. B, Proportions of patients without reexacerbation in the per-protocol analysis. Survival curves did not differ significantly when compared by the log-rank test. Hazard ratios for the short-term vs conventional treatment group were 0.95 (90% CI, 0.70-1.29; P for noninferiority = .006) in the intention-to-treat analysis and 0.93 (90% CI, 0.68-1.26; P for noninferiority = .005) in the per-protocol analysis. P values were obtained using the Wald test.

Figure 3. Overall Survival of Patients With Chronic Obstructive Pulmonary Disease



A, Proportion of patients alive (intention-to-treat analysis). B, The survival curve for the combined outcome death, reexacerbation, or both. Survival curves did not differ significantly when compared by the log-rank test ($P = .87$ for time to death, $P = .57$ for time to reexacerbation or death).

mained stable thereafter (FIGURE 4). In a longitudinal analysis, there were almost no differences between groups. Similarly, significant amelioration of dyspnea (eFigure 1A), bronchitis-associated quality of life (eFigure 1B), and patient-assessed overall performance (eFigure 1C) occurred during the first 5 days of the study; respective scores did not change significantly thereafter.

The number of patients receiving open-label glucocorticoid therapy during the index exacerbation and during follow-up did not differ between treatment groups, nor did time to open-label glucocorticoid therapy during the index exacerbation and additional steroid dose after completion of the study medication (Table 3). In an analysis of patients with complete follow-up data, the short-term group had a median of 200 mg (IQR, 200-310) and mean cumulative prednisone dose of 379 mg (95% CI, 311-446 mg); the conventional treatment group had a median of 560 mg (IQR, 560-773) and mean cumulative prednisone dose of 793 mg (95% CI, 710-876 mg), $P < .001$.

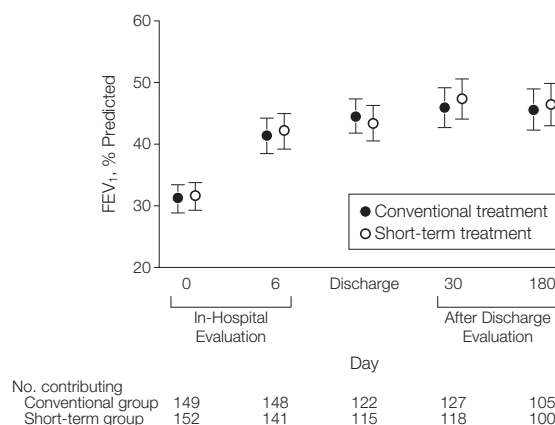
Blood glucose concentrations and blood pressure were assessed daily during the hospital stay. Hypertension developed or worsened in 15 patients (11.6%) in the short-term group and 23 patients (17.8%) in the conventional treatment group ($P = .22$). New or worsened hyperglycemia was observed in 74 patients (56.9%) in the short-term group and 74 (57.4%) in the conventional group, ($P > .99$; Table 3). We did not observe differences in infection rates and other potentially glucocorticoid-associated adverse effects such as gastrointestinal bleeding, insomnia, fractures, psychiatric symptoms, or heart failure.

DISCUSSION

To date, data proving clinical noninferiority of short-term glucocorticoid therapy in acute exacerbation of COPD have been insufficient.^{6,23}

Our results show that in patients with exacerbations requiring hospital admission, a 5-day treatment course of 40

Figure 4. Measures of Forced Expiratory Volume in One Second



Time course of forced expiratory volume in the first second (FEV₁), assessed at study entry and hospital discharge, as well as on follow-up days on which patients were seen for clinical visits. Data markers represent the mean and the error bars, 95% CI. Numbers contributing data at study day 0 were smaller than the number of randomized subjects because of missing data from severely ill patients. Data from patients discharged from the emergency department contributed to the time point 0 but not discharge. Hospitalized patients who were discharged within 5 days returned to the trial site and contributed data on day 6. Time points included in the discharge data ranged from 1 to 37 days, according to the length of hospital stay. In the full factorial model with factors group and time, the interaction between group and time was not significant ($P = .51$). In the main effects model, the factor time was significant ($P < .001$), whereas the factor group was nonsignificant ($P = .94$).

mg of prednisone daily is noninferior to a 14-day treatment course with respect to reexacerbation. We chose time to next exacerbation as a clinically meaningful primary end point because, as evidenced by the Systemic Corticosteroids in Chronic Obstructive Pulmonary Disease Exacerbations (SCCOPE) trial, the benefit of glucocorticoid therapy on treatment failure rate diminishes during follow-up and is no longer different from placebo after 180 days.¹⁰ We therefore expected to observe differences between groups in the first few weeks of follow-up, if at all. As in earlier trials,^{9,10} we observed rapid improvement of FEV₁ by about one-third after 5 days of treatment. There were no detectable differences in expiratory volume between groups at any time. Similarly, dyspnea, quality of life, and self-assessed overall performance improved markedly during the first 5 days of the study, with minute differences between treatment groups at any time. Notably, duration of hospital stay was significantly shorter in the 5-day treatment group. Because we did not observe significant differences in glucocorticoid-

related, short-term adverse effects, we cannot readily explain this observation, which might be a chance finding.

Our study has several limitations. When we designed this noninferiority trial, there was no standard glucocorticoid regimen for the treatment of exacerbated COPD. In the SCCOPE trial,¹⁰ patients received an approximate cumulative dose of 2.6 g of prednisone equivalent in the 8-week intervention group or 2 g of prednisone-equivalent in the 2-week intervention group. Since adverse effects of glucocorticoids correlate with the cumulative dose, we chose a lower dose for the conventional treatment group. Another randomized clinical trial compared 40 mg of prednisone for 10 days with placebo in patients who were admitted to the emergency department and treated on an outpatient basis.¹¹ Relapse rates in the active group were 27% and 43% in the control group. In our study, the reexacerbation rate in both groups was about one-third, indicating a sufficient glucocorticoid dose.

Patients in our trial were treated with inhaled, long-acting β -agonists, gluco-

corticoids, and tiotropium throughout the study period. Therefore, some of them may have been overtreated based on current guidelines, which may explain the lower than expected reexacerbation rates, implying that our power estimates may have been too high. Nevertheless, our results strongly support the hypothesis of noninferiority.

Although we observed less hypertensive patients in the short-term treatment group, the difference between groups was not significant. For the detection of hyperglycemia and hypertension, we focused on the hospitalization period, during which these parameters were assessed daily, excluding reporting bias. We surmise that the length of hospital stay was insufficient to detect significant differences in blood pressure and blood glucose levels between groups, because these glucocorticoid adverse effects do not develop immediately after initiation of treatment.

All patients in our study received antibiotic treatment regardless of sputum purulence or procalcitonin levels,²⁴ which may not always have complied with current guidelines. By standardizing disease management in the acute and follow-up phases, we aimed at eliminating all possible confounding factors so that any potential difference in outcome could be attributed to the different glucocorticoid treatment regimes.

Most of our patients had severe or very severe COPD; therefore, our results cannot necessarily be applied to less severe disease grades. However, it seems unlikely that patients with GOLD grades 1 and 2 would benefit from longer glucocorticoid treatment for COPD exacerbations. Finally, all our patients were current or past smokers. Although we presume that our findings equally apply to never smokers with COPD (approximately 30% of the Swiss COPD population),²⁵ we cannot formally prove this assumption.

In summary, in our study a 5-day glucocorticoid treatment course was noninferior to a 14-day course with respect to reexacerbation during 6 months of follow-up. There was no sig-

nificant difference in recovery of lung function and disease-related symptoms, but the shorter course resulted in a significantly reduced glucocorticoid exposure.

Published Online: May 21, 2013. doi:10.1001/jama.2013.5023

Author Affiliations: Clinic of Internal Medicine (Drs Leuppi, Drescher, Miedinger, Scherr, and Ms Maier), Interdisciplinary Emergency Department (Drs Bingisser and Bodmer), Basel Institute for Clinical Epidemiology and Biostatistics (Dr Briel), Clinic of Endocrinology, Diabetology, and Metabolism (Drs Drescher, Stoekli, and Ms Duerring), and Clinic of Pneumology (Drs Scherr and Tamm), University Hospital of Basel, Switzerland; Medical University Clinic, Kantonsspital, Aarau, Switzerland (Drs Schuetz and Mueller); Department of Internal Medicine, Kantonsspital, Luzern, Switzerland (Dr Henzen); Biozentrum (Dr Rutishauser) and Swiss Tropical and Public Health Institute (Dr Schindler), University of Basel, Switzerland; Arthritis Research UK Epidemiology Unit, Manchester Academic Health Science Center, the University of Manchester, United Kingdom (Dr Viatte); Respiratory Medicine Clinic, University Hospital Bern, Inselspital, Switzerland (Dr von Garnier); and Department of Medicine, Clinic of Internal Medicine, Hospital Center of Biel-Bienne, Switzerland (Drs Rutishauser, Viatte, and Ms Leibbrandt).

Author Contributions: Drs Rutishauser and Schindler had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Leuppi and Schuetz contributed equally.

Study concept and design: Leuppi, Schuetz, Bingisser, Briel, Müller, Schindler, Tamm, Rutishauser.

Acquisition of data: Leuppi, Schuetz, Bingisser, Bodmer, Briel, Drescher, Duerring, Henzen, Leibbrandt, Maier, Miedinger, Scherr, Stoekli, Viatte, von Garnier, Tamm, Rutishauser.

Analysis and interpretation of data: Leuppi, Schuetz, Bingisser, Briel, Leibbrandt, Schindler, Viatte, Tamm, Rutishauser.

Drafting of the manuscript: Leuppi, Schuetz, Bodmer, Müller, Schindler, Rutishauser.

Critical revision of the manuscript for important intellectual content: Schuetz, Bingisser, Bodmer, Briel, Drescher, Duerring, Henzen, Leibbrandt, Maier, Miedinger, Müller, Scherr, Schindler, Stoekli, Viatte, von Garnier, Tamm, Rutishauser.

Statistical analysis: Schuetz, Briel, Schindler.

Obtained funding: Leuppi, Schuetz, Bingisser, Henzen, Rutishauser.

Administrative, technical, or material support: Leuppi, Bingisser, Drescher, Duerring, Leibbrandt, Maier, Scherr, Stoekli, Tamm, Rutishauser.

Study supervision: Leuppi, Bingisser, Briel, Henzen, Leibbrandt, Müller, Tamm, Rutishauser.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Leuppi reported receiving grants from Freie Akademische Gesellschaft, Gottfried und Julia Bangerter-Rhyner-Stiftung, AstraZeneca, and the Clinic for Internal Medicine at the University Hospital Basel; serving as board member of Merck Sharp & Dohme Chibret, Nycomed, and Novartis; consulting for Merck Sharp & Dohme Chibret; pending grants with Boehringer Ingelheim and AstraZeneca; payment for lectures from Boehringer Ingelheim, Merck Sharp & Dohme Chibret, Nycomed, and Pharmaxis; and receiving payment for developing educational presentations for AstraZeneca. Dr Schuetz reported receiving consulting and lecture fees from Thermo Fisher Scientific and bioMerieux. Dr Bingisser reported being a board member for Daiichi Sankyo, Eli Lilly, Merck Sharp & Dohme

Chibret, GE, Philipps, and sanofi-aventis; receiving grants from Bayer, Pfizer, and Brahms; payment for lectures from AstraZeneca; and patents pending with Brahms. Dr Rutishauser reported receiving grants from the Department of Medicine at the University Hospital of Basel, the Clinic of Internal Medicine at the Hospital Center of Biel-Bienne, Freiwillige Akademische Gesellschaft, Fonds für Lehre und Forschung, AstraZeneca, Viollier Laboratories, and Gottfried und Julia Bangerter-Rhyner-Stiftung; serving as board member for the Swiss Society of General Internal Medicine; employment with the Hospital Center of Biel-Bienne; grants pending from the Swiss National Science Foundation; and payment for lectures in various Swiss hospitals. No other disclosures were reported.

Funding/Support: The REDUCE trial was an investigator-initiated study supported by the Department of Medicine, University Hospital Basel; the Clinic of Internal Medicine, Hospital Center of Biel-Bienne; Freie Akademische Gesellschaft; Fonds für Lehre und Forschung; AstraZeneca; Viollier Laboratory; Gottfried und Julia Bangerter-Rhyner-Stiftung für Medizinische Forschung.

Role of the Sponsor: None of the sponsors had any role in design and conduct of the study; collection, management, analysis and interpretation of the data; and preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

The REDUCE Study Group Collaborators: Sandrina Bervini, MD, Konstantin Burgmann, MD, Linh Dang, MD, Silvia Ernst, MD, Sandra Fatio, MD, Michael Grob, MD, Harold Köndgen, MD, Anne-Chantal Lambert, MD, Susanne Nüesch, MD, Philipp Oswald, MD, Madeleine Rothen, MD, Jörg Salomon, MD, Julian Schardt, MD, Michael Schäfer, MD, Lucien Weiss, MD (Department of Medicine, Clinic of Internal Medicine, Hospital Center of Biel-Bienne).

Online-Only Material: eTables, eFigures, and the Author Audio Interview are available at <http://www.jama.com>.

Additional Contributions: We thank Jürgen Drewe, MD, and Simon Spitzmüller, MD (University Hospital Basel), for programming and testing the randomization code. We are grateful to Ursula Schild, RN, Katharina Regez, RN, Vreni Wyss, RN, (University Hospital Basel), Monika Wüthrich, RN (University Hospital Bern), and Gaby Fahrni, RN (Kantonsspital Luzern), for expert nursing support. All acknowledged persons received compensations within the scope of their regular employment as physicians or study nurses.

REFERENCES

- Hansel TT, Barnes PJ. New drugs for exacerbations of chronic obstructive pulmonary disease. *Lancet*. 2009;374(9691):744-755.
- Soler-Cataluña JJ, Martínez-García MA, Román Sánchez P, Salcedo E, Navarro M, Ochando R. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. *Thorax*. 2005;60(11):925-931.
- Jochmann A, Neubauer F, Miedinger D, Schafroth S, Tamm M, Leuppi JD. General practitioner's adherence to the COPD GOLD guidelines: baseline data of the Swiss COPD Cohort Study. *Swiss Med Wkly*. 2010;140:w13053.
- Jochmann A, Scherr A, Jochmann DC, et al. Impact of adherence to the GOLD guidelines on symptom prevalence, lung function decline and exacerbation rate in the Swiss COPD cohort. *Swiss Med Wkly*. 2012;142:w13567.
- Wouters EF. Management of severe COPD. *Lancet*. 2004;364(9437):883-895.
- Walters JAE, Wang W, Morley C, Soltani A, Wood-Baker R. Different durations of corticosteroid therapy for exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2011;(10):CD006897.
- Global Initiative for Chronic Obstructive Lung

Disease. Global strategy for the diagnosis, management and prevention of COPD. <http://www.goldcopd.org/guidelines/guidelines-resources.html>. Accessed April 18, 2013.

8. Thompson WH, Nielson CP, Carvalho P, Charan NB, Crowley JJ. Controlled trial of oral prednisone in outpatients with acute COPD exacerbation. *Am J Respir Crit Care Med*. 1996;154(2 pt 1):407-412.
9. Davies L, Angus RM, Calverley PM. Oral corticosteroids in patients admitted to hospital with exacerbations of chronic obstructive pulmonary disease: a prospective randomised controlled trial. *Lancet*. 1999;354(9177):456-460.
10. Niewoehner DE, Erbland ML, Deupree RH, et al; Department of Veterans Affairs Cooperative Study Group. Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease. *N Engl J Med*. 1999;340(25):1941-1947.
11. Aaron SD, Vandemheen KL, Hebert P, et al. Outpatient oral prednisone after emergency treatment of chronic obstructive pulmonary disease. *N Engl J Med*. 2003;348(26):2618-2625.
12. Lindenauer PK, Pekow PS, Lahti MC, Lee Y, Benjamin EM, Rothberg MB. Association of corticosteroid dose and route of administration with risk of treatment failure in acute exacerbation of chronic obstructive pulmonary disease. *JAMA*. 2010;303(23):2359-2367.
13. Groenewegen KH, Schols AM, Wouters EF. Mor-

tality and mortality-related factors after hospitalization for acute exacerbation of COPD. *Chest*. 2003;124(2):459-467.

14. Schuetz P, Leuppi JD, Tamm M, et al. Short versus conventional term glucocorticoid therapy in acute exacerbation of chronic obstructive pulmonary disease—the “REDUCE” trial. *Swiss Med Wkly*. 2010;140:w13109.
15. Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med*. 1987;106(2):196-204.
16. Celli BR, MacNee W; ATS/ERS Task Force. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J*. 2004;23(6):932-946.
17. Piaggio G, Elbourne DR, Pocock SJ, Evans SJW, Altman DG; CONSORT Group. Reporting of noninferiority and equivalence randomized trials: extension of the CONSORT 2010 statement. *JAMA*. 2012;308(24):2594-2604.
18. Pauwels RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS; GOLD Scientific Committee. 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(5):1256-1276.
19. Rodriguez-Roisin R. Toward a consensus defini-

tion for COPD exacerbations. *Chest*. 2000;117(5)(suppl 2):398S-401S.

20. Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax*. 1999;54(7):581-586.
21. Evans AT, Husain S, Durairaj L, Sadowski LS, Charles-Damte M, Wang Y. Azithromycin for acute bronchitis: a randomised, double-blind, controlled trial. *Lancet*. 2002;359(9318):1648-1654.
22. Christ-Crain M, Jaccard-Stolz D, Bingisser R, et al. Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial. *Lancet*. 2004;363(9409):600-607.
23. Sayiner A, Aytemur ZA, Cirit M, Unsal I. Systemic glucocorticoids in severe exacerbations of COPD. *Chest*. 2001;119(3):726-730.
24. Stolz D, Christ-Crain M, Bingisser R, et al. Antibiotic treatment of exacerbations of COPD: a randomized, controlled trial comparing procalcitonin-guidance with standard therapy. *Chest*. 2007;131(1):9-19.
25. Bridevaux PO, Probst-Hensch NM, Schindler C, et al. Prevalence of airflow obstruction in smokers and never-smokers in Switzerland. *Eur Respir J*. 2010;36(6):1259-1269.