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A M E R I C A N C O L L E G E O F
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Oral or IV Prednisolone in the Treatment of COPD Exacerbations*

A Randomized, Controlled, Double-blind Study

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Background: Treatment with systemic corticosteroids for exacerbations of COPD results in improvement in clinical outcomes. On hospitalization, corticosteroids are generally administered IV. It has not been established whether oral administration is equally effective. We conducted a study to demonstrate that therapy with oral prednisolone was not inferior to therapy with IV prednisolone using a double-blind, double-dummy design.

Methods: Patients hospitalized for an exacerbation of COPD were randomized to receive 5 days of therapy with prednisolone, 60 mg IV or orally. Treatment failure, the primary outcome, was defined as death, admission to the ICU, readmission to the ICU because of COPD, or the intensification of pharmacologic therapy during a 90-day follow-up period.

Results: A total of 435 patients were referred for a COPD exacerbation warranting hospitalization; 107 patients were randomized to receive IV therapy, and 103 to receive oral therapy. Overall treatment failure within 90 days was similar, as follows: IV prednisolone, 61.7%; oral prednisolone, 56.3% (one-sided lower bound of the 95% confidence interval [CI], -5.8%). There were also no differences in early (*ie*, within 2 weeks) treatment failure (17.8% and 18.4%, respectively; one-sided lower bound of the 95% CI, -9.4%), late (*ie*, after 2 weeks) treatment failure (54.0% and 47.0%, respectively; one-sided lower bound of the 95% CI, -5.6%), and mean (\pm SD) length of hospital stay (11.9 ± 8.6 and 11.2 ± 6.7 days, respectively). Over 1 week, clinically relevant improvements were found in spirometry and health-related quality of life, without significant differences between the two treatment groups.

Conclusion: Therapy with oral prednisolone is not inferior to IV treatment in the first 90 days after starting therapy. We suggest that the oral route is preferable in the treatment of COPD exacerbations.

Trial registration: Clinicaltrials.gov Identifier: NCT00311961.

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Key words: COPD; exacerbation; IV prednisolone; oral prednisolone

Abbreviations: CCQ = Clinical COPD Questionnaire; CI = confidence interval; GOLD = Global Initiative for Chronic Obstructive Lung Disease; MCID = minimal clinically important difference; SGRQ = St. George Respiratory Questionnaire

COPD is a major health problem worldwide, and both morbidity and mortality are rising.¹ Characteristic of the clinical course of COPD are acute episodes of deterioration in symptoms and respiratory function called *exacerbations*. These exacerbations frequently require hospitalization, which also constitutes the largest component of total health-care costs for COPD.² Systemic corticosteroids have

been demonstrated to be beneficial in the treatment of COPD exacerbations.^{3,4} Systemic corticosteroid

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treatment leads to shorter hospital stays and quicker recovery of FEV₁.⁵ It also leads to a decrease in treatment failure and reduces the relapse rate in

the first 1 to 3 months after initial treatment.^{6,7} These and other smaller studies⁸⁻¹⁴ vary considerably in corticosteroid dosage and length of treatment. Even though current guidelines suggest that the oral route of administration is preferable, the optimal route of administration of systemic corticosteroids in the treatment of exacerbations of COPD has not been rigorously studied. Moreover, the preferred route of administration varies markedly between countries. Many hospitals routinely administer the corticosteroids IV, at least initially. A good rationale for this route lacks, since there is close to 100% bioavailability of prednisolone following oral administration under normal conditions.¹⁵

Oral corticosteroids are more convenient to administer because there is no need for IV access, fewer personnel are required for starting and monitoring therapy, and material costs are smaller. We hypothesized that oral administration is not inferior to IV administration of prednisolone in the treatment of patients hospitalized for an exacerbation of COPD. We therefore conducted a prospective, randomized, double-blind, double-dummy, placebo-controlled, parallel-group clinical study with treatment failure as the primary outcome.

MATERIALS AND METHODS

Patients

Patients referred to the Isala klinieken hospital for an exacerbation of COPD were enrolled in the study from June 2001 to June 2003. Inclusion criteria were an age of > 40 years, a history of at least 10 pack-years of cigarette smoking, and evidence of airflow limitation. Airflow limitation was defined as an FEV₁/FVC ratio of < 70% and an FEV₁ of < 80% predicted (at least Global Initiative for Chronic Obstructive Lung Disease [GOLD] severity stage II).^{16,17} An exacerbation of COPD was defined as a history of increased breathlessness and the presence of at least two of the following symptoms for at least 24 h: increased cough frequency or severity; increased sputum volume or purulence; and increased wheeze. Excluded were patients who had signs of a very severe exacerbation on hospital admission (arterial pH < 7.26 or PaCO₂ > 9.3 kPa), with significant or unstable comorbidity, who had a history of asthma, had participated in another study within the 4 weeks before hospital admission, were previously randomized into this study, had clinically significant

findings on chest radiography other than fitting with signs of COPD, a known hypersensitivity to prednisolone, or who were known to be totally noncompliant. The study was approved by the hospital medical ethics committee, and all patients gave written informed consent.

Study Design

Patients were randomized using a computer minimization program¹⁸ for the following 10 parameters: use of oral prednisolone; use of inhaled corticosteroids; theophylline use 30 days before hospital admission; admission to the hospital because of an exacerbation of COPD in the last year; age (< 65 or ≥ 65 years); gender; smoking history (< 50 or ≥ 50 pack-years); use of supplemental oxygen at home; PCO₂ (< 5.4 or ≥ 5.4 kPa); and time since the diagnosis of COPD (*ie*, < 5, 5 to 10, 10 to 15, or > 15 years, or unknown). Patients received either a 5-day course of IV or oral prednisolone, 60 mg, together with placebo medication. Active and placebo medication had a similar appearance. After 5 days, all patients received oral prednisolone in a dosage of 30 mg once daily, which subsequently was tapered with 5 mg daily to 0 mg or a prior maintenance dosage. All patients received nebulized ipratropium bromide and albuterol four times daily together with oral amoxicillin/clavulanate. In case of allergy to this regimen, doxycycline was prescribed. Spirometry was measured on days 1 and 7.¹⁹ On the same days, health status was measured using the St. George Respiratory Questionnaire (SGRQ),²⁰ a change in score of ≥ 4 points, constituting the minimal clinically important difference (MCID).²¹ Health-related quality of life was measured daily in the first week using the 24-h version of the Clinical COPD Questionnaire (CCQ),²² with a change of ≥ 0.4 points constituting the MCID.²³ The respiratory physician decided the date of hospital discharge and was free to intensify pharmacologic therapy if clinical improvement was not satisfactory. Patients were free to withdraw at any time. The follow-up period was 90 days with outpatient visits at days 42 and 90.

Study End Points

The primary outcome was treatment failure, defined as death from any cause, admission to the ICU, readmission to the hospital because of COPD, or the necessity to intensify pharmacologic treatment. The intensification of pharmacologic treatment was defined as the prescription of open-label corticosteroids, theophylline, or antibiotics. Treatment failure was subdivided into early failure, the first 2 weeks after randomization, and late failure, from 2 weeks to 3 months. When patients received additional medication, as mentioned above, from their general practitioner, this was also labeled as treatment failure. Secondary outcomes were changes from days 1 to 7 in FEV₁, SGRQ scores, CCQ scores, and length of hospital stay.

Statistical Analysis

The study was designed as a noninferiority study. The planning committee decided that if results with IV prednisolone were > 15% better (that is, produced a treatment failure rate that was 15% lower) than the rate with oral prednisolone, then clinicians would judge that the benefits of IV therapy clearly outweigh the advantages of oral administration. A difference in the rate of treatment failure of ≤ 15% was deemed to be sufficient to accept that oral corticosteroids were not inferior to IV therapy in patients admitted to the hospital with COPD. In total, 256 patients were required to have 80% power with a one-sided α -statistic of 5% and an expected treatment failure rate of 37%.⁶ To determine noninferiority in accordance with the study design, the lower bound of a one-sided 95% confidence interval (CI) for differences was used.

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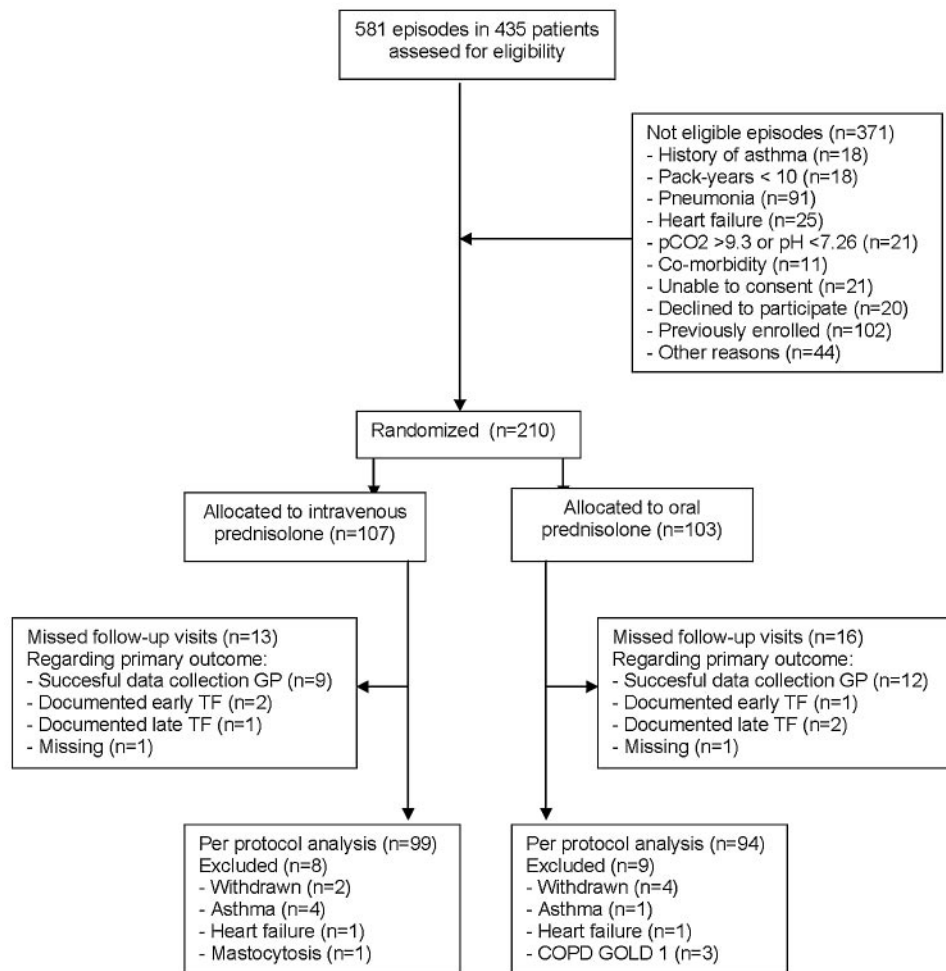


FIGURE 1. Flow chart for study inclusion and reasons for exclusion. GP = general practitioner; TF = treatment failure.

Unpaired *t* tests were used to compare the secondary outcomes. The secondary analyses were performed on the basis of available cases. The two-sided 95% CI for differences will be presented when applicable. Data are shown as the means \pm SD.

RESULTS

Study Population

A total of 435 individuals with a total of 581 exacerbation episodes were referred to the Isala klinieken for an exacerbation of COPD. A total of 210 patients were eligible, of whom 107 were randomized to receive IV prednisolone, and 103 to receive oral prednisolone. Six patients withdrew consent before day 4 of the study, two patients in the IV prednisolone group and four patients in the oral prednisolone group. Another 11 patients were excluded from the per-protocol analysis because they did not fulfill inclusion or exclusion criteria. Per-protocol analysis was performed with 99 patients in

the IV prednisolone group and 94 patients in the oral prednisolone group (Fig 1). Demographic characteristics did not differ between the two groups at baseline (Table 1), nor did day 1 SGRQ and CCQ scores. For one patient in each group, the data regarding primary outcome were missing. Regarding the secondary outcomes, < 5% of data was missing.

Primary Outcomes

Figure 2 shows the Kaplan-Meier estimates of cumulative rates of early and late treatment failure. Intention-to-treat analysis showed no difference between the two groups in treatment failure rate, as follows: IV treated group, 61.7%; orally treated group, 56.3% (one-sided 95% CI lower bound for the difference, -5.8%). There were also no differences between the groups in terms of the rate of early or late treatment failure, as follows: IV treated group, 17.8%; orally treated group, 18.4%; one-sided

Table 1—Patient Characteristics*

Characteristics	Oral	
	IV Prednisolone Group (n = 107)	Prednisolone Group (n = 103)
Age,† yr	69.8 ± 8.6	71.6 ± 8.1
Male sex,† %	76.6	72.8
FEV ₁		
L	1.0 ± 0.43	1.0 ± 0.40
% predicted	36 ± 14	39 ± 17
Smoking history,† pack-yr	37.2 ± 20.2	40.5 ± 23.1
Body mass index, kg/m ²	26.1 ± 4.8	25.7 ± 5.0
Medication 30 d before hospitalization†		
Oral prednisolone	80 (75)	82 (80)
Inhaled corticosteroids	91 (85)	86 (84)
Theophylline	7 (7)	9 (9)
Hospitalization for COPD in previous year†	24 (22)	27 (26)
Supplemental oxygen therapy at home†	13 (12)	13 (13)
CCQ day 1 total score	3.3 ± 0.9	3.3 ± 0.9
SGRQ day 1 total score	64.2 ± 13.3	61.4 ± 15.0

*Values are given as the mean ± SD or No. (%), unless otherwise indicated.

†Parameters used in the minimization method to allocate patients to a treatment group by using a computer program.

95% CI lower bound, -9.4%). Also, 54% vs 47%, respectively, experienced late failure (one-sided 95% CI lower bound, -5.6%). Per-protocol analysis gave essentially the same results. The implications of the results in the light of a design aiming to prove noninferiority are depicted in Figure 3. The oral

administration of prednisolone is not inferior to IV administration since none of the one-sided 95% CI values underpasses the lower bound of 15% better treatment with IV therapy. The reasons for treatment failure are listed in Table 2. The most common reason for treatment failure was intensification of pharmacologic therapy, especially the prescription of open-label prednisolone.

Secondary Outcomes

The mean FEV₁ improved similarly in the IV and orally treated groups (by 0.10 ± 0.23 and 0.12 ± 0.19 L, respectively, from day 1 to 7 of the study (95% CI, -0.09 to 0.04 L). There was also no difference in improvement in health-related quality of life. The mean SGRQ total score improved from day 1 to 7 by 4.4 ± 14.2 and 3.7 ± 12.6 points, respectively, in the IV and orally treated group (95% CI, -3.3 to 4.7 points). The mean CCQ total score improved by 1.0 ± 1.0 and 1.1 ± 1.0 points, respectively, in the IV and orally treated group (95% CI, -0.4 to 0.19 points). The MCID of 4 points in the SGRQ score was reached by 48% of the patients in the IV prednisolone group and 52% of the patients in the oral prednisolone group. Similarly, 67% and 79%, respectively, reached the MCID in CCQ score. Patients in the IV treatment group had a mean length of hospital stay of 11.9 ± 8.6 vs 11.2 ± 6.7 days in the orally treated group (95% CI, -1.5 to 2.9).

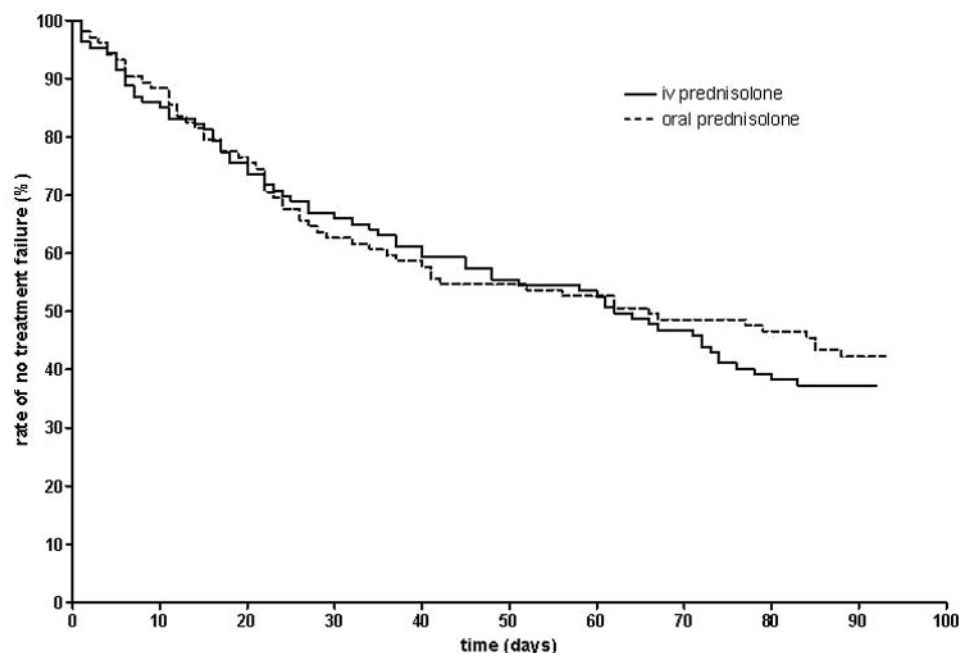


FIGURE 2. Kaplan-Meier estimates of rates of no treatment failure (p = 0.6).

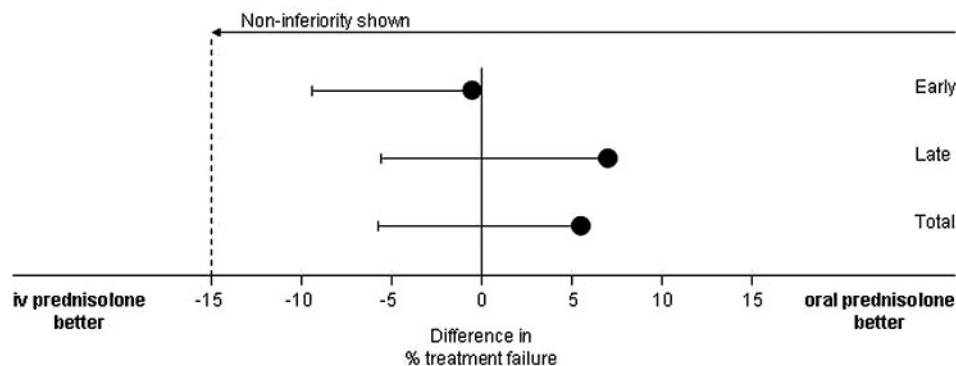


FIGURE 3. Graphic representation of the interpretation of this noninferiority study. Point estimates of total, early, and late treatment failure rates with a one-sided 95% CI lower bound are shown.

Subgroup Analysis

On hospital admission, 162 patients (77%) used oral corticosteroids that had been prescribed by their general practitioner in an attempt to contain the severity of the exacerbation and to keep them out of the hospital. Twenty-three patients (11%) used corticosteroids on a regular basis. Intention-to-treat analysis showed no differences according to primary outcome between the pretreated and corticosteroid-naïve groups of patients

in overall treatment failure (59.9% and 56.3%, respectively; one-sided 95% CI lower bound, -7.6%), early treatment failure (18.5% and 16.7%, respectively; one-sided 95% CI, -6.9%), and late treatment failure (51.5% and 47.5%, respectively; one-sided 95% CI, -10.9%). Analysis within the two groups, regarding the response to orally administered prednisolone vs IV administered prednisolone, gave essentially the same results. There was no significant difference in mean

Table 2—All, Early, and Late Treatment Failures for Both Treatment Groups*

Primary Outcome	IV Prednisolone Group (n = 107)	Oral Prednisolone Group (n = 103)	95% CI Lower Bound
All treatment failures			
Total	66 (61.7%)	58 (56.3%)	-5.8%
Death	5	2	
Hospital readmission for COPD	13	11	
Intensification of pharmacologic therapy	48	45	
Open-label prednisolone	37	34	
Theophylline	6	6	
Antibiotics	15	18	
Prethcamide	0	3	
Early treatment failures			
Total	19 (17.8%)	19 (18.4%)	-9.4%
Death	3	0	
Hospital readmission for COPD	0	0	
Intensification of pharmacologic therapy	16	19	
Open-label prednisolone	12	14	
Theophylline	6	6	
Antibiotics	1	5	
Prethcamide	0	3	
Late treatment failures			
Total	47 (54.0%) [†]	39 (47.0%) [†]	-5.6%
Death	2	2	
Hospital readmission for COPD	13	11	
Intensification of pharmacologic therapy	32	26	
Open-label prednisolone	25	20	
Theophylline	0	0	
Antibiotics	14	13	
Prethcamide	0	0	

*Data are presented as No. unless otherwise indicated.

[†]Data for one patient were missing.

improvement in FEV₁ in the group pretreated with prednisolone (0.09 ± 0.21 L between day 1 and 7) compared to that in patients not having received oral corticosteroids (0.16 ± 0.23 L between days 1 and 7; 95% CI, -0.15 to 0.01 L). There were no significant differences in improvements in health-related quality of life measures between the group pretreated with oral corticosteroids and the group not pretreated. The mean SGRQ scores improved by 3.3 ± 13.4 and by 6.9 ± 13.6 points, respectively, from day 1 to 7 in the two groups (95% CI, -8.6 to 1.4 points), and the mean CCQ scores improved by 1.0 ± 1.1 and 1.1 ± 0.9 points, respectively (95% CI, -0.48 to 0.19 points).

DISCUSSION

The administration of systemic corticosteroids for treatment of exacerbations of COPD was already widespread long before good evidence for its use became available in 1999.^{5,6} At least 10 studies⁵⁻¹⁴ have now studied the effects of systemic steroids in the treatment of exacerbations of COPD, but these studies varied considerably in terms of corticosteroid dosage, length of treatment, and route of administration. Customs vary considerably between and within countries. The GOLD,¹⁶ the National Institute for Clinical Excellence,²⁴ and the new combined European Respiratory Society/American Thoracic Society guidelines²⁵ recommend the oral route. However, so far the optimal route for the administration of corticosteroids in the treatment of COPD exacerbations has not been rigorously studied. One study²⁶ found that therapy with IV corticosteroids in combination with bronchodilators administered using a wet nebulizer was as effective as therapy with oral corticosteroids in combination with bronchodilators administered using a metered-dose inhaler with a spacer, thereby comparing changes in two components of treatment simultaneously. Moreover, the study was small (38 patients), and although it was randomized, it was not blinded. In contrast to the situation regarding COPD exacerbations, there have been several studies²⁷⁻³¹ of asthma exacerbations that have shown a similar efficacy for IV and oral corticosteroids.

We encountered a relatively high treatment failure rate. Compared to a 37% treatment failure rate in the study by Niewoehner et al,⁶ our 59% rate is high. The same primary end point was used as in the study by Niewoehner et al,⁶ who compared systemic steroids with placebo in patients hospitalized for COPD exacerbations. Several factors could explain the difference. First of all, in the latter study, systemic steroids were dosed much higher and for a longer period of time; the cumulative prednisolone intake was 1,680 mg in the 15-day treatment group and 2,345 mg in the 57-day treatment group, compared

to 405 mg in our 11-day treatment regime. They found no advantage for the more prolonged course of steroid administration over the shorter course. It remains to be studied whether lower doses such as those used in our study and even lower doses, such as those used by Davies et al⁵ (30 mg) and Aaron et al⁷ (40 mg), may give similar results. In any case, treatment using both the oral and IV administration of prednisolone was effective in our study, as demonstrated by the improvements in FEV₁, SGRQ scores, and CCQ scores. Second, we actively collected treatment failure data from the patient's general practitioner when follow-up visits were missing, thereby aiming to prevent artificially lower treatment failure rates due to missing data. The most common reason for treatment failure was the intensification of pharmacologic therapy. When general practitioners prescribed antibiotics or steroids in the outpatient setting in the 90-day follow-up period, this was scored as a treatment failure. These prescriptions are the reason for 58 treatment failures, which counts for 47% of all treatment failures. Probably, the prescription habits of general practitioners differ among countries. Important for the outcome, the number of treatment failures due to the intensification of medication by general practitioners was similar in both groups.

In contrast to other studies that compared the effects of systemic corticosteroids and placebo in patients experiencing COPD exacerbations, we did not exclude patients who had used systemic corticosteroids to treat an exacerbation of COPD prior to hospital admission. A hospitalization can be avoided in many patients when oral steroids are administered early in the outpatient setting.³² By preselecting patients who had not received prior oral steroid treatment on an outpatient basis, the extrapolation of results to common practice would have been unduly compromised. Nevertheless, a subgroup analysis did not show significantly poorer results in patients who had already used oral steroids prior to hospital admission.

There are limitations to our study. Above all, it is important to emphasize that the results do not pertain to patients experiencing a very severe exacerbation (arterial pH < 7.26 or PaCO₂ > 9.3 kPa). A future study should test whether our findings apply also to the most severe exacerbations. Second, the number of patients we aimed to study according to the protocol was not attained because of a lower than expected recruitment rate. Noninferiority trials require more patients than conventional superiority trials. Based on the data acquired in this study, a power of 74% has been reached to demonstrate the noninferiority of oral prednisolone therapy. Nevertheless, the fact that the observed difference for overall treatment failure is in

favor of oral treatment suggests to us that the results are important for future clinical practice.

Given the fact that oral prednisolone therapy was not inferior in this study in which all patients received IV therapy (prednisolone or placebo infusions), we suggest that oral prednisolone therapy is the preferred route of administration for most patients admitted to the hospital with an exacerbation of COPD. Oral therapy has several advantages over IV therapy for patients and hospital staff. It is more convenient and cheaper because there is no need for IV access, which is more labor intensive and is associated with risks of infection. Oral therapy will theoretically lead to earlier hospital discharge.

We conclude that orally administered prednisolone in the dose studied is not inferior to IV administered prednisolone in the clinical treatment of an exacerbation of COPD. We therefore suggest that oral prednisolone therapy is the preferred route of administration for most patients admitted to the hospital with an exacerbation of COPD.

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