Eosinophil-guided corticosteroid therapy in patients admitted to hospital with COPD exacerbation (CORTICO-COP): a multicentre, randomised, controlled, open-label, non-inferiority trial

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Summary

Background Treatment with systemic corticosteroids in patients with acute exacerbations of chronic obstructive pulmonary disease (COPD) is associated with debilitating adverse effects. Therefore, strategies to reduce systemic corticosteroid exposure are urgently required and might be offered by a personalised biomarker-guided approach to treatment. The aim of this study was to determine whether an algorithm based on blood eosinophil counts could safely reduce systemic corticosteroid exposure in patients admitted to hospital with acute exacerbations of COPD.

Methods We did a multicentre, randomised, controlled, open-label, non-inferiority trial at the respiratory departments of three different university-affiliated hospitals in Denmark. Eligible participants were patients included within 24h of admission to the participating sites, aged at least 40 years, with known airflow limitation (defined as a post-bronchodilator FEV_1/forced vital capacity [FVC] ratio ≤0·70) and a specialist-verified diagnosis of COPD, who were designated to start on systemic corticosteroids by the respiratory medicine physician on duty. We randomly assigned patients (1:1) to either eosinophil-guided therapy or standard therapy with systemic corticosteroids. Both investigators and patients were aware of the group assignment. All patients received 80 mg of intravenous methylprednisolone on the first day. The eosinophil-guided group were from the second day given 37·5 mg of prednisolone oral tablet daily (for a maximum of up to 4 days) on days when their blood eosinophil count was at least $0·3\times10^9$ cells per L. On days when the eosinophil count was lower, prednisolone was not administered. If a patient was discharged during the treatment period, a treatment based on the last measured eosinophil count was prescribed for the remaining days within the 5-day period (last observation carried forward). The control group received 37·5 mg of prednisolone tablets daily from the second day for 4 days. The primary outcome was the number of days alive and out of hospital within 14 days after recruitment, assessed by intention to treat (ITT). Secondary outcomes included treatment failure at day 30 (ie, recurrence of acute exacerbation of COPD resulting in emergency room visits, admission to hospital, or need to intensify pharmacological treatment), number of deaths on day 30, and duration of treatment with systemic corticosteroids. The non-inferiority margin was 1·2 days (SD 3·8). This trial is registered at ClinicalTrials.gov, number NCT02857842, and was completed in January, 2019.

Findings Between Aug 3, 2016, and Sept 30, 2018, 159 patients in the eosinophil-guided group and 159 patients in the control group were included in the ITT analyses. There was no between-group difference for days alive and out of hospital within 14 days after recruitment: mean 8·9 days (95% CI 8·3–9·6) in the eosinophil-guided group versus 9·3 days (8·7–9·9) in the control group (absolute difference –0·4, 95% CI –1·3 to 0·5; p=0·34).Treatment failure at 30 days occurred in 42 (26%) of 159 patients in the eosinophil-guided group and 41 (26%) of 159 in the control group (difference 0·6%, 95% CI –9·0 to 10·3; p=0·90). At 30 days nine patients (6%) of 159 in the eosinophil-guided group and six (4%) of 159 in the control group had died (difference 1·9%, 95% CI –2·8 to 6·5; p=0·43). Median duration of systemic corticosteroid therapy was lower in the eosinophil-guided group: 2 days (IQR 1·0 to 3·0) compared with 5 days (5·0 to 5·0) in the control group, p<0·0001.

Interpretation Eosinophil-guided therapy was non-inferior compared with standard care for the number of days alive and out of hospital, and reduced the duration of systemic corticosteroid exposure, although we could not entirely exclude harm on some secondary outcome measures. Larger studies will help to determine the full safety profile of this strategy and its role in the management of COPD exacerbations.

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Research in context

Evidence before this study

We searched PubMed for publications using the following search items: "chronic obstructive pulmonary disease (COPD)" AND "eosinophil count" AND "corticosteroids" with no language or date limitations. We limited the search to studies with adult humans and excluded studies on children and those in which the association between inhaled corticosteroids and eosinophil count was assessed. Most publications were post-hoc analyses of randomised clinical trials and observational studies. Only one randomised controlled trial was identified. This study concluded that eosinophil-guided corticosteroid treatment could be used safely in patients with moderate exacerbations of COPD. In this trial, patients treated with prednisolone for 2 weeks were compared with a biomarker-guided group (receiving prednisolone or placebo based on a single exacerbation blood-eosinophil count). The results of this study showed no difference in health status or treatment failure rates between the groups.

Added value of this study

To our knowledge, this is the first randomised trial to show non-inferiority in treating hospitalised patients with severe COPD exacerbation through biomarker-guided corticosteroid therapy compared with standard care, and simultaneously reducing the overall exposure to systemic corticosteroids by approximately half. Implementation of a strategy of biomarker-guided corticosteroid therapy would most likely reduce, both on individual and societal levels, the burden of corticosteroid adverse effects substantially in a large and vulnerable patient group. Additionally, since the differential count of white blood cells is inexpensive and readily available in most hospital settings, this strategy can easily be implemented, without establishing new hospital infrastructure, even in resource-constrained environments.

Implications of all the available evidence

Our findings might improve patient care and clinical practice in patients with COPD exacerbations. Reducing ineffective treatment with systemic corticosteroids is important because of their well known long-term adverse effects. However, larger studies would help to establish the full safety profile of the strategy of eosinophil-guided systemic corticosteroid treatment.

Introduction

Acute exacerbations of chronic obstructive pulmonary disease (COPD) substantially contribute to high morbidity and mortality, and poor quality of life worldwide.[1,2] Orally administered systemic corticosteroids are frequently used to treat acute exacerbations of COPD to improve recovery from symptoms and prevent treatment failure. However, the use of systemic corticosteroids do not affect the long-term decline in lung function, re-exacerbation of COPD after the first month, the length of stay in hospital intensive care units (ICU), or mortality rates.[3] Evidence regarding the optimum dose and treatment duration of systemic corticosteroids is inadequate, and physicians might be reluctant to shorten the length of the treatment.[3–5] Systemic corticosteroid overuse should be avoided, as this might cause serious harm to the patient, including osteoporotic fractures, adrenal insufficiency, increased blood glucose concentration or worsening of diabetes, sepsis, and venous thromboembolism.[6–8] Increasing knowledge of these side-effects and the ineffectiveness of systemic corticosteroids in reducing neutrophil-associated inflammation along with the recognition of COPD as a heterogeneous disease has led to increasing interest in a more targeted approach to systemic corticosteroid treatment.[9,10]

Eosinophilic inflammation has been shown in 20–40% of patients with acute exacerbations of COPD.[11–13] Evidence supports the use of peripheral blood eosinophil counts as a diagnostic biomarker to define an eosinophilic COPD phenotype.[13,14] An eosinophilic phenotype based on a peripheral blood eosinophil count of at least 300 cells per µL is associated with an increased risk of acute exacerbations of COPD,[15,16] and patients with higher peripheral blood eosinophil counts are more likely to benefit from treatment with inhaled corticosteroids and systemic corticosteroids.[17–19] Therefore, this biomarker has been proposed as a useful tool to guide systemic corticosteroid treatment of acute exacerbations of COPD.[14,17,20] One randomised trial[17] used blood eosinophils to direct systemic corticosteroid treatment in patients with moderate exacerbations of COPD. The main finding was non-inferior treatment response, and increased harm in patients with a low blood eosinophil count (<2%) who received systemic corticosteroid treatment. Other studies have shown a more favourable treatment response to systemic corticosteroids in patients with higher blood eosinophil counts.[18,21,22] In daily clinical practice, the administration of systemic corticosteroids seems to lead to a decrease in blood eosinophils, and the clinical improvement thereafter indicates that systemic corticosteroids might be able to reduce eosinophilic inflammation. However, it is not known whether day-to-day adjustments of corticosteroid treatment based on blood eosinophil counts can safely reduce exposure to systemic corticosteroids in patients admitted to hospital with acute exacerbations of COPD. The hypothesis of this trial was that an eosinophil-guided reduction of the dose of systemic corticosteroids for hospitalised patients with acute exacerbations of COPD did not lead to inferior treatment effect for the outcome of days alive and out of hospital within 14 days after recruitment compared with standard care.

Methods

Study design and participants

We did a multicentre, investigator-initiated, randomised, controlled, open-label, non-inferiority trial in the respiratory departments at three university hospitals in Denmark (CORTICOsteroid reduction in COPD [CORTICO-COP]). The trial was carried out in accordance with the published trial protocol,[23] the International Conference on Harmonisation-good clinical practice guideline,[24] the applicable government requirements, the Helsinki Declaration[25] and the CONSORT guideline and checklist requirements.[26] Both the study protocol and the statistical analysis plan are available online and in the appendix, and were available on our website (www.coptrin.dk) before recruitment stopped. This study was approved by the Ethics Committees of all participating sides (H-15012207), the Danish Medicines Agency (EudraCT no 2015-003441-26) and the Danish Data Protection Agency (HGH-2015-038 and I-Suite number 04014). It was monitored according to Good Clinical Practice (GCP) by the GCP unit of the Capital Region of Denmark. No financial incentive was provided to the investigators or participants.

All consecutive patients admitted to the participating sites were eligible if they were included within 24 h of admission, were aged at least 40 years, with known airflow limitation (defined as postbronchodilator FEV_1/forced vital capacity [FVC] ratio ≤0·70) and a specialist verified diagnosis of COPD based on stable disease state data. Exacerbations were defined according to the consensus definition, stated by the Global Initiative for Chronic Obstructive Lung Disease committee: an acute worsening of respiratory symptoms that result in additional therapy.[27] Patients for whom the primary reason for admittance was not acute exacerbations of COPD, including cardiovascular disease, were not included in the study. Patients who met the inclusion criteria were invited to participate in the trial.

Exclusion criteria included the following: (1) self-reported or physician-diagnosed asthma, (2) life expectancy of less than 30 days, (3) severe COPD exacerbation requiring invasive ventilation or admission to the intensive care unit (ICU), (4) allergy to systemic corticosteroids, (5) severe mental illness that could not be controlled by medication, (6) people detained under the act of the use of coercion in psychiatry, (7) severe language difficulties or the inability to provide a written informed consent, (8) pregnancy or lactation, (9) systemic fungal infections, or (10) patients receiving more than 10 mg of chronic systemic corticosteroids daily. Written informed consent was obtained from patients before randomisation. Patients could only participate in the trial once.

Randomisation and masking

Patients were randomly assigned (1:1) to receive treatment either according to guidance based on the daily peripheral blood eosinophil count (eosinophil-guided group) or the standard of care (control group). The randomisation sequence was generated using the sealed envelope sequence generator stratified according to site and age (>70 years *vs* ≤70 years). Online inclusion of patients according to the concealed sequence was done with an independent, centralised, 24h-available, web-based system. The randomisation sequence was prepared by the study director (J-USJ), who did not take part in the recruitment of patients. Treatment allocation was concealed by our web-based system, and no-one had access to the sequence after the trial started. However, on a single patient basis, both investigators and patients were aware of the treatment assignment after randomisation. The investigators became aware of the treatment assignment by a system-generated email following randomisation and assigned thereafter patients to the trial groups. Then, the investigators informed the research nurses, who were not masked to treatment assignment, when and with whom they had to do the follow-up. The investigators analysing the data were fully masked to group assignments.

For more on **the web-based system** see https://www.sealedenvelope.com

For the **study protocol** see http://coptrin.dk/wp-content/uploads/2018/09/CORTICO-COP-study-protocol_v8_25092018_Sivapalan.pdf

See **Online** for appendix

Procedures

The baseline date, which was also the calendar date of recruitment in the trial, was named as day 1. In accordance with the Danish national guidelines, all patients with acute exacerbations of COPD had systemic corticosteroids (80 mg of intravenous methylprednisolone) administered by the respiratory medicine physician on duty, shortly after admission to hospital; therefore, all patients recruited for the trial received an initial dose of systemic corticosteroids on day 1. Thus eosinophil-guided strategy was solely applied on days 2 through 5. Patients were assigned to one of the two treatment arms: (1) the intervention (eosinophil-guided) group: 80 mg of intravenous methylprednisolone on the first day followed by 37·5 mg of prednisolone oral tablet daily (for a maximum of up to 4 days) on days when their blood eosinophil count was at least $0·3\times10^9$ cells per L. On days with eosinophil counts less than $0·3\times10^9$ cells per L, systemic corticosteroids were not administered. If a patient was discharged during the treatment period, a treatment based on the last measured eosinophil count was prescribed for the remaining days within the 5-day period (last observation carried forward). Or (2) the standard care (control) group: 80 mg of intravenous methylprednisolone on the first day followed by 37·5 mg of prednisolone tablets daily for 4 days. If methylprednisolone had been mistakenly left out before recruitment, we assured that this dose was administered immediately after recruitment to ensure comparability.

The study did not interfere with the treating physician's decision to commence systemic corticosteroids, because this decision was made before the patients could be recruited for the trial. Treating physicians were always advised to contact the investigators if they wished to deviate from the protocol algorithm. This approach was applied to reduce non-protocol adherence. The decision to

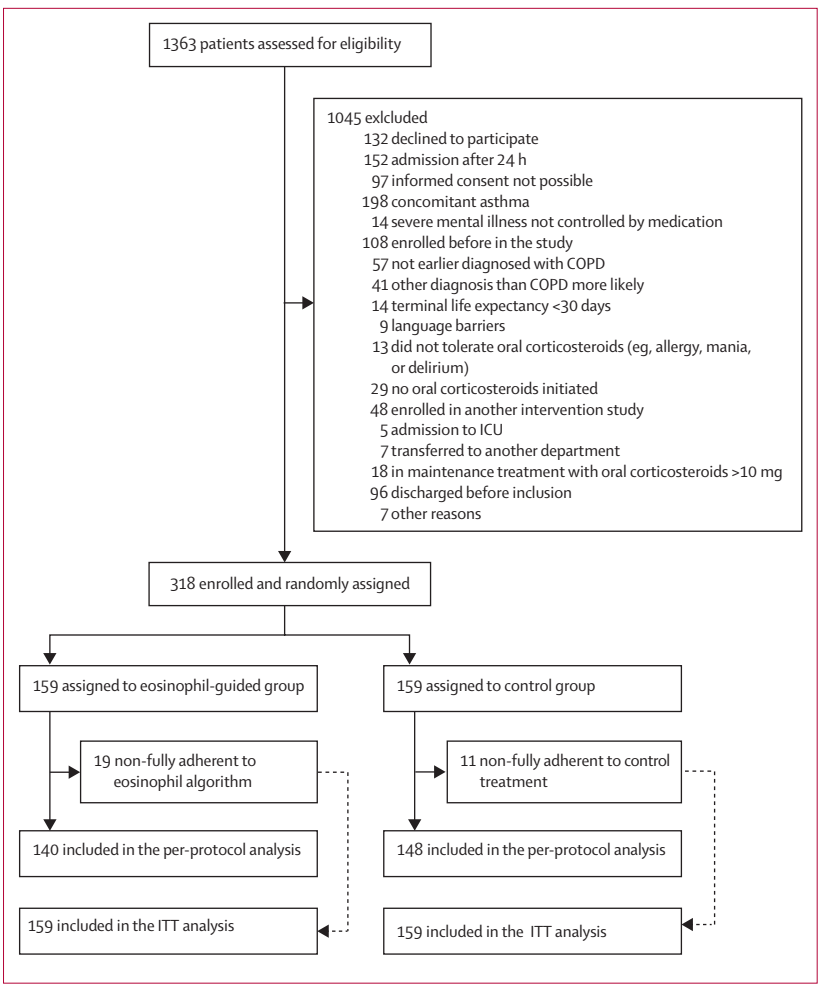

Figure 1: **Trial profile**
COPD=chronic obstructive pulmonary disease. ICU=intensive care unit. ITT=intention to treat.

discharge patients was made by the treating physicians, and the sites were encouraged not to involve the investigators in the decision to discharge patients included in the trial. Baseline measurements were obtained on the calendar date of recruitment. For patients assigned to the eosinophil-guided group, the measurements of blood eosinophil counts were done once per day in the morning and made available to the attending physicians. Blood eosinophil count was only measured in the control group on the day of inclusion to avoid spillover treatment switching.

Increased dyspnoea, increased sputum volume, increased sputum purulence (compared with normal values) and cough were registered at recruitment. Blood glucose was measured in a standardised manner every day for 5 days at the first blood sampling round in the morning, and was thus not influenced by the investigators. The COPD assesment test (CAT) score, spirometry (FEV_1, FVC, and FEV_1/ FVC ratio), body-mass index (BMI), and dyspnoea measured with the Medical Research Council (MRC) dyspnoea scale were assessed at baseline and at 30 and 90 days after discharge. Spirometry was also assessed at day 3.

Outcomes

The primary efficacy endpoint was days alive and out of hospital within 14 days after recruitment (non-inferiority approach). The primary endpoint measure was chosen to focus on a positive outcome during the first 14 days rather than more negative outcomes such as death or being still admitted to hospital.[28] Among other advantages, lead-time bias due to death was avoided using this endpoint measure (ie, patients who died early would not be counted as a short length of stay).

The secondary endpoints recorded from the baseline visit were: treatment failure within 30 days (recurrence of acute exacerbations of COPD resulting in emergency room visits, admission to hospital, or need to intensify pharmacological treatment); readmission with acute exacerbations of COPD or death within 30 days; time to readmission with acute exacerbations of COPD or death within 30 days; cumulative corticosteroid dose during hospitalisation on days 30 and 90; mortality by day 30; hyperglycaemia during index admission (ie, fasting plasma glucose ≥7·0 mmol/L); new onset of diabetes at day 30 (glycated haemoglobin A_{1c} [HbA_{1c}] ≥48 mmol/mol); and worsening of diabetes at day 30 (any increase in HbA_{1c}). The following endpoints were assessed on day 90 after recruitment: all infections requiring antibiotic treatment; changes in parathyroid hormone and vitamin D status (appendix, p 26); and dyspepsia, ulcer complications, or initiation of new proton-pump inhibitor treatment. The following endpoints were assessed on days 30 and 90 from baseline: spirometric changes (also on day 3) and changes in BMI, CAT scores, and MRC dyspnoea scores. All patients were planned for outpatient visits on days 30 and 90. If the patients did not attend the follow-up visits (eg, if they found it too strenuous), our project nurses did home visits. If patients were discharged before day 5, we made a phone call on day 5 to record the real-time use of, and adherence to, systemic corticosteroids.

Statistical analysis

The aim of this trial was to establish whether the strategy of eosinophil-guided reduced corticosteroid therapy was non-inferior in terms of clinical outcome (assessed as days alive and out of hospital within 14 days after recruitment) compared with the standard guideline-based systemic corticosteroid therapy. We estimated that 318 patients would be required for the trial to have 80% power (1-β) and a one-sided significance level (α) of 0·025. The maximum decrease of the primary outcome was set at 1·2 days, and the SD based on other reports was set at 3·8 days (appendix p 25).[3,29] This non-inferiority margin was based on the most recent Cochrane meta-analysis on administration of systemic corticosteroids

	Eosinophil–guided group (n=159)	Control group (n=159)
Age (years)	75 (69–81)	75 (68–82)
Sex		
Male	73 (46%)	70 (44%)
Female	86 (54%)	89 (56%)
Body-mass index (kg/m²)	24·2 (20·8–26·6)	23·6 (20·3–27·9)
Smoking		
Current	54 (34%)	50 (31%)
Past	103 (65%)	105 (66%)
Pack-year history	45 (30–57)	48 (35–56)
Pulmonary function and symptoms		
COPD assessment test	21 (17–26)	21 (15–26)
Non-invasive ventilation	4 (3%)	5 (3%)
Increased dyspnoea	146 (92%)	151 (95%)
Increased sputum volume	33 (21%)	34 (21%)
Increased sputum purulence and cough	45 (28%)	47 (30%)
Medical Research Council dyspnoea scale	4 (3–5)	4 (3–5)
FEV1 (L)	0·7 (0·5–0·9)	0·7 (0·5–0·9)
FEV1 (% predicted)	32 (23·0–38·5)	30 (23·0–40·5)
FVC (L)	1·6 (1·2–2·1)	1·6 (1·2–2·1)
FVC (% predicted)	56 (42–72)	57 (44–70)
FEV1/FVC ratio (%)	0·45 (0·37–0·55)	0·44 (0·35–0·54)
Medication		
Long-acting β2 agonist	125 (79%)	127 (80%)
Long-acting muscarinic antagonist	118 (74%)	130 (82%)
Inhaled corticosteroid	80 (50%)	96 (60%)
Prednisolone prescription 2 weeks before recruitment	8 (5%)	12 (8%)
Maintenance corticosteroid therapy (≤10 mg)	10 (6%)	7 (4%)
Severity factors		
Diabetes	24 (15%)	15 (9%)
Ischaemic heart disease	22 (14%)	15 (9%)
Essential hypertension	64 (40%)	61 (38%)
Hypercholesterolaemia	19 (12%)	19 (12%)
Chronic renal failure	12 (8%)	10 (6%)
Heart failure	17 (11%)	13 (8%)
Osteoporosis	33 (21%)	26 (16%)
Activities of Daily Living (score 1–2)*	123 (77%)	127 (79%)
Activities of Daily Living (score 3–5)†	36 (23%)	32 (20%)
Severe exacerbation rate in previous 12 months (mean [95% CI])	0·64 (0·45–0·83)	0·69 (0·44–0·94)
Clinical findings		
Systolic blood pressure (mm Hg)	130 (117–142)	127 (116–139)
Diastolic blood pressure (mm Hg)	70 (62–78)	70 (62–80)
Heart rate (beats per min)	89 (79–99)	89 (81–99)
Oxygen saturation with nasal oxygen (%)	95% (93–96)	95% (93–96)
Oxygen supply (L/min)	2 (1–2)	2 (1–2)
Respiratory rate (breaths per min)	20 (18–22)	20 (18–22)
Temperature (°C)	36·6 (36·3–36·9)	36·6 (36·4–36·9)
Laboratory findings		
Infiltrate on chest X-ray	45 (28%)	56 (35%)
Leukocytes (10^9 cells per L)	9·8 (7·5–13·5)	9·9 (7·9–13·1)
Eosinophils (10^9 cells per L)	0·10 (0·01–0·30)	0·06 (0·01–0·20)
pH	7·42 (7·38–7·46)	7·42 (7·39–7·45)
$PaCO_2$ (kPa)	5·4 (4·7–6·2)	5·3 (4·7–6·4)
PaO_2 (kPa)	9·1 (8·2–10·2)	8·8 (7·9–10·1)
Ion–Ca (mmol/L)	1·18 (1·15–1·22)	1·19 (1·15–1·22)

(Table 1 continues in next column)

(Continued from previous column)

Data are n (%) or median (IQR) unless otherwise specified. COPD=chronic obstructive pulmonary disease. FVC=forced vital capacity. PaO_2=partial pressure of oxygen. $PaCO_2$=partial pressure of carbon dioxide. *Score 1–2: living in own home with nurse help once per day or no help. †Score 3–5: living in a nursing home or own home with nurse help several times a day.

Table 1: **Baseline characteristics of the intention-to-treat population**

compared with placebo, which showed 1·2 days shorter admission.[3] We included no loss to follow-up in the sample size estimate because of a complete follow-up of the primary outcome in central registries. Thus, we did not accept any loss to follow-up in the case report form. This sample size calculation was done on the basis of a group sequential design derived from the approach of O'Brien and Fleming,[30] normal distribution of the means, one-sided non-inferiority, and two interim analyses of the first third and two-thirds of patients recruited (analyses done on Nov 27, 2017, and April 2, 2018, respectively; appendix pp 4, 24). The primary outcome was presented as mean (95% CI), according to the protocol, statistical analysis plan, and assessment of the distributions.

We compared the baseline characteristics and outcomes with a *t* test or Mann-Whitney *U* test for continuous outcomes and a χ^2 test for nominal outcomes. We calculated a cumulative event estimate using a hazard ratio (HR) with 95% CI. Mixed linear models were used to test the differences between the eosinophil-guided group and the control group for FEV_1 percentage predicted, CAT scores, MRC dyspnoea grades, and BMI after controlling for the baseline value. Post hoc, a multiple regression model for the primary outcome measure was done to adjust for pre-existing disability (activity of daily living, previous exacerbation history, and comorbidities). Activity of daily living was divided into either living in a nursing home or own home with nurse help several times a day; or living in own home with no help or with help maximally once daily (appendix p 27). To explore whether early

	Eosinophil-guided group	Control group	Between-group absolute difference	p value
Primary endpoint				
Days alive and out of hospital within 14 days after recruitment				
Intention-to-treat (n=318)	8·9 (8·3 to 9·6)	9·3 (8·7 to 9·9)	−0·4 (−1·3 to 0·5)	0·34
Per-protocol (n=288)*	9·1 (8·4 to 9·8)	9·4 (8·8 to 10·0)	−0·3 (−1·2 to 0·7)	0·49
Secondary endpoints				
Treatment failure within 30 days	42 (26·4%)	41 (25·8%)	0·6% (−9·0 to 10·3)	0·90
Readmission with acute exacerbations of COPD or death within 30 days, HR (95% CI)†	1·5 (0·9 to 2·5)	1 (Ref)	..	0·09
New onset of diabetes in patients without diabetes by day 30‡ (n=279)	6 (4·4%)	6 (4·2%)	0·2% (−4·5 to 5·1)	0·91
Worsening of diabetes control in the diabetes group at day 30§ (n=39)	2 (8·3%)	10 (66·6%)	−58·3% (−84·6 to −32·0)	0·0001
Dyspepsia, ulcer complication, or new proton pump inhibitor treatment within 90 days	11 (6·9%)	12 (7·5%)	−0·6% (−6·3 to 5·1)	0·83
Cumulative corticosteroid dose				
Length of treatment (days; median [IQR])	2·0 (1·0 to 3·0)	5·0 (5·0 to 5·0)	3·0	<0·0001
Day 5 (mg)	121·3 (112·7 to 130·0)	225·2 (222·1 to 228·3)	−103·9(−113·0 to−94·7)	<0·0001
Day 30 (mg)	173·8 (151·1 to 196·6)	292·7 (272·7 to 312·7)	−118·9(−148·9 to 88·8)	<0·0001
Day 90 (mg)	260·8 (216·1 to 305·5)	420·7 (353·1 to 488·3)	−159·9 (−242·5 to 77·3)	0·0002
Blood glucose				
Day 1	8·1 (7·6 to 8·6)	8·0 (7·6 to 8·4)	0·1 (−0·5 to 0·7)	0·68
Day 2	6·9 (6·5 to 7·2)	6·9 (6·5 to 7·2)	0·0 (−0·5 to 0·5)	0·97
Day 3	6·1 (5·8 to 6·4)	6·6 (6·1 to 7·1)	−0·5 (−1·0 to 0·1)	0·13
Day 4	6·2 (5·9 to 6·6)	6·2 (5·9 to 6·5)	0·0 (−0·5 to 0·5)	0·93
Day 5	6·1 (5·8 to 6·5)	6·7 (6·2 to 7·3)	−0·6 (−1·2 to 0·0)	0·04
Stratified by pneumonia				
Days alive and out of hospital within 14 days after recruitment				
Patients without pneumonia (n =217)	9·4 (8·7 to 10·2)	10·0 (9·3 to 10·7)	−0·6 (−1·6 to 0·4)	0·26
Patients with pneumonia (n=101)	7·8 (6·4 to 9·2)	8·7 (7·7 to 9·7)	−0·9 (−2·5 to 0·8)	0·29

Data are mean (95% CI) or n (%) unless otherwise specified.COPD=chronic obstructive pulmonary disease . HR=hazard ratio. *All analyses are intention-to-treat except for the per-protocol analysis. †Cox proportional hazards model. ‡According to definition of glycated haemoglobin A_{1c} (HbA_{1c}) ≥48 mmol/L (≥6·5%). §Defined as increasing HbA_{1c} from baseline to day 30.

Table 2: **Primary and secondary endpoint measures**

eosinophils counts of at least $0·3×10^9$ per L (on day 1 or day 2) predicted later eosinophilia, we did an unadjusted logistic regression analysis. Furthermore, we analysed how the eosinophil inflammation responded to systemic corticosteroid therapy by measuring eosinophils before and after treatment. Because of the risk of multiple comparisons, Bonferroni correction was done for the five secondary endpoints (appendix p 26). Statistical analyses were done using the SAS statistical software 9.4 and the statistical software R (version 3.4.3). The sample size calculation was done using StudySize 3.0 (Frölunda, Sweden).

An independent data and safety monitoring board (DSMB) reviewed the trial's progress and assessed the safety, efficacy, and data completeness during the trial (appendix p 24). The study group, including the steering committee, was masked to the data until they had been entered into the database for the scheduled primary analyses. When the processes of recruitment and follow-up were completed, the database was locked and all data that could not unmask the principal investigator were made accessible for analysis. This trial was registered as an international standard randomised controlled trial with ClinicalTrials.gov, number NCT02857842.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The principal investigator (PradS) had full access to all the data in the study after follow-up was complete (at locking of the database on Jan 10, 2019, 2 days after follow-up of the last patient), except for data on the treatment assignment, blood eosinophils, and corticosteroid use, to which he had access after the unblinding meeting on Jan 25, 2019. Prad S had final responsibility for the decision to submit for publication.

Results

Between Aug 3, 2016, and Sept 30, 2018, we screened 1363 patients. Patients were recruited and followed up

between August, 2016, and January, 2019 (the last patient was recruited on Sept 30, 2018, and followed up to Jan 8, 2019). 318 patients (23%) of 1363 were randomly assigned to either the eosinophil-guided group (n=159) or the control group (n = 159) within 24 h of admission (figure 1). There was an adherence to the eosinophil-guided algorithm of 88·1% and 93·1% in the control group (appendix p 24). 137 (86%) of 159 patients in the eosinophil-guided group and 143 (90%) of 159 patients in the control group were discharged without involving the investigators. On average, the first eosinophil count was made 63 min before administration of methylprednisolone (median –63 min, IQR –250 to –5). In the eosinophil-guided group, inhaled corticosteroids were used at discharge in 93 (59%) of 159 patients *vs* 94 (59%) of 159 patients in the control group, p=0·91; there were numerically fewer patients on inhaled corticosteroids in the eosinophil-guided group at study admission. All 318 randomly assigned patients entered the intention-to-treat analysis. The treatment groups were well balanced at baseline with respect to demographic and disease characteristics (table 1). The follow-up for the primary endpoint, re-exacerbation, death, infections requiring antibiotic treatment, and corticosteroid use during admission was complete (100%) for all patients.

There was no between-group difference for the primary outcome of days alive and out of hospital within 14 days after recruitment, assessed by intention to treat: mean 8·9 days (95% CI 8·3–9·6) in the eosinophil-guided group versus 9·3 days (8·7–9·9) in the control group (absolute difference –0·4, 95% CI –1·3 to 0·5; p=0·34; table 2). Results for the per-protocol population were similar (table 2).

There were no between-group differences over the first 30 days in treatment failure (table 2). Readmission with acute exacerbations of COPD or death at 30 days occurred in 39 (24·5%) of 159 patients in the eosinophil-guided group and 27 (17·0%) of 159 in the control group (figure 2; difference of 7·5%, 95% CI –1·3 to 16·4; p=0·10). After 30 days, nine (6%) of 159 patients had died in the eosinophil-guided group compared with six (4%) of 159 in the control group (difference 1·9%, 95% CI –2·8 to 6·5; p=0·43). The length of treatment with systemic corticosteroids and the mean cumulative systemic corticosteroid dose on day 5 were lower in the eosinophil-guided group than in the control group (p <0·0001 for both; table 2, figure 3). The difference in the mean cumulative corticosteroid dose continued throughout days 30 and 90 (figure 3, table 2).

During the 90-day follow-up, there were no differences in infections requiring antibiotic treatment in the eosinophil-guided group compared with the control group: 55 (34·6%) of 159 patients versus 68 (42·8%) of 159; difference of –8·2%, 95% CI –18·8 to 2·5; p=0·13, figure 2. Furthermore, there were no between-group differences in dyspepsia, ulcer complications, or initiation of new proton-pump inhibitor treatment at 90 days

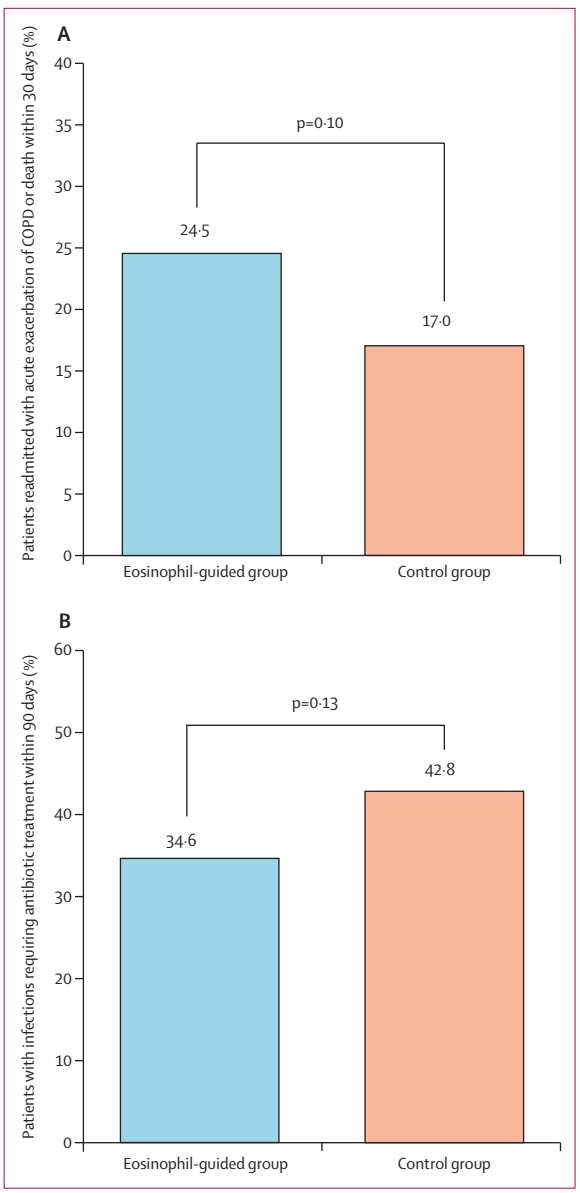

Figure 2: **(A) Readmission with acute exacerbation of COPD or death and (B) Infections requiring antibiotic treatment during follow-up**
COPD=chronic obstructive pulmonary disease.

(table 2). During the 30-day follow-up, no differences occurred in the new onset of diabetes for patients without pre-existing diabetes (table 2). However, the worsening of diabetes (increasing HbA_{1c} from baseline to day 30) in patients with pre-existing diabetes was higher in the control group (table 2). Blood glucose concentrations during admission were either equal or lower in the eosinophil-guided group from days 3 to 5 but only significantly different between the groups on day 5 (table 2). At all timepoints measured, the mean change from the baseline in FEV_1, CAT scores, BMI, and MRC dyspnoea grades did not differ between the two groups (figure 4). Furthermore, no between-group differences

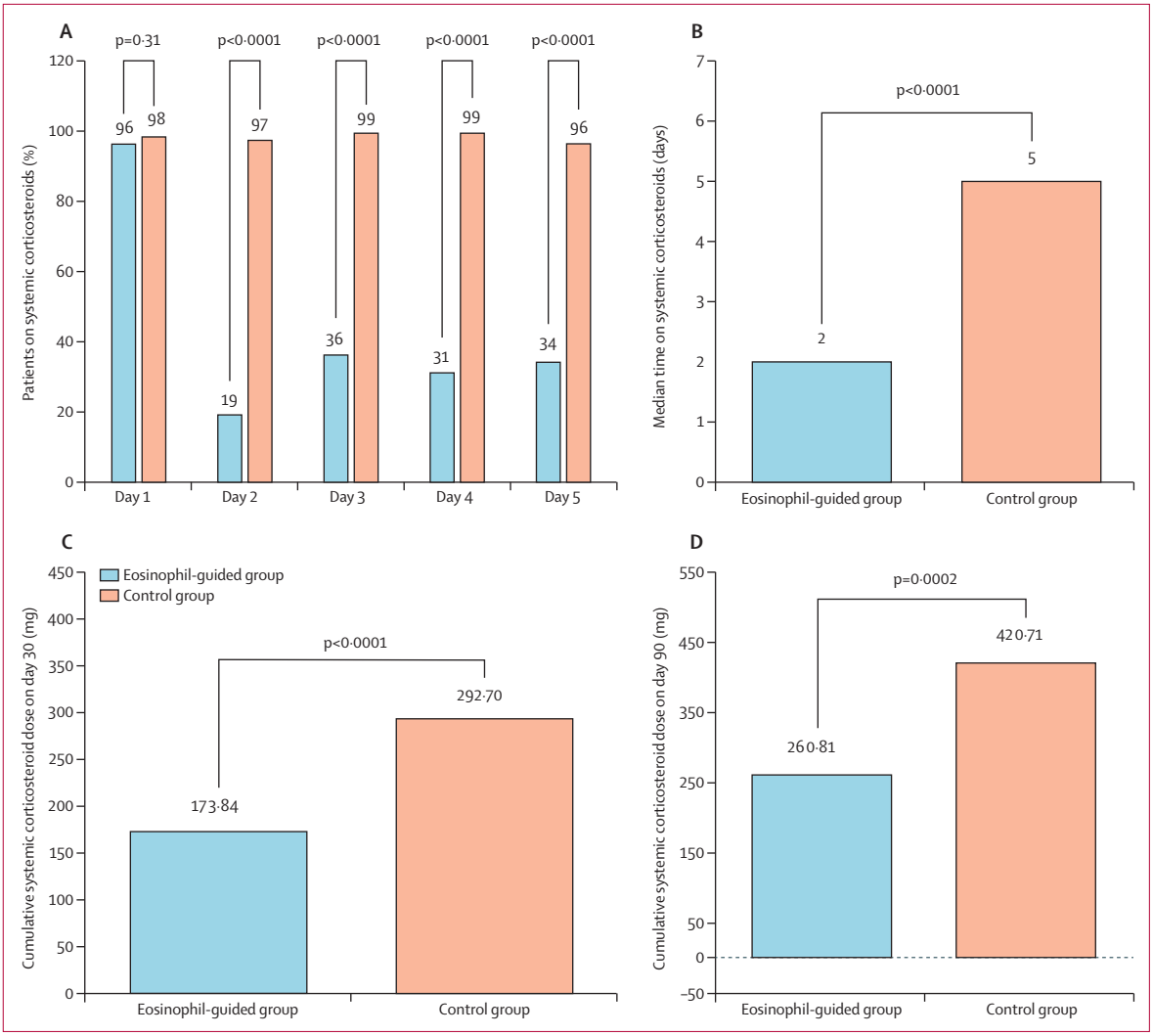

Figure 3: **Systemic corticosteroid use**
Graphs show (A) the proportion of patients on systemic corticosteroids on days 1 to 5; (B) median duration of systemic corticosteroid use during the first 5 days; and mean cumulative systemic corticosteroid dose (mg) during follow-up on day 30 (C) and day 90 (D).

were recorded in the mean change of parathyroid hormone and vitamin D at 90 days (appendix p 26).

Post-hoc analyses for the primary outcome while adjusting for the activity of daily living, the number of severe acute exacerbations of COPD in the previous year, and all baseline comorbidities (table 1), and stratified by baseline evidence of pneumonia did not affect the findings (table 2, appendix p 27). An unadjusted logistic regression analysis supported early eosinophilia predicting later eosinophilia: odds ratio 3·2 (95% CI 1·6–6·4); p=0·0011. Furthermore, when we analysed how the eosinophil inflammation responded to systemic corticosteroid therapy by measuring eosinophils before and after treatment, we noted a decrease in blood eosinophils following administration of systemic corticosteroids (appendix p 29). For the eosinophil-guided group, additional exploratory analyses did not show any difference between patients with an eosinophil count of at least $0·3\times10^9$ per L with regard to the primary outcome, COPD re-exacerbation and FEV_1 change, compared with patients with an eosinophil count of fewer than $0·3\times10^9$ per L (appendix pp 28–30).

Discussion

In patients with severe acute exacerbations of COPD requiring hospital admission, an eosinophil-guided algorithm where systemic corticosteroids were withheld whenever the daily eosinophil count was less than $0·3\times10^9$ cells per L did not result in fewer days alive or out of hospital within 14 days after recruitment than standard guideline based treatment. This strategy, however, did reduce the duration of systemic corticosteroid exposure to less than half, compared with standard care.

Although the absolute risk was moderate, there were 12 more readmissions with acute exacerbations of COPD or death (of these, three were fatalities) within the first month in the eosinophil-guided group. These differences were not statistically significant; however, because the study was not powered to detect differences in this absolute risk range, we cannot rule out that this was an actual harm effect from the interventional strategy. A meta-analysis[3] of placebo versus guideline-based systemic corticosteroid therapy in more than 1300 patients with acute exacerbations of COPD did not detect any benefit or harm regarding mortality (hazard ratio 1·0, 95% CI 0·6–1·7), and thus we consider it unlikely that our algorithm could cause a worse outcome regarding mortality than placebo. Within 90 days, 13 patients more in the control group had infections requiring antibiotic treatment, a non-significant difference, and worsening of existing diabetes within 30 days was significantly more common in the control group. The absence of apparent differences for other side-effects might, apart from insufficient power for these endpoints, have been due to the short follow-up, which might not have captured side-effects that take a long time to develop; eg, osteoporotic fractures. Blood glucose concentrations on day 5 were slightly higher among patients in the control group than in the eosinophil-guided group. Although these results could be interesting from a physiological point of view, the clinical relevance is not clear.

We wanted to ensure that the tested interventional strategy of eosinophil-guided systemic corticosteroids in acute exacerbations of COPD would not result in worsening of the outcome of length of stay, compared with not using systemic corticosteroids at all. Thus, we chose as the non-inferiority boundary a maximum worsening in the primary outcome measure of 1·2 days, equal to the effect of systemic corticosteroids versus placebo in a meta-analysis.[3] The tested strategy was successful in reducing the exposure to systemic corticosteroids, but we cannot exclude the possibility that a more aggressive algorithm, such as a single dose of systemic corticosteroid, might have been more effective. In most patients, the first eosinophil count was done before administration of methylprednisolone, but in a subset, the initial dose of systemic corticosteroids might have affected the eosinophil count. This followed the rationale of the trial that on days where eosinophil inflammation was not evident, a new dose of corticosteroids was not needed.

In another randomised trial[17] with 109 patients with moderate acute exacerbations of COPD of whom only ten were admitted to hospital, patients were randomly assigned to receive either oral prednisolone for 14 days, or prednisolone or placebo according to a single exacerbation eosinophil count. Without any obvious harm, the use of systemic corticosteroids was reduced substantially.[17] However, this trial differed markedly from ours because those patients were less severely ill, the biomarker guidance was done on a single eosinophil count, and the sample size was smaller. In another randomised, controlled multicentre trial[5] of 314 patients admitted to hospital with severe acute exacerbations of COPD, in which corticosteroid treatment was not guided by eosinophils, non-inferiority was shown regarding clinical outcome and systemic corticosteroid therapy was reduced from 14 days to 5 days. Since that trial was published, more knowledge has been acquired on eosinophilic inflammation in COPD and additionally, the importance of reducing corticosteroid exposure has been increasingly acknowledged.[6]

Our trial had some limitations. First, although our trial was multicentre and randomised, the design was open-label. The investigators were masked to the database, and the investigators doing the interim and final analyses were unaware of the study group assignments. However, the physicians, nurses and patients were aware of the assignments, and this might have resulted in some non-protocolised co-interventions; eg, in a few cases, the investigator was involved in conference decisions to discharge patients, which could potentially have affected some of the endpoints.

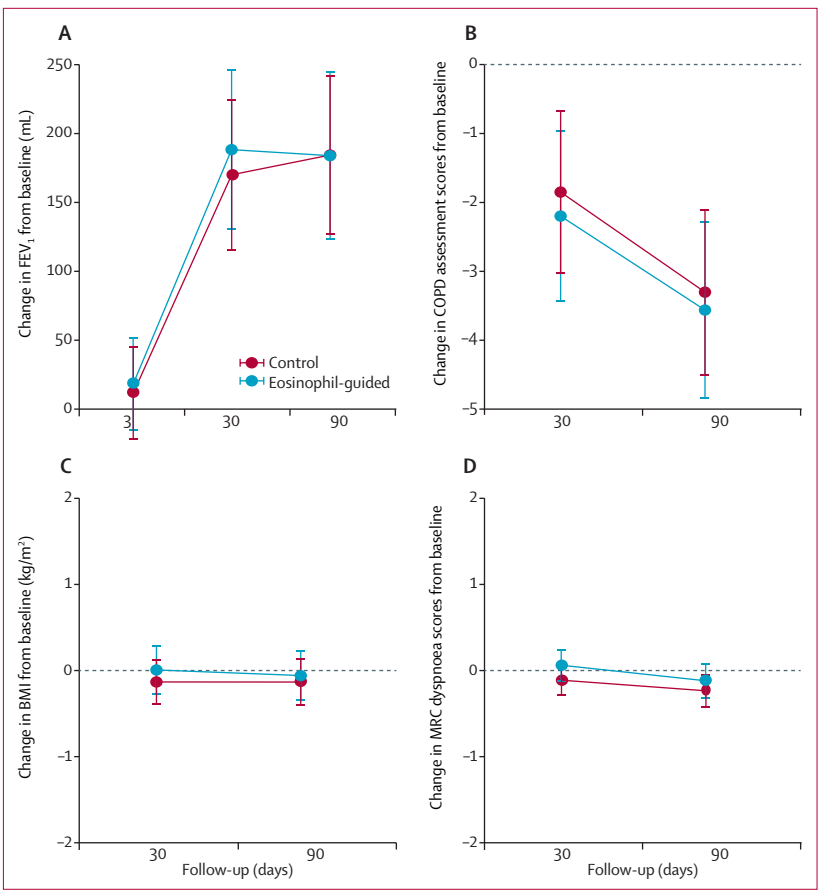

Figure 4: **Endpoints assessed on days 30 and 90**
Graphs show changes from randomisation to end of follow-up for (A) FEV_1, (B) COPD assessment test scores, (C) BMI, and (D) MRC dyspnoea scores. COPD=chronic obstructive pulmonary disease. BMI=body-mass index. MRC=Medical Research Council.

Second, our study did not have sufficient power to detect possible differences in mortality rate. However, the 30-day mortality was low in both treatment arms (6% *vs* 4%) compared with published data from admissions at 4500 US hospitals[31] in which 30-day mortality ranged from 5·9% to 13·5%. Third, the adherence to our eosinophil-guided algorithm was complete in only 88% for all intervention days (day 2 through 5). The main reason for non-adherence was the refusal of ten treating physicians. However, this fraction was less than that of other trials using biomarker-guided algorithms.[32] For the standard group, adherence was higher (93%), but was still not complete for all days.

Fourth, it was not possible to measure the eosinophil count after discharging patients in the intervention group from hospital. We could have visited the discharged patients at home to do this; however, we decided not to do so, since we wanted to test an intervention that could be implemented directly. We acknowledge that these measurements may have been informative. Fifth, we did not have long-term follow-up data for our patients. For some endpoints such as infections, adrenal insufficiency, venous thromboembolisms, and osteoporotic fractures,[33,34] this might be important, but awaiting these events to happen would have delayed the reporting of the trial results for several years. Additionally, BMI, MRC dyspnoea scores, and CAT scores were analysed on day 30, which was not the optimum timepoint to analyse these; capturing these data at an earlier timepoint might have been more sensitive.

Sixth, only about one in four of the screened patients were recruited and we cannot be sure that our strategy can be implemented with the same result among patients similar to those screened but not eventually recruited. Seventh, all patients in both treatment groups received methylprednisolone initially before recruitment. Thus, the eosinophilic guidance started at the time of the decision of whether the patient should have a second dose of systemic corticosteroids. Although this strategy might not have been ideal for the trial, it was a pragmatic choice that had to be made, as we judged that according to current guidelines, withholding systemic corticosteroids before informed consent was signed would not be ethically feasible. The administered dose of systemic corticosteroids at admission, before recruitment into the trial, followed national Danish recommendations and was higher than that recommended by GOLD.[27] Thus, all our patients in both treatment groups received an 80 mg initial dose, which might have affected the corticosteroid-sparing effect of our intervention. Data are scarce on which dose is optimal regarding effect and harm; however, observational data[35] suggest that higher accumulated doses can lead to higher incidence of hyperglycaemia and longer duration of admittance. Our corticosteroid-sparing regimen is nevertheless, to our knowledge, the most restrictive in reducing the accumulated dose of corticosteroids, but we cannot exclude the possibility that the results might have been different had we chosen a lower initial dose – or none. Finally, approximately 2% of the patients were never-smokers. Although this is a low frequency and smoking history is not a formal criterion for COPD diagnosis,[27] we acknowledge that this is disputed.

In conclusion, this study showed that a reduction in potentially inappropriate systemic corticosteroid duration can be achieved by using an eosinophil-guided algorithm to aid clinical judgement in highly vulnerable patients with acute exacerbations of COPD requiring hospital admission. Although there were no differences in the primary outcome of days alive and out of hospital within two weeks compared with standard care, we did not have sufficient statistical power to detect discrete worsening in important outcome measures such as readmission with acute exacerbations of COPD and death. Thus, we cannot entirely rule out harm caused by the intervention. Larger trials powered to detect such differences should be done.

Contributors

The study director J-USJ and the principal investigator PradS of the CORTICO-COP trial take responsibility for the integrity and the accuracy of their analysis. J-USJ, JV, NS, JTW, and PradS generated the hypothesis for the study. PradS and J-USJ wrote the first protocol, obtained funding for the study, and initiated the study. PradS, TSL, RRL, FSH, CSB, PralS, KA, CM, JE, JJ, MM, TPS, EB, and AKMA recruited and followed up patients. PradS and JE did the statistical analyses. PradS, TSL, and RRL coordinated the trial and were responsible for monitoring. All authors designed the study; collected and interpreted the data; and critically revised the manuscript. All authors read and approved the final manuscript.

Declaration of interests

PradS reports personal fees from Novartis outside of the submitted work. JV reports personal fees from GlaxoSmithKline, Chiesi Pharmaceuticals, Boehringer-Ingelheim, Novartis, and AstraZeneca; and is supported by the National Institute of Health Research Manchester Biomedical Research Centre (Manchester, UK). All other authors declare no competing interests.

Data sharing

Data collected for this study, including individual participant data and a data dictionary defining each field in the set, will be made available to others in form of deidentified participant data. The study protocol and statistical analysis plan for the original study is available at www.coptrin.dk. Informed consent forms will not be available according to Danish legislation. These data will become available from Jan 1, 2023, upon request from investigators. Such requests, including study protocol with clear hypotheses should be sent to the principal investigator, and the CORTICO-COP steering committee will review such a request. If the hypothesis does comply with the informed consent supplied by the participants, and the hypothesis is judged to be valid, a data transfer agreement will be prepared, after which the data will be transferred. If the hypothesis is not covered by the informed consent, the CORTICO-COP steering committee will assist in preparing an application for dispensation to our ethics committee.

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