Treatment of COPD Groups GOLD A and B with Inhaled Corticosteroids in the COSYCONET Cohort – Determinants and Consequences

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Original Research

Background: In COPD patients of GOLD groups A and B, a high degree of treatment with inhaled corticosteroids (ICS) has been reported, which is regarded as overtreatment according to GOLD recommendations. We investigated which factors predict ICS use and which relationship it has to clinical and functional outcomes, or healthcare costs.

Methods: We used pooled data from visits 1 and 3 of the COSYCONET cohort (n=2741, n=2053, interval 1.5 years) including patients categorized as GOLD grades 1–4 and GOLD group A or B at both visits (n=1080). Comparisons were performed using ANOVA, and regression analyses using propensity matching and inverse probability weighting to adjust for differences between ICS groups. These were defined as having ICS at both visits (always) vs no ICS at both visits (never). Measures were divided into predictors of ICS treatment and outcomes.

Results: Among 1080 patients, 608 patients were eligible for ICS groups (n=297 never, n=311 always). Prior to matching, patients with ICS showed significantly (p<=0.05 each) impaired lung function, symptoms and exacerbation history. After matching, the outcomes generic quality of life and CO diffusion capacity were increased in ICS patients (p<=0.05 each). Moreover, costs for respiratory medication, but not total health care costs, were significantly elevated in the ICS group by 780€ per year.

Conclusion: ICS therapy in COPD GOLD A/B patients can have small positive and negative effects on clinical outcomes and health care costs, indicating that the clinical evaluation of ICS over-therapy in COPD requires a multi-dimensional approach.

Keywords: COPD, inhaled corticosteroids, GOLD groups, overtreatment

Introduction

In recent years, a number of studies revealed a high degree of overtreatment with respiratory medication, in particular with inhaled corticosteroids (ICS), in patients with COPD and especially in GOLD groups A and B.¹⁻⁵ Despite the narrow indication for the prescription of ICS in COPD, their use has been reported in up to 70% of patients in some European countries, such as Switzerland, Greece, and the UK.⁶⁻⁸ In line with this, data from the COSYCONET COPD cohort also showed that about 2/3 of patients received an inhaled corticosteroid, though this would have been indicated in only about 50% according to GOLD 2017 recommendations.⁹ This is relevant, as ICS have side effects, such as a higher rate of pneumonia, diabetes mellitus, osteoporosis, oropharyngeal candidiasis and hoarseness.¹⁰¹¹ Overtreatment also has economic consequences; for the
Netherlands, for example, savings of 84 million Euro per year have been estimated, if ICS therapy would be reduced to the essential level.12

To guide therapeutic decisions, recommendations, such as those given by GOLD,13 provide basic orientation but the final decision might depend on additional factors such as drug intolerances and interactions, patients’ preferences, impairments in lung function, and comorbidities such as dementia, depression,14,15 or cardiac diseases associated with increased symptom burden16 but not necessarily higher exacerbation rate.

Based on this, a thorough analysis of data from COPD patients with ICS overtreatment could help to understand, which factors determine the therapeutic decision for ICS, and conversely, which negative and potentially positive, effects overtreatment has on clinical and functional outcomes. The results of such an analysis might be useful for a refinement of treatment recommendations. We addressed these questions using data of the large and well-characterized multi-center COPD cohort COSYCONET (COPD and Systemic Consequences-Comorbidities Network).17

Materials and Methods
Study Population
The present analysis used data of the baseline visit 1 (n=2741) and the 18-month follow-up visit 3 (n=2053) of COSYCONET. Visits took place between 2011 and 2015. The observational COPD cohort study COSYCONET investigates the interaction of lung disease, comorbidities and systemic inflammation. Within COSYCONET, patients aged 40 years and older with a physician-based diagnosis of COPD (according to the GOLD criteria) or chronic bronchitis were included and repeatedly re-examined in 31 study centres across Germany. Further details on recruitment, inclusion/exclusion criteria and the assessment of medication can be found elsewhere.17

We only included patients categorized as GOLD grades 1–418 and GOLD groups A or B (according to mMRC) at both visits (n=1080). Since for groups A/B in the absence of the comorbidity asthma ICS are considered as over-treatment, we focused our analysis on the A/B groups, further excluding patients with the physician-based diagnosis of asthma (n=133) or alpha 1-antitrypsin deficiency (n=58). Patients of GOLD groups C and D were not considered, as in these groups, the use of ICS is not necessarily overtreatment.

The treatment groups used for analysis were based on patients’ reports on the intake of ICS at visits 1 and 3. Patients with ICS at both visits were categorized as “ICS always”, those with no intake at both visits as “ICS never”. In doing so, a stable ICS use over at least 1.5 years was guaranteed, although the number of patients was reduced.

COSYCONET has been approved by the ethical committees of all study centers, and all patients gave their written informed consent.17

Assessments
The study protocol and procedures of COSYCONET have been described previously.17 All assessments were performed under stable conditions and included patients’ history, clinical state (mMRC, CAT), quality of life (EQ-VAS), St George’s Respiratory Questionnaire (SGRQ), BODE score19 and Fat-Free Mass Index (FFMI),20 guided by standard operating procedures.17 Physical capacity and activity were evaluated using the 6-Minute-Walking Distance (6-MWD) and the International Physical Activity Questionnaire (IPAQ).21 The identification of comorbidities was based on patients’ reports of physician-based diagnoses, combined with the intake of disease-specific medication.22 Lung function assessments obeyed established guidelines.23-25 The measures comprised forced expiratory volume in one second (FEV1), forced vital capacity (FVC) and their ratio (FEV1/FVC) from spirometry, moreover diffusing capacity for carbon monoxide (CO) in terms of transfer factor (TLCO) and transfer coefficient (KCO), moreover intrathoracic gas volume (ITGV), residual volume (RV), total lung capacity (TLC) and the ratio RV/TLC from body plethysmography. Predicted values for spirometry23 and diffusing capacity25 were taken from the Global Lung Function Initiative (GLI), for body plethysmography from ECSC.26

Annual healthcare costs were calculated by multiplying in- and outpatient, rehabilitation and physiotherapy utilization frequencies with German unit costs. The estimation of medication costs was restricted to prescription-only pharmaceuticals and based on information about name, national drug code, defined daily doses, and pharmacy retail prices. All costs were winsorized at the 95th percentile and refer to the price year 2012. Further details on cost estimation have been described elsewhere.27

Statistical Analysis
We performed a combined analysis of visit 1 and 3 data in order to be consistent with the ICS medication groups and to reduce the variability of values while keeping the
degrees of freedom low. There was no hint on differential loss in the ICS groups over the two visits. Correspondingly, for all outcome parameters (see below), mean values of visit 1 and 3 values were taken. The groups “ICS always” vs “ICS never” were compared using chi-square tests for categorical variables, and analysis of variance (ANOVA) or Kruskal–Wallis tests for continuous variables, depending on the data distribution.

Predictors of ICS Treatment and Inverse Probability of Treatment Weighting

To identify independent determinants of ICS treatment we considered as potential predictors those variables that are easily available to treating physicians. These included age, BMI, FEV1%predicted, FEV1/FVC, exacerbation history (any/none), all eight single CAT items to cover COPD symptoms; for these parameters mean values of visits 1 and 3 were taken. Visit 1 values were chosen as predictors for sex, years since COPD diagnosis, GOLD group based on mMRC, smoking status (active vs former/never), and DemTect and PHQ-9 score to address cognitive impairment and depression which might have influenced the therapeutic decisions.

As patients’ characteristics were significantly different between the “never ICS” and “always ICS” groups, we used propensity scores (PS) to adjust for the differences. PS were calculated based on a logistic regression model estimating the probability of receiving ICS on the basis of the predictors mentioned above. In a second step, Inverse Probability of Treatment Weights (IPW) were derived from the PS. As a result, a patient who actually received ICS but had a low probability (PS) for ICS was compared with an untreated patient with equally low PS, as both were similar in clinical characteristics according to their PS. The different PS distributions in the two groups were transformed into statistical weights, enabling a valid comparison between groups. All analyses were performed using SAS software (SAS Institute Inc., Cary, NC, USA, version 9.4), specifically the procedures PSMATCH, LOGISTIC and GENMODE.

Relationship Between ICS Treatment and Outcomes

As outcomes, we chose variables that we considered as unlikely to be available to or used by the treating physicians for treatment decisions regarding ICS. These comprised disease-specific and generic health-related quality of life (HRQL) assessed by the three domains of the SGRQ as well as the VAS scale, moreover physical capacity in terms of 6-MWD, CO diffusing capacity, the BODE score, FFMI, and health care costs. The outcomes were different from the predictors of treatment and computed using IPW in generalized linear regression models, whereby a gamma distribution was chosen for the analysis of the skewed cost data. In addition to the binary ICS variable (always vs never), the covariates from the logistic regression were included for maximal adjustment.

Sensitivity Analyses

We performed several sensitivity analyses to test for the robustness of results regarding the relationship between ICS and outcomes. First, models were recalculated including patients with a physician-based diagnosis of asthma. Second, we excluded patients who reported the intake of oral corticosteroids (OCS). Third, the definition of ICS groups was altered by comparing “always” vs its complement “not-always”, and of “never” vs its complement “not-never”.

Results

Baseline Characteristics

Following the in- and exclusion criteria, 608 patients were of group A or B at both visits, whereby 297 had never ICS and 311 always ICS (Table 1, Figure 1). Unadjusted differences between both groups were significant (p<0.05 each) for age, smoking status, years since diagnosis, distribution of GOLD groups, exacerbation rates, FEV1%predicted, FVC %predicted, FEV1/FVC, RV %predicted, RV/TLC, 6-MWD, SGRQ subscores and total CAT score. This indicated that patients with ICS showed an impaired clinical and functional state compared to patients without ICS. The level of education was not found to differ between groups thus education was not considered as a potential predictor of ICS treatment.

The distribution of comorbidities is shown in Table 2; the only significant difference was that patients with ICS showed a higher proportion of arterial hypertension. Treatment with respiratory medication is shown in Table 3. In the ICS always group, 72% of patients received a combination of LAMA +LABA+ICS. Regarding unadjusted mean annual healthcare costs (Table 4), patients with ICS had significantly higher total costs (+340€/year). With respect to separate cost categories, the difference between groups was greatest for costs of respiratory medication (ATC Code “R”), with +780€/year for the ICS group. On the other hand, patients with ICS showed a trend towards lower inpatient costs (−100€/year), which was, however, not statistically significant.
Table 1 Characteristics of Patients in GOLD Groups A/B Stratified by Treatment with/without ICS

|                                | ICS Never* N = 297 | ICS Always* N = 311 | p-value |
|--------------------------------|--------------------|--------------------|---------|
| Age (y)                        | 65.7 ± 8.4         | 67.3 ± 7.6         | 0.0130  |
| Male                           | 187 (63.0)         | 216 (69.5)         | 0.0906  |
| BMI (kg/m²)                    | 26.7 ± 4.8         | 27.2 ± 5.1         | 0.1888  |
| FFM (kg/m²)*                   | 18.4 ± 2.3         | 18.4 ± 2.6         | 0.9204  |
| Smoking status                 |                    |                    |         |
| Active                         | 117 (39.4)         | 65 (20.9)          | <0.0001 |
| Not active                     | 180 (60.6)         | 246 (79.1)         | <0.0001 |
| Education                      |                    |                    |         |
| Basic                          | 157 (52.9)         | 177 (56.9)         | 0.5192  |
| Secondary                      | 84 (28.3)          | 76 (24.4)          |         |
| Higher                         | 56 (18.9)          | 50 (18.7)          |         |
| Years since COPD diagnosis     | 5.7 ± 5.8          | 8.0 ± 6.1          | <0.0001 |
| GOLD groups (mMRC)            |                    |                    |         |
| A                              | 218 (73.4)         | 191 (61.4)         | 0.0016  |
| B                              | 79 (26.6)          | 120 (38.6)         |         |
| mMRC *                         | 1.19 ± 0.72        | 1.42 ± 0.79        | 0.0001  |
| Exacerbation history           |                    |                    |         |
| None                           | 197 (66.3)         | 158 (50.8)         | 0.0001  |
| Mild/Moderate                  | 100 (33.7)         | 153 (49.2)         |         |
| FEV₁ (%predicted)             | 62.9 ± 17.3        | 54.2 ± 17.6        | <0.0001 |
| FVC (%predicted)               | 86.8 ± 16.8        | 80.1 ± 16.9        | <0.0001 |
| FEV₁/FVC                       | 72.2 ± 13.4        | 67.2 ± 13.5        | <0.0001 |
| ITGV (%predicted)              | 140.5 ± 29.2       | 144.0 ± 31.1       | 0.1551  |
| RV (%predicted)                | 154.4 ± 39.4       | 166.1 ± 43.2       | 0.0007  |
| RV/TLC                         | 123.0 ± 22.0       | 132.2 ± 23.7       | <0.0001 |
| TLCO (%predicted)              | 62.0 ± 19.1        | 59.5 ± 21.5        | 0.1351  |
| KCO (%predicted)               | 67.1 ± 24.1        | 68.2 ± 25.0        | 0.5718  |
| OCS                            | 12 (4.0)           | 24 (7.7)           | 0.0549  |
| DemTest                        | 15.4 ± 2.8         | 15.4 ± 2.7         | 0.8905  |
| PHQ-9                          | 4.8 ± 3.9          | 5.1 ± 4.0          | 0.2480  |
| 6-MWD (m) *                    | 466.6 ± 85.7       | 433.1 ± 99.6       | <0.0001 |
| IPAQ *                         | 4808.8 ± 3777.8    | 4386.4 ± 3632.8    | 0.1632  |
| BODE *                         | 1.31 ± 1.40        | 2.14 ± 1.77        | <0.0001 |
| SGRQ symptoms                  | 43.3 ± 19.6        | 48.3 ± 19.6        | 0.0021  |
| SGRQ activity *                | 44.1 ± 23.5        | 51.3 ± 23.4        | 0.0002  |
| SGRQ impacts *                 | 19.2 ± 15.2        | 22.6 ± 17.4        | 0.0114  |
| EQ-VAS *                       | 65.2 ± 16.4        | 62.6 ± 16.3        | 0.0603  |
| CAT total score                | 142 ± 6.1          | 159 ± 6.5          | 0.0007  |

Notes: *ICS always was coded as yes, if a patient reported the intake of ICS at both visits. ICS never was defined as no ICS prescription at both visits. †Used as outcome; other variables were used as predictors of treatment with ICS. ‡Ex- or never-smoker. Mean values and standard deviations, as well as absolute numbers are given. Comparisons between groups were performed by chi-square tests, ANOVA and Kruskal–Wallis tests, as appropriate.
Predictors of ICS Use
Among the variables included as potential predictors of ICS therapy, active smoking, having had a mild or moderate exacerbation, lower FEV$_1$%predicted, a longer time since diagnosis, higher scores of CAT item 2 (phlegm) and higher PHQ$_9$ score, as well as lower scores of CAT items 3 (chest tightness) and 8 (energy) turned out to be significant (Table S1). Figure 2 illustrates the standardized mean differences between the two ICS groups before and after applying the IPW matching. It can be seen that after the weighting process differences were lower than 0.25, which is generally considered as the maximum acceptable bound to assure comparability; they even satisfied the stronger requirement of being <0.1. Thus, the matching procedure was successful and ensured statistical comparability between groups.

Comparison of Outcome Measures Regarding ICS Treatment
Table 5 shows the associations between ICS treatment and outcome measures expressed as differences between ICS groups after IPW-based adjustment for differences in patient characteristics. ICS was associated with higher EQ-VAS (p=0.0163) and higher TLCO %predicted (p=0.0030). Furthermore, there was a trend (p<0.10) towards higher KCO and lower FFMI in patients treated with ICS.

Regarding annual direct healthcare costs, the results are shown in Figure 3. The difference in total direct costs (see Table 4) was no longer significant after IPW-based adjustment. In contrast, ICS was associated with 1.31-times higher total medication costs, specifically with 1.79-times higher costs for respiratory medication (p<0.05 each).

Table 2 Prevalence of Comorbidities

| Comorbidity               | ICS Never N = 297 | ICS Always N = 311 | p-value |
|---------------------------|-------------------|--------------------|---------|
| Diabetes                  | 32 (10.8)         | 39 (12.5)          | 0.4980  |
| Gastrointestinal disorders* | 112 (37.7)       | 117 (37.6)         | 0.9818  |
| Hyperuricemia             | 39 (13.1)         | 58 (18.7)          | 0.0633  |
| Hyperlipoproteinemia       | 126 (42.4)        | 133 (42.8)         | 0.9323  |
| Osteoporosis *            | 30 (10.1)         | 35 (11.3)          | 0.6456  |
| Hypertension *            | 154 (51.9)        | 186 (59.8)         | 0.0483  |
| Cardiac disease #         | 65 (21.9)         | 58 (18.7)          | 0.3208  |

Notes: *Self-reported information was combined with disease-specific medication. #At least one out of: Coronary artery disease, heart failure, myocardial infarction. Absolute numbers and percentages are given. p-values refer to the comparison between patients without and with ICS and were derived from Chi-square statistics.
Table 3 Treatment with Respiratory Medication

|                      | ICS Never N = 297 | ICS Always N = 311 |
|----------------------|---------------------|---------------------|
| No respiratory medication | 83 (27.9)           | 106 (35.7)          |
| Only LAMA            | 62 (20.9)           | 4 (1.3)             |
| Only LABA            | 46 (15.5)           | 224 (72.0)          |
| LAMA + LABA          |                     |                     |
| Only ICS             |                     |                     |
| LAMA + ICS           | 9 (2.9)             |                     |
| LABA + ICS           | 74 (23.8)           |                     |
| LAMA + LABA + ICS    |                     |                     |

Notes: Absolute numbers and row percentages are given. All numbers are based on information assessed at visit 1.

Table 4 Mean Annual Direct Healthcare Costs in €

|                      | ICS Never N = 297 | ICS Always N = 311 | p-value  |
|----------------------|---------------------|---------------------|----------|
| Total direct costs   | 4206 ± 4854         | 4547 ± 3822         | <0.0001  |
| Medication costs     | 1490 ± 1286         | 2191 ± 1004         | <0.0001  |
| Respiratory medication| 750 ± 408            | 1528 ± 495          | <0.0001  |
| Other medication     | 740 ± 1143          | 663 ± 826           | 0.4162   |
| Inpatient costs      | 1336 ± 2437         | 1224 ± 2312         | 0.9826   |
| Outpatient costs     | 616 ± 459           | 660 ± 458           | 0.1844   |
| Rehabilitation costs | 194 ± 445           | 201 ± 485           | 0.9733   |
| Physiotherapy costs  | 76 ± 139            | 79 ± 143            | 0.9131   |

Notes: Medication costs was restricted to prescription-only pharmaceuticals and based on information about name, national drug code, defined daily doses, and pharmacy retails prices. Mean values and standard deviations are given. p values were based on Kruskal-Wallis test. All costs refer to the price year 2012.

Sensitivity Analysis

When excluding patients with oral steroids, the results remained virtually unchanged regarding magnitude and significance level of effects. Conversely, when including patients with the diagnosis of asthma (n=133), the results were also in accordance with our main analysis, however effect sizes were smaller. Moreover, when using regression models adjusting for all covariates but without using IPW, slightly higher p-values resulted.

In addition to the comparison always vs never ICS, we performed comparisons of always vs not-always, and of never vs not-never. These contrasts were less sharp than that between always vs never but had the advantage that the total data set could be used. Regarding the differences in outcomes, both sensitivity analyses confirmed the results of the always vs never analysis.

Discussion

The present study had the aim to evaluate determinants and consequences of ICS therapy in COPD patients of GOLD groups A/B without the comorbidity asthma, in whom ICS therapy is not generally recommended.29,30 Compared to patients without ICS, those receiving ICS showed impairments in a variety of clinical and functional measures. These impairments could be either the reason for the use of ICS, or its consequence, or both. To reveal the effects of ICS therapy under these circumstances, proper adjustment was indispensable. We achieved this by propensity score matching and corresponding weighted regression analysis. The matching used variables that may be argued to have an influence on the decision to prescribe ICS in clinical practice. After matching, nearly all differences in outcome measures between patients with vs without ICS therapy were no more significant. Remarkably, however, generic quality of life and CO diffusing capacity turned out to be slightly improved in association with ICS. The costs for all medication and respiratory medication remained significantly elevated after matching, in contrast to total health care costs. These data indicate that in COPD patients of GOLD A/B groups, ICS therapy might have small positive as well as negative effects on outcomes including health care costs.

In GOLD A/B patients without concomitant asthma, initial treatment with short- or long-acting bronchodilators is commonly considered to be standard of care.29,31 This was also true until 2015 when the measurements underlying the present analysis were completed. Recent data demonstrated a high frequency of ICS use in A/B patients in several countries.5-8 Among the consequences, increased medication costs have already been addressed.12,32 The side effects of ICS are known to depend on dosage and type of ICS (eg fluticasone, budesonide, beclomethasone) and probably occur across all severity grades of COPD33,34 including groups A/B. This raises the question of the functional consequences of ICS therapy in A/B patients but also on potential positive effects, which has not been studied until now.

The analysis was rendered difficult through the fact that patients with ICS therapy showed impairments in many clinical and functional parameters compared to those without ICS. The impairments might have been among the factors leading to the prescription of ICS, or they might be consequences of the prescription. This can only be resolved by adjustment procedures, such as propensity score matching, that aim to achieve comparability between groups.

We distinguished between predictors and outcomes of ICS therapy. As predictors, we chose those measures of which it could be reasonably assumed that they were both available to and used by treating physicians in the decision
pro vs con ICS. This excluded complex tools such as the SGRQ which we considered useful only as an outcome measure. The same applied to 6-MWD, IPAQ, BODE and FFMI. Regarding CO diffusing capacity, it also seemed not likely that physicians would use this measure for the decision on ICS treatment. Exacerbations (no versus mild/moderate) were only predictors, and severe exacerbations were by definition excluded as they would have led into GOLD C and D categories.

The controversy about the usefulness of ICS in COPD is reflected by its cautious consideration in GOLD A/B patients in the most recent recommendations. In the last years, the decision has often been linked to blood eosinophil counts.

A recent study showed a reduction in exacerbation rate as a function of eosinophilic count: the higher the eosinophilia, the greater the benefit of ICS within triple therapy compared with LAMA/LABA without ICS. Accordingly, there was a 16% reduction of hospitalizations due to severe exacerbations by ICS, and in another trial, the reduction of moderate and severe exacerbations by ICS was even 52%. These data included group C and D patients and were thus not comparable to our data in A/B patients. We also did not include eosinophil count as it was available only in 131 patients. A direct comparison of the groups always vs never ICS showed no significant differences (p=0.16) in eosinophil numbers.

**Table 5** Association Between ICS and Outcome Measures (Always vs Never)

| Outcomes                       | Estimate | 95% CI       | p-value |
|--------------------------------|----------|--------------|---------|
| Health-related quality of life |          |              |         |
| EQ-VAS                         | 2.39     | 0.44 to 4.34 | 0.0163  |
| SGRQ symptoms                  | -0.55    | -2.50 to 1.41| 0.5839  |
| SGRQ activity                  | -1.56    | -3.45 to 0.33| 0.1064  |
| SGRQ impacts                   | -1.04    | -2.55 to 0.48| 0.1805  |
| Diffusion capacity             |          |              |         |
| TLCO (%predicted)              | 3.65     | 1.24 to 6.05 | 0.0030  |
| KCO (%predicted)               | 3.16     | -0.48 to 6.8 | 0.0885  |
| Fat free mass index            | -0.20    | -0.41 to 0.00| 0.0502  |
| Physical activity              |          |              |         |
| 6-MWD                          | -2.42    | -13.79 to 8.96| 0.6768  |
| IPAQ                           | 23.43    | -544.22 to 591.0| 0.9355 |

Notes: Estimates with 95% CI for the variable ICS=always are shown. Each row represents a separate linear regression model, adjusted for covariates and including the IPW (based on propensity scores). The symbol next to the estimate indicates the direction of change for estimates with p<0.05: ↑ improvement of outcome, ↓ deterioration of outcome.
After matching all-cause outpatient costs and total health care costs were similar in both ICS groups, whereas respiratory medication costs remained higher in the ICS group, in line with the previous finding. Conversely, all-cause inpatient costs tended to be lower in ICS patients. Due to the definition of A/B groups, this could not have been due to severe exacerbations but must have had other reasons. From the data available in COSYCONET, a more detailed analysis was not possible as the reason for utilization was not recorded. Irrespective of this, our findings indicate that the costs of ICS therapy in A/B patients require a detailed analysis.

Regarding outcome measures, the use of ICS was associated with better generic quality of life as measured by the EQ-VAS scale, in line with findings showing a deterioration of EQ-VAS in patients undergoing ICS withdrawal. This is remarkable, as among our ICS patients of GOLD groups A/B 72% also received LABA/LAMA, ie a potent bronchodilator combination. Unfortunately, only 87 patients received ICS monotherapy or a combination with LAMA or LABA, and therefore, numbers were too low to draw reliable conclusions for patients with ICS but not triple therapy. In the propensity matching, we used mMRC and the single CAT questions as predictors but not the SGRQ that also measures COPD symptoms. The finding that the SGRQ subdomains showed no differences between ICS groups thus indicates that the matching for symptoms was adequate. ICS therapy was also associated with an increased CO diffusing capacity after matching. It is known that structural changes in the peripheral lung cannot be adequately represented by standard spirometric measurements, while diffusing capacity can be used for this purpose. Our observational results are in line with those of randomized controlled studies that showed an improvement of diffusing capacity during treatment with ICS, whereas spirometric values were not found to be significantly altered.

Beyond the effects of ICS on the selected outcome measures, one of the findings of our study was the identification of predictors of ICS therapy. There were associations with exacerbation history and FEV₁%predicted but also a higher symptom burden for the CAT items cough, phlegm, dyspnoea, confidence of leaving home, and sleep disturbance. The fact that only 5 of 8 items were predictors underlined our previous finding that the single CAT items carry different information.

We used the single items as a substitute for informal questions that might be posed by the treating physician in the decision on ICS treatment, even when not using the CAT instrument. This assumption was in accordance with data showing that in the general practitioner setting, ICS treatment was re-initiated after withdrawal mainly due to respiratory symptoms.
Limitations and Strengths

The analysis was based on cross-sectional data and naturally does not allow causal inferences. However, using the propensity score approach we aimed to transform the data set into one representing two matched groups as far as possible, and this was effective. Still, unobserved confounders might have influenced the decision on ICS therapy. We pooled data of visits 1 and 3, although there were small changes over time, and this was done for both outcome measures and predictors, wherever this made sense. The reason was that we wanted to maximize power by reducing variability, whereas the introduction of time effects in a repeated-measures design would have prevented the use of a well-established matching approach. An additional analysis with an adjusted repeated-measures design but without IPW matching yielded qualitatively similar results for the outcome measures; we thus consider the pooling as justified. In addition, the information regarding the eosinophilic phenotype of the patients could not be evaluated. However, we excluded patients with the comorbidity asthma, as well as patients with alpha 1-antitrypsin deficiency due to their high medication cost.\(^{43}\) Exacerbation history derived from self-reported information was sufficient for categorization into GOLD groups as in previous analyses of COSYCONET data but whether there was under-reporting,\(^{44,45}\) is not known. Moreover, the reasons for hospitalizations due to non-respiratory causes were not known, an information which might have been interesting in view of indirect positive effects of ICS on the heart.\(^{46,47}\) Unfortunately, no data on the prevalence of pneumonia or oral candidiasis were collected in COSYCONET, therefore no conclusions can be drawn regarding the known typical side effects of ICS. At least, no significant differences were observed with respect to the prevalence of osteoporosis (see Table 2). On the other hand, the strength of the study was the high quality of clinical, functional and health economic data in combination with a large data set, as well as the sophisticated data analysis by inverse probability weight matching.

Conclusion

In COPD patients of GOLD groups A/B, ICS treatment is considered inappropriate in most circumstances. We found that A/B patients treated with ICS showed impairments in a number of functional and clinical measures compared to those without ICS. To identify the real ICS effects, we adjusted for the differences in predictors that might be used by physicians for therapeutic decisions. After adjustment, most of the differences in measures chosen as outcome disappeared. Still, ICS treatment was linked to improvements in generic quality of life and CO diffusing capacity, but also an increase in the costs of respiratory medication, without effect on total direct health care costs. These data indicate potential beneficial effects of ICS in a subgroup of COPD patients in GOLD groups A and B. However, future studies are needed to clearly define subgroups that might benefit from ICS.

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Data Sharing Statement

The basic data are part of the German COPD cohort COSYCONET (www.asconet.net) and available upon request. The website of the network provides a detailed procedure for respective applications. The data can be obtained after the submission of a proposal that is
evaluated by the steering committee. All results to which the manuscript refers are documented appropriately in the text, figures or tables.

### Ethics Approval and Consent to Participate

All assessments were approved by the central (Marburg (Ethikkommission FB Medizin Marburg) and local (Bad Reichenhall (Ethikkommission bayerische Landesärztekammer); Berlin (Ethikkommission Ärztekammer Berlin); Bochum (Ethikkommission Medizinische Fakultät der RUB); Borstel (Ethikkommission Universität Lübeck); Coswig (Ethikkommission TU Dresden); Donaustauf (Ethikkommission Universitätsklinikum Regensburg); Essen (Ethikkommission Medizinische Fakultät Duisburg-Essen); Gießen (Ethikkommission Fachbereich Medizin); Greifswald (Ethikkommission Universitätsmedizin Greifswald); Großhansdorf (Ethikkommission Ärztekammer Schleswig-Holstein); Hamburg (Ethikkommission Ärztekammer Hamburg); MHH Hannover/Coppenbrügge (MHH Ethikkommission); Heidelberg Thorax/Uniklinik (Ethikkommission Universität Heidelberg); Homburg (Ethikkommission Ärztekammer Saarbrücken); Immenhausen (Ethikkommission Landesärztekammer Hessen); Kiel (Ethikkommission Christian-Albrechts-Universität zu Kiel); Leipzig (Ethikkommission Universität Leipzig); Löwenstein (Ethikkommission Landesärztekammer Baden-Württemberg); Mainz (Ethikkommission Landesärztekammer Rheinland-Pfalz); München LMU/Gauting (Ethikkommission Klinikum Universität München); Nürnberg (Ethikkommission Friedrich-Alexander-Universität Erlangen-Nürnberg); Rostock (Ethikkommission Universität Rostock); Berchtesgadener Land (Ethikkommission Land Salzburg); Schmellenberg (Ethikkommission Ärztekammer Westfalen-Lippe); Solingen (Ethikkommission Universität Witten-Herdecke); Ulm (Ethikkommission Universität Ulm); Würzburg (Ethikkommission Universität Würzburg)) ethical committees and written informed consent was obtained from all patients.

The study was based on 2741 patients recruited within the COSYCONET framework (ClinicalTrials.gov, Identifier: NCT01245933). For further information see Karch A, Vogelmeier C, Welte T, Bals R, Kauczor HU, Biederer J, Heinrich J, Schulz H, Glaser S, Holle R et al: The German COPD cohort COSYCONET: Aims, methods and descriptive analysis of the study population at baseline. Respir Med 2016, 114:27–37.

### Consent for Publication

Within the ethical approval of COSYCONET, the participants of the study gave their consent to publish the data collected without reference to their person.

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