Association of Guideline-Recommended COPD Inhaler Regimens with Respiratory Exacerbations, Exercise Performance, and Quality of Life

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Abstract

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Background: Although inhaled therapy reduces exacerbations among patients with COPD, the effectiveness of providing inhaled treatment according to recent risk-stratification models remains unclear.

Research Question: Are inhaled regimens that align with the 2017 Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy associated with clinically important outcomes?

Study Design and Methods: We conducted secondary analyses of Long-term Oxygen Treatment Trial data. The trial enrolled COPD patients with moderate resting or exertional hypoxemia between 2009-2015. Our exposure was the patient-reported inhaled regimen at enrollment, categorized as either aligning with, undertreating, or potentially overtreating per the 2017 GOLD strategy. Our primary outcome was hospitalization for COPD. Additional outcomes included COPD exacerbation. We generated multivariable Cox proportional-hazard models across strata of GOLD-predicted exacerbation risk (high vs low) to estimate between-group

hazard ratios for outcomes. We adjusted models *a priori* for potential confounders, clustered by site.

Results: The trial enrolled 738 patients; 73.4% were male with mean age 68.8 years. 571 patients (77.4%) were judged to be at low risk for future exacerbations. 233 patients (31.6%) reported regimens aligning with GOLD recommendations; most regimens (54.1%) potentially overtreated. During 2.3-year median follow-up, 257 patients (34.8%) experienced hospitalization for COPD. Among high-risk patients (GOLD groups C/D), undertreatment was associated with a 49% lower risk of experiencing hospitalization for COPD than regimens that aligned with guideline recommendations (HR 0.51, 95% CI: 0.28, 0.91). Among low-risk patients (GOLD groups A/B), we found no difference in the incidence of hospitalization for COPD across categories of inhaled treatment regimens; however, potential overtreatment was associated with a 53% higher risk of COPD exacerbation (HR 1.53, 95% CI: 1.13, 2.07) and a 64% higher risk of pneumonia (IRR 1.64, 95% CI: 1.01, 2.66).

Interpretation: Among COPD patients with moderate hypoxemia, those reporting inhaled regimens that aligned with the 2017 GOLD strategy did not experience improved clinical outcomes compared to those who were undertreated. The relatively narrow patient population and the observational nature of our study limit the interpretation of our findings. Additional studies are needed to establish the effectiveness of risk stratification model-based inhaled treatment strategies.

INTRODUCTION

Over the past two decades, multiple studies have demonstrated the efficacy of inhaled bronchodilators for reducing respiratory exacerbations while improving symptoms and quality of life among patients with COPD.[1-5] The use of ICSs can further reduce the likelihood of acute respiratory illness among patients with frequent exacerbations;[6-8] however, the decision to prescribe ICSs requires weighing the efficacy of this therapy against the potential risk of pneumonia.[9-13] Despite this evidence, the most effective way to implement inhaled therapy for COPD at the population level remains uncertain. As many as 70% of patients with COPD would not meet the inclusion criteria of the above efficacy studies.[14,15] It remains unclear if patients with milder disease achieve the same risk benefit ratio of inhaled therapy. While some clinicians advocate that all patients with COPD use both inhaled bronchodilators and ICSs regardless of disease severity, this approach ignores the high monetary cost of inhaled therapy and the potential harms of ICSs.[16]

Seeking to address this concern, professional societies and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) have developed models to estimate COPD severity and offer inhaled treatment recommendations.[17-19] Of these, the 2017 GOLD statement represents the most widely accepted COPD management strategy in the developed world. The 2017 GOLD statement incorporates evidence from the above efficacy studies as well as known risk factors for future exacerbations and death to guide treatment.[20-25] Specifically, the 2017 GOLD statement recommends that all patients with COPD use an inhaled bronchodilator and suggests that only patients with a history of frequent exacerbations use an ICS.[17] Despite widespread acceptance of the GOLD strategy, no studies to date have evaluated the effectiveness of inhaled treatment for COPD when provided according to these recommendations.

Our objective was to understand how the receipt of current guideline-recommended care influences outcomes in clinical practice. Among a cohort of COPD patients with moderate

hypoxemia who participated in the Long-term Oxygen Treatment Trial (LOTT),[26,27] we determined the association of using an inhaled regimen that aligns with the 2017 GOLD recommendations and clinically important outcomes. We hypothesized that patients who received an aligned regimen, when compared with those who were undertreated, would experience fewer moderate and severe COPD exacerbations, increased exercise performance, and improved disease-specific quality of life. Among patients considered low risk for future exacerbations and without an indication for ICS, we also hypothesized that patients whose inhaled regimens aligned with guideline recommendations would have a lower risk of pneumonia when compared with patients potentially overtreated with ICS.

METHODS

Data and Study Population

We performed a secondary analysis of LOTT data.[26] LOTT was a randomized trial to determine the efficacy of long-term supplemental oxygen among patients age ≥ 40 years with stable COPD and moderate resting or exercise-induced hypoxemia. The trial enrolled 738 patients between 2009 - 2014 at 42 respiratory clinics across the United States, including academic, community-affiliated, and Veterans Affairs (VA) medical centers. To be included in the trial, patients must have met all the following inclusion criteria:

- COPD predominant lung-disease
- ≥ 40 years of age
- ≥ 10 pack-year history of cigarette smoking
- Modified Medical Research Council (mMRC) dyspnea score ≥ 1
- Post-bronchodilator forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) ratio (FEV_1/FVC) < 0.70
- Post-bronchodilator FEV_1 ≤ 70% predicted or study physician determined presence of radiographic emphysema

- Resting pulse oximetry oxygen saturation (SpO_2) 89-93% **or** resting $SpO_2 \geq 94\%$ with desaturation during exercise (SpO2 < 90% for at least 10 seconds during a six-minute walk test)
- Medicare Part A and B beneficiary or insurance willing to pay costs of study or patient willing to self-pay costs
- Approval by study physician for randomization to either group
- No exacerbation requiring new prescription of antibiotics or new/increased prescription of systemic corticosteroids in the 30 days prior to screening
- Willingness to discontinue pre-existing supplemental oxygen therapy if randomized to no long-term supplemental oxygen arm

In addition, study investigators excluded patients who met any of the following criteria:

- COPD exacerbation between screening and randomization
- New prescription for supplemental oxygen between screening and randomization
- Thoracic surgery or other procedure likely to cause pulmonary instability within the prior 6 months
- Non-COPD lung disease that would affect survival or need for oxygen
- Epworth sleepiness scale score > 15
- Desaturation below 80% for at least 1 minute during a six-minute walk test (6MWT)
- Disease expected to cause death within 6 months of enrollment
- Participation in a different interventional study

Patients attended in-person visits at randomization and annually, during which study coordinators performed detailed histories (including medication use), physical examinations, questionnaires, and six-minute walk tests (6MWT). All patients completed spirometry at baseline. The trial conducted telephone interviews twice per year between in-person visits and

mailed questionnaires to patients at 4 months and 16 months of follow-up. The trial determined vital status as of August 31st, 2015 for all patients who enrolled, while 97% had at least one year of hospitalization follow-up data.[26,27]

LOTT found that long-term supplemental oxygen among patients with moderate resting or exertional hypoxemia was **not** efficacious for reducing mortality, decreasing respiratory exacerbations, improving symptoms, nor increasing exercise performance. We thus felt it was reasonable to use the entire cohort to examine our clinical questions.

COPD Disease Severity Assessment

We used the 2017 GOLD recommendations[17] to categorize patients into baseline COPD severity groups. Groups range from A (low symptom burden, low exacerbation risk) through D (high symptom burden, high exacerbation risk) **(Table 1)**. We assessed baseline symptoms using the Modified Medical Research Council Scale (mMRC), with scores ≥ 2 representing high symptom burden.[28] Prior to enrollment, LOTT collected 3 months of outpatient exacerbation and 1 year of hospitalization data. We thus used a modified definition to predict future exacerbation risk, categorizing patients as GOLD group C or D if they reported ≥ 1 outpatient exacerbation requiring antibiotics/steroids in the 3 months prior to enrollment or had ≥ 1 exacerbation causing hospitalization in the preceding year.

We chose the 2017 GOLD recommendations for our primary analyses as this strategy represents the most recent paradigm shift in the management of COPD. Although LOTT occurred prior to the publication of the 2017 recommendations, we believe this approach is reasonable as 1) the diagnostic criteria and classes of inhaled medications available to treat COPD have not changed and 2) our goal was not to assess clinician adherence to guidelines but instead to identify the association of guideline-concordant treatment with outcomes.

Exposures

Our primary exposure was the inhaled regimen reported at enrollment, classified as either 1) aligning with, 2) undertreating, or 3) potentially overtreating based on the 2017 GOLD recommendations **(Table 2)**. Undertreating regimens lacked recommended long-acting bronchodilators while overtreating regimens contained potentially unnecessary ICS. Among patients categorized as low risk for future exacerbations (GOLD groups A or B), we defined a secondary exposure as potential overtreatment with ICS vs not.

Outcomes

Our primary outcome was the occurrence of COPD-related hospitalization (severe COPD exacerbation) during follow-up. Secondary outcomes included the occurrence of moderate or severe COPD exacerbations, the rate of change of exercise performance as measured by the distance achieved during a six-minute walk test (6MWT), and the rate of change of COPD-specific quality of life as measured by the English Language St. George's Respiratory Questionnaire (SGRQ). The LOTT investigators defined COPD exacerbation as an acute respiratory illness for which either antibiotics or steroids were prescribed, and for which either an outpatient (moderate) or inpatient (severe) healthcare encounter occurred.

Among patients categorized as low risk for future exacerbations (GOLD groups A or B), we also determined the incidence of pneumonia during follow-up. We defined pneumonia as any inpatient or outpatient encounter for which the primary/secondary diagnosis was "pneumonia" (including viral and aspiration pneumonia) and/or when specific treatment for pneumonia was administered. Two investigators (TLK and LJS) reviewed all exacerbation and serious adverse event data to discern possible cases of pneumonia. In the event of disagreement, a third investigator (LCF) reviewed cases to determine appropriateness for inclusion.

Statistical Analyses

We report baseline patient characteristics and inhaled medication use as frequencies for categorical variables and mean (standard deviation) for continuous variables.

For the primary exposure, we generated multivariable Cox proportional-hazards models to estimate between-group hazard ratios for the occurrence of COPD-related hospitalization and any moderate or severe COPD exacerbation during follow-up. All models right censored for the competing risk of death using the method described by Fine and Gray.[29] We also right censored for loss to follow-up and end of study. To estimate between-group differences in the rate of change of 6MWT distance and SGRQ total score during follow-up, we constructed transitional models using multivariable linear regression with an exchangeable correlation and robust variance estimators. We included patients who completed at least one measurement (6MWT or SGRQ) during follow-up. Given similar baseline measurements, the β_1 coefficients reported from these models represent the mean difference in the rate of change of 6MWT distance (or SGRQ total score) among patients who reported inhaled regimens that undertreated or potentially overtreated when compared to those who reported regimens that aligned with recommendations in the 2017 GOLD strategy.

We *a priori* hypothesized that future exacerbation risk, as measured by the disease severity assessment outlined above **(Table 1)**, would modify the association of our primary exposure (classification of inhaled treatment) with outcomes. Specifically, we predicted that undertreatment would be more strongly associated with outcomes among patients at high risk (GOLD groups C/D) as compared to those at low risk (GOLD groups A/B) for future exacerbations. We therefore ran separate models across strata of future exacerbation risk (high vs. low) for all of analyses evaluating the primary exposure. We chose *a priori* covariates that might influence the receipt of inhaled regimens and outcomes. Multivariable models adjusted for baseline age, sex, Charlson Comorbidity score, smoking status, number of all-cause

hospitalizations in the year prior to enrollment, GOLD stage airflow obstruction, BODE Index, and study site.

Secondary Analyses

Among patients judged to be at low risk for future exacerbations and without an identifiable indication for ICS (GOLD groups A and B), we determined the association of overtreatment with ICS with the harm of pneumonia. After restricting the cohort to patients in 2017 GOLD groups A/B, we propensity matched patients on the likelihood of receiving ICS at baseline. We used multivariable logistic to assign propensity scores. We chose covariates *a priori* including baseline age, sex, Charlson Comorbidity score, smoking status, BODE Index, GOLD stage airflow obstruction, the number of all-cause hospitalizations in the year prior to enrollment, and study site. Using a caliper size of 0.2*SE, we propensity matched patients via the nearest neighbor method. We then generated a negative binomial regression model with one binary covariate for overtreatment with ICS to estimate the between-group incidence rate ratio for pneumonia.

Updating the 2011 GOLD strategy, the 2017 recommendations removed severity of airflow obstruction from the disease severity assessment. Seeking to understand how this update may have influenced the association of receiving guideline recommended care with outcomes, we repeated analyses after categorizing COPD severity and inhaled regimens per the 2011 GOLD strategy.

We prespecified sensitivity analyses that 1) updated inhaled regimens and primary exposure categories every 12 months 2) excluded patients reporting daily systemic glucocorticoid use adjusted for randomization to long-term supplemental oxygen, and 3) adjusted for randomization to long-term supplemental oxygen. We performed analyses using Stata version 16 (StataCorp, College Station, TX). The institutional review board of the VA Puget Sound Healthcare System approved this study (MIRB 01382).

RESULTS

Patient Characteristics

We included all 738 randomized LOTT participants in our analyses **(Table 3)**. Mean patient age was 68.8 years; 73.4% were male. We classified 163 (22.1%), 408 (55.3%), 37 (5.0%), and 130 (17.6%) patients as 2017 GOLD groups A-D, respectively. Most patients (n=468, 63.4%) had an FEV_1 < 50% predicted. Group A/B patients had no exacerbations in the 3 months prior to enrollment, while group C/D patients reported a mean of 1.1 exacerbations during this period.

Regimen Alignment with GOLD Recommendations

Patients most often reported using combination long-acting beta agonist (LABA), long-acting muscarinic antagonist (LAMA), and ICS (42.6%) ("triple therapy") **(Table 4)**. Combination LABA/ICS was also commonly used (20.7%). Patients infrequently reported LABA or LAMA monotherapy. Compared with group A/B patients, a higher percentage of group C/D patients reported use of daily systemic glucocorticoids. Overall, 233 patients (31.6%) reported regimens that aligned with the 2017 GOLD recommendations. Most baseline regimens were judged to represent overtreatment (54.1%).

Risk of Exacerbations

For the primary outcome, median follow-up was 2.3 years, during which 257 patients (34.8%) experienced hospitalization for COPD. Hospitalization for COPD occurred for 186 patients (32.6%) in groups A or B and 71 patients (42.5%) in groups C or D **(Figure 1, panel A)**. Among patients at low risk for future exacerbations (groups A/B), we found no appreciable difference in the risk of hospitalization for COPD among those reporting baseline inhaled regimens that undertreated or potentially overtreated compared to those reporting regimens that aligned with recommendations in the 2017 GOLD strategy **(Table 5a)**. However, among

patients categorized as high risk for future exacerbations (groups C/D), those reporting regimens that undertreated were 49% less likely to experience hospitalization for COPD compared to patients whose regimens aligned with strategy recommendations (HR 0.51, 95% CI: 0.28, 0.91). Similarly, those reporting regimens that potentially overtreated were 56% less likely to experience hospitalization compared to those whose regimens aligned with the 2017 strategy (HR 0.44, 95% CI: 0.15, 1.32) **(Table 5b)**.

A total of 513 patients (69.5%) experienced either a moderate or severe COPD exacerbation during a median follow-up of 1.1 years. An exacerbation occurred among 374 patients (65.5%) in groups A or B and 139 patients (83.2%) in groups C or D **(Figure 1, panel B)**. Among patients in groups A/B, those reporting regimens that potentially overtreated were 53% more likely to experience a COPD exacerbation during follow-up compared to patients reporting regimens that aligned with strategy recommendations (HR 1.53, 95% CI: 1.13, 2.07) **(Table 5a)**. Among group C/D patients, we found no appreciable difference in the risk of COPD exacerbation across categories of baseline inhaled regimens.

Exercise Performance and Quality of Life

Overall, 572 patients completed at least one follow-up 6MWT, while 645 patients had at least one follow-up SGRQ score. Among low-risk patients (groups A/B), the mean difference in the rate of change in 6MWT distance was 38 ft further (95% CI: 5 ft, 71 ft) among those reporting inhaled regimens that undertreated compared to those reporting regimens that aligned with the 2017 strategy. We observed a similar relationship among patients at high-risk for future exacerbation (mean difference in rate of change of 6MWT distance 19 ft further for those undertreated vs. aligned, 95% CI: -9 ft, 48 ft). There was no appreciable difference in the rate of change of mean SGRQ scores by category of baseline inhaled regimen, regardless of future exacerbation risk **(Table 6)**.

Secondary Analyses

Risk of Pneumonia

After restricting the cohort to patients judged to be at low-risk for future exacerbations (groups A/B), we propensity-matched patients on the likelihood of reporting baseline ICS use. The matched cohort contained 332 patients (166 per group), with small differences in baseline characteristics and similar likelihood of receiving ICS between groups **(Table 7, Figure 2)**. A total of 49 patients (29.5%) who used ICSs and 31 patients (18.7%) who did not use ICSs developed pneumonia (mean episodes 0.43 vs 0.25, respectively) **(Figure 3)**, with those reporting ICS use 64% more likely to develop pneumonia during follow-up (IRR 1.64, 95% CI: 1.01, 2.66). We obtained similar results using an adjusted negative binomial regression model instead of propensity matching (IRR 1.73, 95% CI: 1.00 – 3.00).

GOLD 2011 Analyses

When we assessed baseline disease severity according to the 2011 GOLD strategy,[19] we classified 209 patients (28.3%) as low-risk (groups A/B) and 529 patients (71.7%) as high-risk (groups C/D) for future exacerbations **(Table 8)**. Overall, 490 patients (66.4%) reported baseline inhaled regimens that aligned with the 2011 GOLD strategy **(Table 9)**. In general, the results of the 2011 analyses were similar to those for 2017 **(Table 10, Figure 4)**. However, we no longer observed a lower risk of hospitalization for COPD among group C/D patients who were undertreated or potentially overtreated compared to those who regimens aligned with the 2011 strategy. In addition, we now observed a higher risk of COPD exacerbation among potentially overtreated patients across strata of predicted future risk (2011 group A/B patients: HR 2.08, 95% CI 1.43 to 3.04; 2011 group C/D patients: HR 1.29, 95% CI 0.93 to 1.80).

Sensitivity Analyses

We obtained similar results when we updated patient-reported inhaled regimens at 12-month intervals **(Table 11)**, excluded patients reporting daily systemic glucocorticoid use **(Table 12)**, or adjusted for randomization to supplemental oxygen **(Table 13)**.

DISCUSSION

The efficacy of inhaled therapy in the management of COPD is well established, with recent studies focusing on the comparative effectiveness of individual regimens.[6,30] To our knowledge, our study is the first to evaluate the relationship between receiving inhaled treatment in accordance with the 2017 GOLD recommendations and developing clinically important outcomes. Among a cohort of patients with moderate hypoxemia, we found that patients whose inhaled regimens aligned with 2017 GOLD recommendations did not experience lower risk of COPD-related hospitalization or exacerbation when compared with patients whose regimens were judged to be undertreating their COPD. Quality of life was also similar between groups. Interestingly, among high-risk patients, both patients judged to be undertreated or overtreated experienced lower risk of hospitalization than those whose regimens aligned with recommendations. Among this subgroup, we also found no appreciable difference in the risk of COPD exacerbation across categories of baseline inhaled regimens. However, among low-risk patients, potential overtreatment with ICSs was associated with a higher risk of experiencing a COPD exacerbation and a higher risk of pneumonia.

Our findings suggest that choosing inhaled regimens based on the 2017 GOLD strategy provides little added benefit when compared with approaches that undertreat. One possible explanation is that the inhaled treatment recommendations are overly broad, allowing for multiple “acceptable” regimens within each disease severity group. Clinical trials demonstrating the efficacy of inhaled therapies typically compare two or three regimens.[2,4-6,8] In contrast, our study evaluated the relative effectiveness of treatment categories containing a wide range of

inhaled therapies.[17] Narrowing treatment recommendations within disease severity groups (e.g., at least dual bronchodilator therapy among patients with frequent exacerbations)[4,5,8] might improve outcomes.

Alternatively, the disease severity assessment in the 2017 GOLD strategy may lack the precision necessary to adequately risk-stratify patients and guide treatment. Studies evaluating the predictive accuracy of the 2007, 2011, and 2017 GOLD strategies for mortality and exacerbations reported a low area under the receiver operator curves (between 0.62 – 0.68).[15,31,32] While prior exacerbations strongly predict future events,[23] additional independent risk factors for future exacerbations exist.[24,25,33-35] Moreover, COPD is a heterogenous disease with multiple phenotypes. For example, COPD patients with elevated eosinophil levels experience more frequent exacerbations and may benefit from eosinophil-targeted treatment.[36-40] Although the 2019 strategy incorporates this latter evidence,[18] the 2017 risk prediction models and treatment recommendations follow a "one size fits all" approach. The observed outcomes among patients in our cohort may reflect this misclassification by the 2017 strategy.

It is also possible, however, that inhaled therapy is less effective when applied to the broader population using recent risk-stratification models. Trials establishing the efficacy of inhaled regimens were almost exclusively performed among patients with high symptom burden, moderate to severe obstruction, and at least one exacerbation in the year prior to enrollment.[4,5,8] In contrast, comparative effectiveness studies have evaluated inhaled treatments without accounting for a patient's GOLD group.[6,30] Our findings suggest that additional studies are necessary to truly establish the effectiveness of providing inhaled treatment based on GOLD risk models.

The higher exacerbation risk we observed among potentially overtreated, low-risk patients is intriguing. As LOTT collected only 3 months of outpatient exacerbation data, we may have misclassified patients who are truly high-risk for exacerbation. We performed multiple comparisons and a type 1 error could also explain this result. However, if either explanation

were true, we would not have expected the 2011 analyses (in which we reclassified over 300 patients from low to high risk) to yield similar results. Alternatively, it is possible that both the 2011 and 2017 strategies misclassified the exacerbation risk of patients in our cohort. Consistent with prior studies,[14,41] regimens in our cohort that potentially overtreated contained ICS. Clinically, COPD exacerbations are often diagnosed concurrently with pneumonia, which may explain the observed difference in exacerbation risk. As we also observed a higher risk of harm from pneumonia among low-risk patients potentially overtreated with ICSs, our findings support the 2017 strategy's recommendations to limit ICS use only to patients with a history of recurrent exacerbations.

Our findings are consistent with the only prior study evaluating outcomes in association with adherence to inhaled treatment recommendations based on risk-stratification models.[42] Among Swiss adults with clinician-diagnosed COPD, the authors found no difference in symptoms or exacerbation frequency among patients whose regimens aligned with the 2011 GOLD strategy compared to those whose regimens did not. However, nearly 50% of patients initially enrolled in that study were lost to follow-up. Moreover, the investigators were unable to ensure the validity of spirometry data, possibly leading to inaccuracy of COPD diagnoses. In contrast, outcomes were ascertained, and the validity of spirometry was confirmed, for all patients in our study.

Our study has several strengths. We had robust ascertainment of outcomes during a median follow-up of 2.3 years. Few studies have as comprehensive data regarding spirometry, medication use, symptoms, and exercise performance. Although LOTT was a pragmatic randomized trial performed throughout the United States, certain aspects of this study limit the generalizability of our findings. LOTT recruited participants from respiratory clinics only. Moreover, all patients who enrolled in the LOTT cohort had moderate hypoxemia and airflow obstruction confirmed by spirometry. None had a respiratory exacerbation within 30 days of screening. Future studies should address these limitations.

Multiple aspects of our study limit our conclusions. As with all observational pharmacoepidemiology studies, we cannot exclude confounding by indication. Clinicians in LOTT may have recognized other independent risk factors for future exacerbations not captured by the GOLD strategies and escalated inhaled treatment accordingly. Both the lower risk of hospitalization for COPD among "high-risk" undertreated patients and the higher exacerbation risk among potentially overtreated, "low-risk" patients could have resulted from this bias. Although we adjusted for multiple confounders, additional unmeasured factors may have influenced our results. LOTT relied upon patient report to ascertain inhaled medication use and patients may not have been taking the regimens they reported. This might explain why only 86% of patients reported use of short-acting bronchodilators. We classified relatively few regimens as under- or potentially over-treating, which produced the imprecise variance estimates observed among group C/D patients. Moreover, we performed multiple comparisons, which increases the risk of type 1 error. Finally, we used a modified definition of increased exacerbation risk and may have inadvertently misclassified as low-risk patients whom the 2017 strategy would have considered high-risk for future exacerbations. However, the distribution of disease severity groups and categories of inhaled regimens in our study was similar to those observed in prior investigations based on the 2017 strategy.[14-16,41] It is thus unlikely that our modified definition of exacerbation risk affected our results.

INTERPRETATION

In this post-hoc secondary analysis of LOTT data, patients reporting regimens that aligned with recommendations in the 2017 GOLD strategy did not experience a lower risk of COPD exacerbations, higher exercise performance, or improved quality of life compared to those who were undertreated, regardless of future exacerbation risk. Among high-risk patients, regimens judged to represent undertreatment and potential overtreatment were associated with a lower risk of hospitalization for COPD than those aligning with recommendations. Among low-

risk patients, potential overtreatment was associated with a higher risk of COPD exacerbation and a higher risk of pneumonia. The observational nature and relatively narrow patient population limit our study's interpretation. Our findings highlight the need for additional studies to evaluate the effectiveness of risk stratification model-based inhaled treatment strategies in real-world practice.

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TABLES

Table 1: COPD severity groups adapted from the 2017 GOLD strategy

Symptoms	Exacerbation Risk	
	Low-Risk[a] Prior Year: 0 COPD hospitalizations Past 3 months: 0 exacerbations	High-Risk[b] Prior Year: 1+ COPD hospitalizations Past 3 months: 1+ exacerbations
mMRC < 2	A	C
mMRC ≥ 2	B	D

[a] all criteria must be met
[b] the presence of any one of these criteria would categorize patients as high-risk
mMRC = Modified Medical Research Council dyspnea score

Table 2: Categorization of baseline inhaler regimens based on the 2017 GOLD strategy

2017 GOLD Group	Aligned	Not Aligned	
		Undertreated	Potentially Overtreated
A	SABD only or LABA only or LAMA only or LABA+LAMA	No inhaled therapy or ICS only	LABA+ICS or LAMA+ICS or LABA+LAMA+ICS
B	LABA only or LAMA only or LABA+LAMA	No inhaled therapy or SABD only or ICS only	LABA+ICS or LAMA+ICS or LAMA+LABA+ICS
C	LAMA only or LAMA+LABA or LABA+ICS LAMA+ICS	No inhaled therapy or SABD only or ICS only or LABA only	LABA+LAMA+ICS
D	LAMA only or LAMA+LABA or LABA+ICS or LAMA+ICS or LAMA+LABA+ICS	No inhaled therapy or SABD only or LABA only or ICS only	N/A

SABD = short-acting bronchodilator (includes short-acting beta agonist and short-acting muscarinic antagonists); LABA = long-acting beta agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroid

Table 3: Baseline patient characteristics, stratified by future exacerbation risk

Variable	Overall Cohort (n = 738)	Low Risk Groups A/B (n = 571)	High Risk Groups C/D (n = 167)
Demographics			
Age (years), mean [sd]	68.8 [7.5]	69.0 [7.5]	68.1 [7.4]
Male, n (%)	542 (73.4)	422 (73.9)	120 (71.9)
BMI (kg/m^2), mean [sd]	28.6 [6.5]	28.4 [6.6]	29.2 [5.7]
Current Smoker n (%)	202 (27.4)	165 (28.9)	37 (22.2)
Pack-Year History, mean [sd]	61.4 [32.9]	61.5 [32.7]	61.0 [33.9]
Randomized to Oxygen, n (%)	368 (49.9)	287 (50.2)	81 (48.5)
24hr Oxygen	220 (29.8)	170 (29.8)	50 (29.9)
Nocturnal/Ambulatory Oxygen Only	148 (20.0)	117 (20.4)	31 (18.6)
Indication for Supplemental Oxygen			
Resting SpO2 88% – 94%	133 (18.0)	105 (18.4)	28 (16.8)
Ambulatory SpO2 80% - 88%	319 (43.2)	239 (41.9)	80 (47.9)
Both	286 (38.8)	227 (39.8)	59 (35.3)
Charlson Score, mean [sd]	5.0 [1.9]	5.0 [1.9]	4.9 [1.9]
Prior Pneumonia, n (%)	394 (53.4)	283 (49.6)	111 (66.5)
Pulmonary Rehabilitation, n (%)	220 (29.8)	157 (27.5)	63 (37.7)
COPD Severity			
BODE Index, n (%)[a]			
0-2	165 (22.7)	136 (24.2)	29 (17.5)
3-4	282 (38.7)	217 (38.6)	65 (39.2)
5-6	210 (28.8)	155 (27.6)	55 (33.1)
7-10	71 (9.8)	54 (9.6)	17 (10.2)
GOLD Stage, n (%)			
1	26 (3.5)	24 (4.2)	2 (1.2)
2	244 (33.1)	185 (32.4)	59 (35.3)
3	357 (48.4)	279 (48.9)	78 (46.7)
4	111 (15.0)	83 (14.5)	28 (16.8)
Exacerbations in past 3 months, mean [sd]	0.3 [0.6]	0.0 (0.0)	1.1 (0.9)
Baseline SGRQ total score, mean [sd]	50.0 [17.9]	48.9 [17.9]	53.8 [17.7]
Baseline 6MWT distance (ft), mean [sd][a]	1044 [326]	1055 [332]	1008 [300]

[a] n = 728, 10 patients could not complete baseline 6MWT

sd = standard deviation; BMI = body mass index; SGRQ = St. George Respiratory Questionnaire; 6MWT = six-minute walk test

Table 4: Baseline COPD treatment regimens, stratified by future exacerbation risk

Treatment Regimen	Overall Cohort (n = 738)	Groups A/B (n = 571)	Groups C/D (n = 167)
Inhalers, n (%)			
Any short-acting	637 (86.3)	475 (83.2)	162 (97.0)
LABA only	17 (2.3)	15 (2.6)	2 (1.2)
LAMA only	72 (9.8)	60 (10.5)	12 (7.2)
ICS only	35 (4.7)	26 (4.6)	9 (5.4)
LABA+LAMA	23 (3.2)	19 (3.3)	4 (2.4)
LAMA+ICS	28 (3.8)	31 (3.7)	7 (4.2)
LABA+ICS	153 (20.7)	127 (22.2)	26 (15.6)
LABA+LAMA+ICS	314 (42.6)	219 (38.4)	95 (56.9)
Systemic Medications, n (%)			
Glucocorticoids	61 (8.3)	32 (5.6)	29 (17.4)
Theophylline	50 (6.8)	37 (6.5)	13 (7.8)
2017 GOLD alignment, n (%)			
Not aligned	505 (68.4)	461 (80.7)	44 (26.3)
Undertreated	106 (14.4)	83 (14.5)	23 (13.8)
Potentially Overtreated	399 (54.1)	378 (66.2)	21 (12.6)
Aligned	233 (31.6)	110 (19.3)	123 (73.7)

LABA = Long-acting beta agonist; LAMA = Long-acting muscarinic antagonist; ICS = Inhaled Corticosteroid

Table 5: Relative risk of COPD exacerbations by COPD treatment classification, 2017 GOLD strategy

A. 2017 Groups A/B (N = 571)				
Outcome by Exposure	**Number Experiencing Outcome**	**Person-years at risk**	**Crude Hazard Ratio (95% CI)**	**Adjusted Hazard Ratio[a] (95% CI)**
Hospitalization for COPD				
Aligned	30	268.8	Referent	Referent
Undertreated	22	244.1	0.84 (0.48 – 1.45)	0.90 (0.49 – 1.64)
Overtreated	134	996.5	1.24 (0.83 – 1.85)	1.10 (0.68 – 1.80)
COPD Exacerbation				
Aligned	58	204.3	Referent	Referent
Undertreated	44	172.9	0.93 (0.62 – 1.38)	0.97 (0.61 – 1.53)
Overtreated	272	566.8	1.68 (1.27 – 2.21)	1.53 (1.13 – 2.07)
B. 2017 Groups C/D (N = 167)				
Outcome by Exposure	**Number Experiencing Outcome**	**Person-years at risk**	**Crude Hazard Ratio (95% CI)**	**Adjusted Hazard Ratio[a] (95% CI)**
Hospitalization for COPD				
Aligned	60	286.1	Referent	Referent
Undertreated	7	59.6	0.52 (0.23 – 1.15)	0.51 (0.28 – 0.91)
Overtreated	4	45.0	0.41 (0.15 – 1.10)	0.44 (0.15 – 1.32)
COPD Exacerbation				
Aligned	102	141.3	Referent	Referent
Undertreated	19	33.7	0.82 (0.51 – 1.31)	0.82 (0.48 – 1.83)
Overtreated	18	17.0	1.30 (0.83 – 2.03)	1.11 (0.68 – 1.83)

a. Cox proportional-hazard models adjusted for baseline age, sex, Charlson score, smoking status, baseline GOLD stage, BODE Index, number of all-cause hospitalizations in year before randomization, and site. All models account for the competing risk of death.

Table 6: Mean difference in rate of change of 6MWT distance and total SGRQ score by COPD treatment classification

Outcome by Exposure	2017 Group A/B		2017 Group C/D	
	Crude β_1 Coefficient (95% CI)	Adjusted β_1 Coefficient[a] (95% CI)	Crude β_1 Coefficient (95% CI)	Adjusted β_1 Coefficient[b] (95% CI)
6MWT (ft)				
Aligned	Referent	Referent	Referent	Referent
Undertreated	30 (-10, 48)	38 (5, 71)	24 (-47, 94)	24 (-75, 122)
Overtreated	19 (0, 62)	19 (-9, 48)	-26 (-103, 51)	-75 (-175, 25)
Total SGRQ score				
Aligned	Referent	Referent	Referent	Referent
Undertreated	-1.1 (-2.9, 0.6)	-1.1 (-3.1, 0.9)	-0.5 (-3.2, 2.3)	-0.3 (-3.2, 2.7)
Overtreated	0.2 (-1.0, 1.5)	0.2 (-1.1, 1.5)	0.1 (-3.6, 3.9)	0.3 (-3.7, 4.3)

a. Multivariable linear regression model with an exchangeable correlation matrix linked on patient identity, adjusted for baseline 6MWT distance, age, gender, Charlson score, smoking status, BODE Index, GOLD stage, and site. A total of 572 patients had at least one outcome measure.

b. Multivariable linear regression model with an exchangeable correlation matrix linked on patient identity, adjusted for baseline SGRQ score, age, gender, Charlson score, smoking status, BODE Index, GOLD stage, and site. A total of 645 patients had at least one outcome measure.

Table 7: Baseline patient characteristics of the propensity matched cohort

Variable	Overall (n = 332)	Overtreated with ICS (n = 166)	Aligned (no ICS) (n = 166)
Demographics			
Age, mean [sd]	70.4 [7.4]	71.1 [7.2]	69.7 [7.5]
Male, n (%)	232 (69.9)	116 (69.9)	116 (69.9)
Current Smoker, n (%)	94 (28.3)	47 (28.3)	47 (28.3)
Comorbidities, n (%)			
Anemia	57 (17.2)	30 (18.7)	27 (16.3)
Angina	41 (12.4)	23 (13.7)	18 (10.8)
Heart Failure	31 (9.3)	16 (9.6)	15 (9.0)
Prior Pneumonia	159 (47.9)	83 (50.0)	76 (45.8)
Charlson Score, mean [sd]	5.4 [2.0]	5.5 [2.0]	5.2 [1.8]
COPD Severity			
BODE Index, n (%)			
0-2	105 (31.6)	60 (36.1)	45 (27.1)
3-4	143 (43.1)	74 (44.6)	69 (41.6)
5-6	46 (13.9)	12 (7.2)	34 (20.5)
7-10	38 (11.4)	20 (12.1)	18 (10.8)
GOLD Stage, n (%)			
1	20 (6.0)	10 (6.0)	10 (6.0)
2	163 (49.1)	97 (58.4)	66 (39.8)
3	130 (39.2)	54 (32.5)	76 (45.8)
4	19 (5.7)	5 (3.0)	14 (8.4)

ICS = inhaled corticosteroid; sd = standard deviation

Table 8: COPD severity groups adapted from the 2011 GOLD strategy

Symptoms	Exacerbation Risk	
	Low-Risk[a] Prior Year: 0 COPD hospitalizations Past 3 months: 0 exacerbations FEV_1: ≥ 50% predicted	High-Risk[b] Prior Year: 1+ COPD hospitalizations Past 3 months: 1+ exacerbations FEV_1: < 50% predicted
mMRC < 2	A	C
mMRC ≥ 2	B	D

[a] all criteria must be met
[b] the presence of any one of these criteria would categorize patients as high-risk
mMRC = Modified Medical Research Council dyspnea score

Table 9: Categorization of baseline inhaler regimens based on the 2011 GOLD strategy

2017 GOLD Group	Aligned	Not Aligned	
		Undertreated	Potentially Overtreated
A	SABD only or LABA only or LAMA only	No inhaled therapy or ICS only	SABD+ICS or LAMA+LABA or LABA+ICS or LAMA+ICS or LABA+LAMA+ICS
B	SABD only or LABA only or LAMA only or LABA+LAMA	No inhaled therapy or ICS only	SABD+ICS or LABA+ICS or LAMA+ICS or LAMA+LABA+ICS
C	SABD only or LAMA only or LAMA+ICS or LABA+ICS or LAMA+LABA	No inhaled therapy or ICS only or LABA only	LABA+LAMA+ICS
D	SABD only or LAMA or LAMA+LABA or LABA+ICS or LAMA+ICS or LAMA+LABA+ICS	No inhaled therapy or LABA only or ICS only	N/A

SABD = short-acting bronchodilator (includes short-acting beta agonist and short-acting muscarinic antagonists); LABA = long-acting beta agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroid

Table 10: Relative risk of COPD exacerbations by COPD treatment classification, 2011 GOLD strategy

A. 2011 Groups A/B (N = 209)				
Outcome by Exposure	**Number Experiencing Outcome**	**Person-years at risk**	**Crude Hazard Ratio (95% CI)**	**Adjusted Hazard Ratio[a] (95% CI)**
Hospitalization for COPD				
Aligned	10	174.1	Referent	Referent
Undertreated	3	59.8	0.87 (0.25 – 2.98)	1.01 (0.37 – 2.70)
Overtreated	35	347.8	1.74 (0.86 – 3.53)	1.58 (0.72 – 3.49)
COPD Exacerbation				
Aligned	26	136.4	Referent	Referent
Undertreated	9	43.6	0.95 (0.48 – 1.89)	1.05 (0.40 – 2.73)
Overtreated	86	198.5	2.19 (1.40 – 3.42)	2.08 (1.43 – 3.04)
B. 2011 Groups C/D (N = 529)				
Outcome by Exposure	**Number Experiencing Outcome**	**Person-years at risk**	**Crude Hazard Ratio (95% CI)**	**Adjusted Hazard Ratio[a] (95% CI)**
Hospitalization for COPD				
Aligned	176	1054.2	Referent	Referent
Undertreated	15	133.9	0.67 (0.40 – 1.14)	0.67 (0.36 – 1.27)
Overtreated	18	130.3	0.85 (0.53 – 1.37)	0.91 (0.56 – 1.49)
COPD Exacerbation				
Aligned	315	606.3	Referent	Referent
Undertreated	32	89.8	0.71 (0.50 – 1.00)	0.74 (0.50 – 1.08)
Overtreated	45	61.4	1.29 (0.99 – 1.69)	1.29 (0.93 – 1.80)

a. Cox proportional-hazard models adjusted for baseline age, sex, Charlson score, smoking status, baseline GOLD stage, BODE Index, number of all-cause hospitalizations in year before randomization, and site. All models account for the competing risk of death.

Table 11: Relative risk of COPD exacerbations by time-varying COPD treatment classification, 2017 GOLD strategy

Outcome by Exposure	2017 Group A/B		2017 Group C/D	
	Crude Hazard Ratio (95% CI)	Adjusted Hazard Ratio[a] (95% CI)	Crude Hazard Ratio (95% CI)	Adjusted Hazard Ratio[a] (95% CI)
Hospitalization for COPD				
Aligned	Referent	Referent	Referent	Referent
Undertreated	0.95 (0.52 – 1.75)	0.98 (0.47 – 2.04)	0.72 (0.36 – 1.47)	0.76 (0.50 – 1.16)
Overtreated	1.62 (1.03 – 2.51)	1.38 (0.82 – 2.32)	0.54 (0.23 – 1.34)	0.62 (0.25 – 1.55)
COPD Exacerbation				
Aligned	Referent	Referent	Referent	Referent
Undertreated	0.87 (0.57 – 1.33)	0.87 (0.52 – 1.45)	0.87 (0.50 – 1.52)	0.90 (0.35 – 2.29)
Overtreated	1.72 (1.28 – 2.30)	1.54 (1.11 – 2.13)	1.41 (0.98 – 2.07)	1.24 (0.85 – 1.81)

a. Cox proportional-hazard models adjusted for baseline age, sex, Charlson score, smoking status, baseline GOLD stage, BODE Index, and number of all-cause hospitalizations in year before randomization, accounting for the competing risk of death. Patient reported inhaler regimens were ascertained at 12-month intervals and exposure status (aligned, undertreated, overtreated) was adjusted accordingly. Patient COPD severity status (GOLD groups) was ascertained at baseline only as the annual incidence of inpatient and outpatient respiratory exacerbations was not adjudicated by the original LOTT investigators. While we could have independently adjudicated the annual incidence of COPD exacerbations during follow-up, this would have resulted in discrepancies in the cumulative number of COPD exacerbations.

Table 12: Relative risk of COPD exacerbations by COPD treatment classification, 2017 GOLD strategy (exclusion of oral glucocorticoid users)

Outcome by Exposure	2017 Group A/B		2017 Group C/D	
	Crude Hazard Ratio (95% CI)	Adjusted Hazard Ratio[a] (95% CI)	Crude Hazard Ratio (95% CI)	Adjusted Hazard Ratio[a] (95% CI)
Hospitalization for COPD				
Aligned	Referent	Referent	Referent	Referent
Undertreated	0.84 (0.48 – 1.47)	0.87 (0.46 – 1.65)	0.47 (0.19 – 1.15)	0.41 (0.19 – 0.89)
Overtreated	1.18 (0.78 – 1.78)	1.04 (0.61 – 1.78)	0.51 (0.19 – 1.38)	0.40 (0.14 – 1.12)
COPD Exacerbation				
Aligned	Referent	Referent	Referent	Referent
Undertreated	0.92 (0.61 – 1.39)	0.95 (0.60 – 1.51)	0.81 (0.47 – 1.38)	0.80 (0.44 – 1.45)
Overtreated	1.68 (1.26 – 2.24)	1.51 (1.10 – 2.08)	1.44 (0.87 – 2.39)	1.16 (0.73 – 1.85)

a. Cox proportional-hazard models adjusted for baseline age, sex, Charlson score, smoking status, baseline GOLD stage, BODE Index, number of all-cause hospitalizations in year before randomization, and randomization to O2, accounting for the competing risk of death

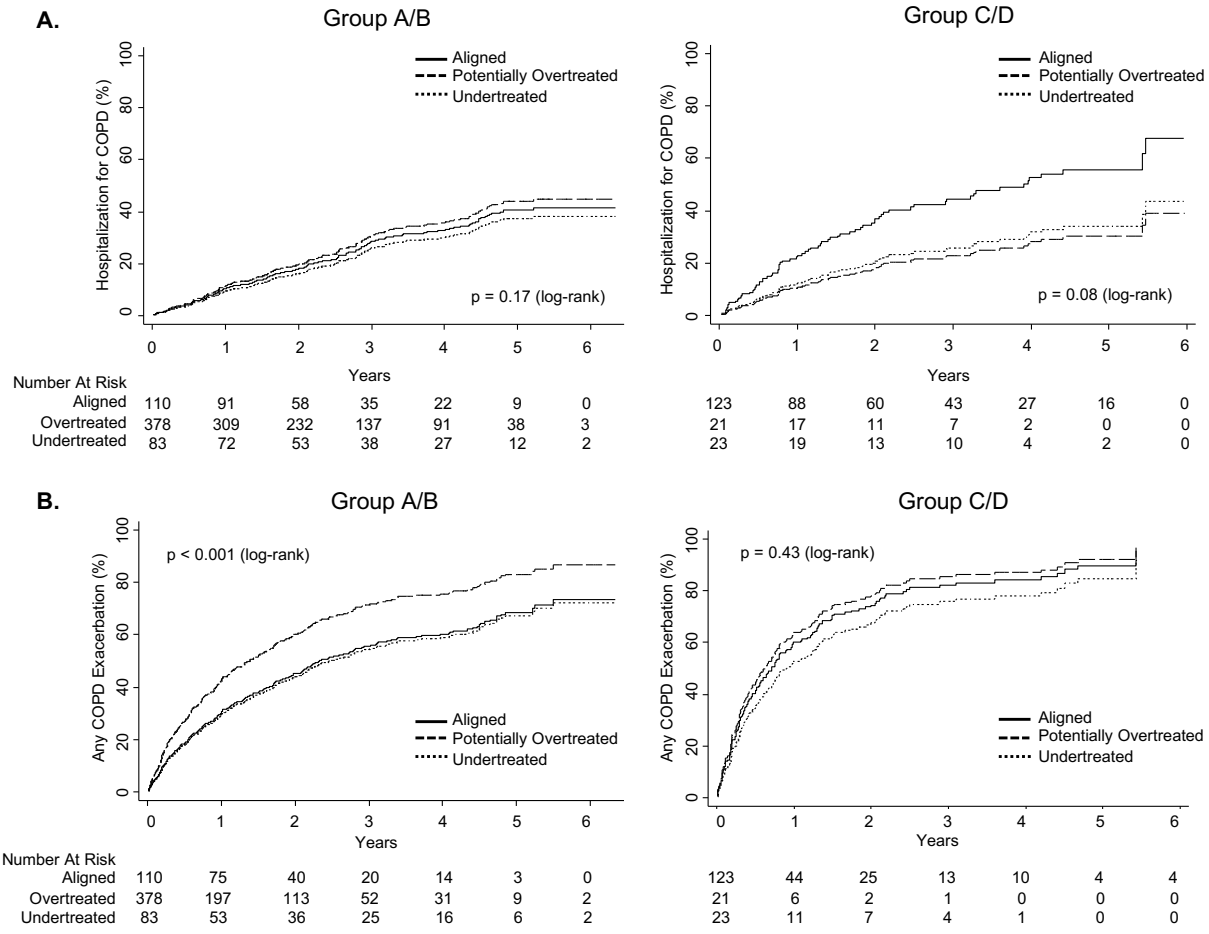
Table 13: Relative risk of COPD exacerbations by COPD treatment classification, 2017 GOLD strategy (adjusted for randomization to oxygen)

Outcome by Exposure	2017 Group A/B		2017 Group C/D	
	Crude Hazard Ratio (95% CI)	Adjusted Hazard Ratio[a] (95% CI)	Crude Hazard Ratio (95% CI)	Adjusted Hazard Ratio[a] (95% CI)
Hospitalization for COPD				
Aligned	Referent	Referent	Referent	Referent
Undertreated	0.84 (0.48 – 1.45)	0.90 (0.48 – 1.68)	0.52 (0.23 – 1.15)	0.51 (0.28 – 0.94)
Overtreated	1.24 (0.83 – 1.85)	1.08 (0.66 – 1.77)	0.41 (0.15 – 1.10)	0.44 (0.15 – 1.28)
COPD Exacerbation				
Aligned	Referent	Referent	Referent	Referent
Undertreated	0.93 (0.62 – 1.38)	0.95 (0.61 – 1.50)	0.82 (0.51 – 1.31)	0.85 (0.51 – 1.42)
Overtreated	1.68 (1.27 – 2.21)	1.51 (1.12 – 2.03)	1.30 (0.83 – 2.03)	1.15 (0.73 – 1.83)

a. Cox proportional-hazard models adjusted for baseline age, sex, Charlson score, smoking status, baseline GOLD stage, BODE Index, number of all-cause hospitalizations in year before randomization, and randomization to O2, accounting for the competing risk of death

FIGURES

Figure 1. Cumulative incidence of COPD exacerbations by COPD treatment classification, 2017 GOLD strategy



Panel A shows the cumulative incidence of hospitalization for COPD after accounting for the competing risk of death, stratified by exacerbation risk (n=738); median follow-up 2.29 yrs. Data for patients who neither died nor had a first hospitalization for COPD were censored at the time of their last interview. A total of 186 patients (32.6%) in groups A/B and 71 patients (42.5%) in groups C/D experienced the outcome. Panel B shows the cumulative incidence of COPD exacerbation after accounting for the competing risk of death, stratified by exacerbation risk (n=738); median follow-up 1.11 yrs. Data for patients who neither died nor had a first COPD exacerbation were censored at the time of their last interview. A total of 374 patients (65.5%) in groups A/B and 139 patients (83.2%) in groups C/D experienced the outcome. P values were generated from log-rank tests.

Figure 2: Histogram of the predicted likelihood of receiving ICS by reported ICS use

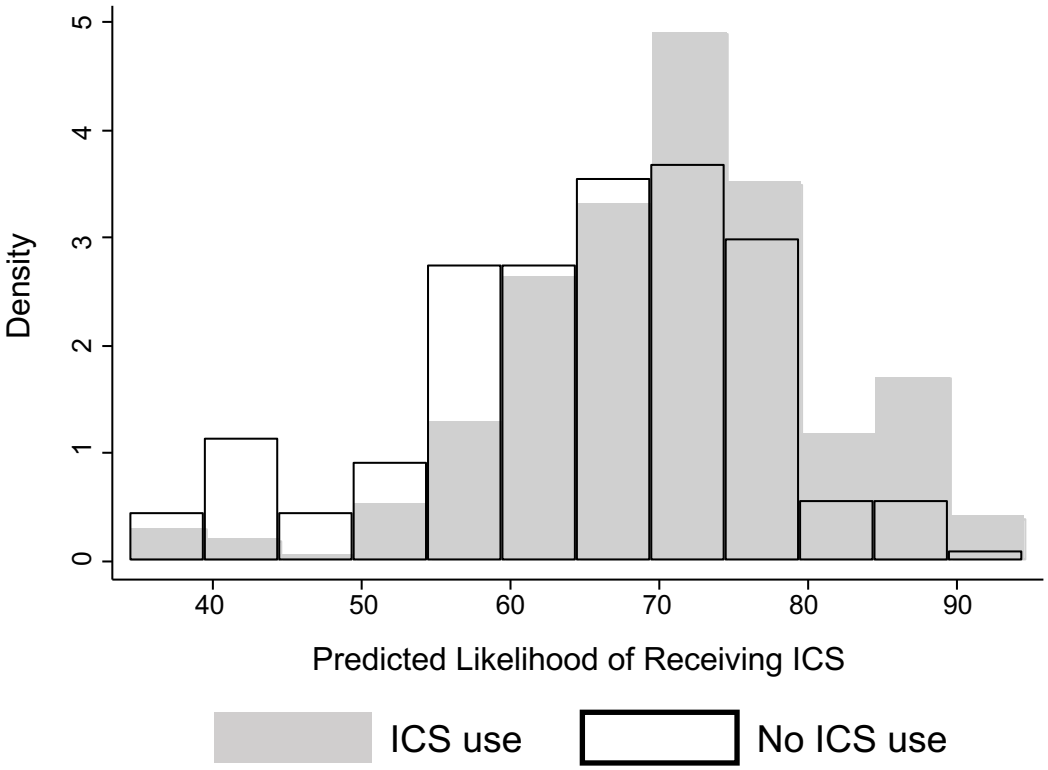


Figure 3: Episodes of pneumonia among propensity matched cohort, by inhaled corticosteroid use

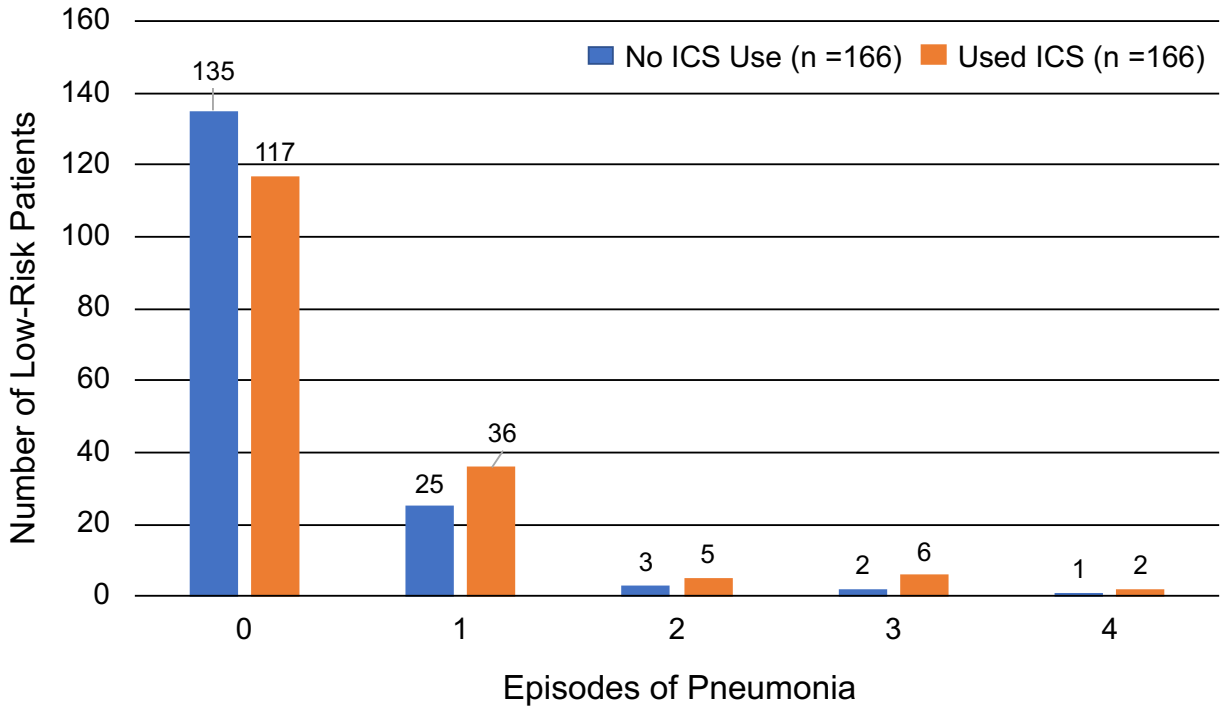
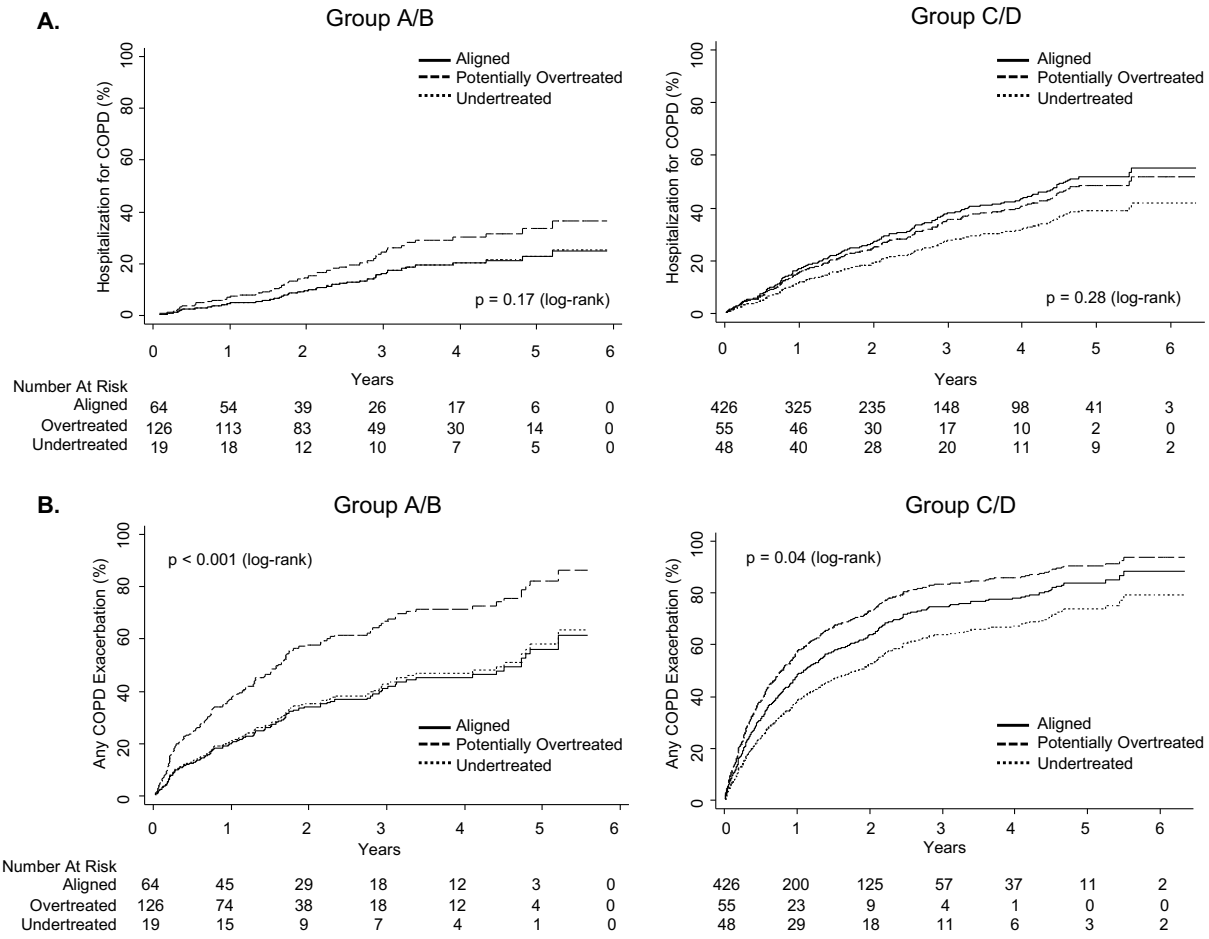


Figure 4. Cumulative incidence of COPD exacerbations by COPD treatment classification, 2011 GOLD strategy



Panel A shows the cumulative incidence of hospitalization for COPD after accounting for the competing risk of death, stratified by exacerbation risk (n=738); median follow-up 2.29 yrs. Data for patients who neither died nor had a first hospitalization for COPD were censored at the time of their last interview. A total of 48 patients (23.0%) in groups A/B and 209 patients (39.5%) in groups C/D experienced hospitalization. Panel B shows the cumulative incidence of COPD exacerbation after accounting for the competing risk of death, stratified by exacerbation risk (n=738); median follow-up 1.11 yrs. Data for patients who neither died nor had a first COPD exacerbation were censored at the time of their last interview. A total of 121 patients (57.9%) in groups A/B and 392 patients (74.1%) in groups C/D experienced an exacerbation. P values were generated from log-rank tests.