Low-value Inhaled Corticosteroids in Chronic Obstructive Pulmonary Disease and the Association with Health Care Utilization and Costs

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Abstract

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Rationale: Inhaled corticosteroids (ICS) are not first-line therapy for patients with chronic obstructive pulmonary disease (COPD) at low risk of exacerbation, but are commonly prescribed despite evidence of harm. We consider ICS prescription in this population "low-value." The association of low-value ICS with subsequent health care utilization and costs is unknown. Understanding this relationship could inform efforts to reduce the delivery of low-value care.

Objective: To determine whether low-value ICS prescribing is associated with higher outpatient health care utilization and costs among patients with COPD who are at low risk of exacerbation.

Methods: We performed a cohort study between January 1, 2010 and December 31, 2018, identifying a cohort of Veterans with COPD who performed pulmonary function tests (PFTs) at 21 Veterans Affairs Medical Centers nationwide. Patients were defined as having low exacerbation risk if they experienced <2 outpatient exacerbations and no hospital admissions for COPD in the year prior to PFTs. Our primary exposure was the receipt of an ICS prescription in the 3-months prior to the date of PFTs. Our primary outcomes were outpatient utilization and outpatient costs in the 1 year after PFTs. For inference, we generated negative binomial models for utilization and generalized linear models for costs, adjusting for confounders.

Results: We identified a total of 31,551 patients with COPD who were at low risk of exacerbation. Of these patients, 9,742 were prescribed low-value ICS (mean [SD] age, 69 [9] years) and 21,809 were not prescribed low-value ICS (mean [SD] age, 68 [9] years). Compared to unexposed patients, those exposed to low-value ICS had 0.53 more encounters per patient per year (95% CI, 0.23-0.83) and incurred $154.72 higher costs per patient per year (95% CI, $45.58-$263.86).

Conclusions: Low-value ICS prescription was associated with higher subsequent outpatient health care utilization and costs. Potential mechanisms for the observed association are that (1) low-value ICS may be a marker of respiratory poor symptom control, (2) there is confounding by indication or (3) low-value ICS results in increased drug costs or utilization. Health systems should identify low-value ICS prescriptions as a target to improve value-based care.

Introduction

Prescription drugs account for around 9% of health care spending ($335 billion) in the United States (1) and grew at an annualized rate of 6% in the last two decades (2,3). Optimizing the value of medications is one important strategy proposed to reduce drug costs (4–6). Low-value prescribing is not only directly wasteful to both patients and health systems, but may be associated with harms which increase subsequent costs and utilization (7). Understanding which low-value medications are associated with higher utilization and costs is necessary to prioritize health system efforts to improve prescribing practices and value-based care delivery. Studying the health system consequences of prescribing low-value medications is particularly important for chronic, non-communicable diseases, which make up 85% of total prescription drug spending (3).

The prescription of inhaled corticosteroids (ICS) in chronic obstructive pulmonary disease (COPD) represents a common low-value prescribing practice (8). The Global Initiative for Chronic Obstructive Lung Disease (GOLD) statement recommends against ICS use among patients at low risk of exacerbation (GOLD groups A and B) (9), citing evidence of harm and the availability of superior alternative therapies such as long-acting muscarinic antagonists (LAMA) or long-acting beta agonists (LABA) (10,11). Harms associated with ICS include higher rates of pneumonia, osteoporosis, poor diabetes control and cataracts (12–16). Despite these harms, ICS use remains high among patients with COPD (17), with nearly 84% of patients receiving ICS prescriptions discordant with the 2017 GOLD recommendations (18).

Value in medicine is often defined as an outcome achieved per unit cost (19). As ICS is not a first-line therapy for patients at a low risk of exacerbation (GOLD groups A or B) and carries a risk of harm, we consider ICS prescription in this population "low-value." It is unknown if low-value ICS prescription is associated with downstream health system effects. Among COPD patients at low-risk for exacerbation, we performed a retrospective cohort study to 1) determine the association of low-value ICS use with subsequent outpatient health care utilization and costs, and 2) identify whether the association is greater in prevalent or incident low-value ICS users. We hypothesized that low-value ICS use would be associated with higher health care utilization and costs, particularly among incident ICS users.

Methods

Study Design, Data and Cohort Selection

We conducted an observational cohort study of Veterans with COPD who received pulmonary function tests (PFTs) at one of 21 Veterans Affairs (VA) Medical Centers from January 1, 2010 and December 31, 2018. We created the cohort with data from the VA Corporate Data Warehouse (CDW), which captures information on patient demographics, encounters and prescriptions. We extracted cost data from the VA Managerial Cost Accounting System (MCA), an activity-based cost allocation system. The MCA uses staff activity reports and health care services to generate estimates of encounter-level costs (20).

We included patients who had 1) a clinical diagnosis of COPD by International Statistical Classification of Diseases (ICD) 9 or 10 code, 2) spirometric evidence of airflow obstruction

(forced expiratory volume in 1 second (FEV1) / forced vital capacity (FVC) < 0.7) (9), 3) a low risk of future exacerbation, and 4) prescription of a long-acting inhaler. We considered patients at low risk of future exacerbation (GOLD groups A/B) if they had fewer than 2 outpatient exacerbations and no hospital admissions for COPD in year prior to the PFTs (index date) (9). Patients were excluded if they had any indication for ICS, including a diagnosis of asthma (by ICD9/10) or GOLD C/D disease, defined as ≥2 outpatient exacerbations or ≥1 inpatient exacerbation in the prior year (9).

Exposure

ICS inhalers are prescribed in 30-day increments within the VA. In an attempt to reduce the possibility of including empiric month-long treatment trials, we defined our exposure as the receipt of greater than a 30-day supply of an ICS (either ICS single inhaler or ICS/LABA combination inhaler) in the 3 months prior to the index date (21). We used an active control group to mitigate confounding by indication (22), consisting of individuals receiving other long-acting inhalers with greater than a 30-day supply. Long-acting inhalers included in the control group were LAMA, LABA and LAMA/LABA combination inhalers.

We defined the subgroups of incident and prevalent ICS users a priori to evaluate if any identified association with utilization and costs was driven primarily by new or chronic ICS use. We defined incident ICS use as no prior ICS prescriptions in the 9 months preceding the index ICS prescription and prevalent ICS as any ICS prescription in the 9 months preceding the index ICS prescription.

Outcomes

The primary outcomes were 1-year outpatient health care utilization per patient and 1-year outpatient costs per patient after the index date. We defined health care utilization as the total count of primary care, mental health, pulmonary, cardiology, telephone, urgent care and ED encounters. We identified visits in these categories using VA stop codes, which denote the type of clinical services provided at a given location (23). We examined cost from the perspective of the health system, defined as the sum of the cost of outpatient encounters and COPD-related medications. We inflation-adjusted dollar amounts to 2018 dollars using the Consumer Price Index (24,25).

Secondary outcomes were death, a composite binary outcome of pneumonia (inpatient and outpatient) or death, a composite binary outcome of COPD exacerbation (inpatient and outpatient) or death, and a composite binary outcome of hospitalization for COPD exacerbation or pneumonia. We used the composite outcomes that include death to account for the competing risk of death. We used the composite hospitalization outcome as a measure of inpatient utilization. Pneumonia was identified using ICD 9/10 codes. Inpatient COPD exacerbations were identified using a principal discharge diagnosis of COPD or a diagnosis of respiratory failure with a secondary diagnosis of COPD. Outpatient COPD exacerbations were identified using ICD 9/10 codes with the prescription of an oral steroid or antibiotic within 2 days of the encounter.

Covariates

We selected multiple covariates a priori to adjust for confounding based on previously published work regarding utilization and costs within VA (26,27). These were age, sex, race, VA service

connected status, body mass index (BMI), smoking status, Elixhauser Comorbidity Index (28), FEV1 less than 50% and drive distance to the closest VA primary care clinic. In particular, VA service connected status and drive distance have previously been associated with health care utilization (29–31). In utilization models, we adjusted for lagged health care utilization, defined as encounter counts in the year prior to PFTs. In cost models, we adjusted for lagged cost, defined as tertiles of cost in the year prior to PFTs.

Statistical analysis

To compare balance between measured variables, we reported standardized mean differences (SMD) (32). We generated both univariable and adjusted multivariable negative binomial regression models to determine the association of our primary exposure with 1-year outpatient health care utilization. We used an offset independent variable for the length of time at risk of utilizing health care, set to 365 days in a calendar year for all patients that remained alive for the full year of follow-up, and reduced to the number of days in the year alive for patients that died during the follow-up period. We applied both univariable and adjusted multivariable generalized linear models (GLM) to estimate the association of our primary exposure with 1-year health care costs. We assumed a gamma distribution and a log link, which were determined using the modified Park test and the Box-Cox test (33,34). Given that the likelihood of receiving a prescription of ICS and utilizing health care is in part related to the care delivery system itself, all models were adjusted for intracluster correlation at the VA facility level.

In the subgroup analyses, we estimated separate univariable and adjusted multivariable negative binomial and GLM models for the primary outcomes of utilization and cost, with prevalent ICS

and incident ICS modeled as categorical exposure variables. In the secondary analyses, we estimated univariable and adjusted multivariable logistic regression models to estimate the association between ICS and the secondary outcomes of death, pneumonia/death and COPD exacerbation/death.

For inference, the results of all univariable and multivariable analyses for the primary outcomes were expressed as average marginal effects (AME). AMEs for utilization reflect the change in 1-year encounters per patient associated with exposure to low-value ICS. AMEs for cost reflect the change in 1-year cost in dollars per patient associated with exposure to low-value ICS. The results of the secondary analyses were expressed as odds ratios. A p-value of 0.05 was used to test statistical significance. All statistical analyses were performed using STATA (Version 16.0, College Station, TX). This study was conducted as a quality improvement project under the VA Quality Enhancement Research Initiative (QUERI) program sponsored by the Office of Specialty Care Services (QUE 15-271).

Results

Patient Characteristics

In total, we identified 58,213 patients with a diagnosis of COPD who completed PFTs. Of those, we excluded 6,802 patients with a diagnosis of asthma, 6,431 patients with GOLD C/D disease, and 14,828 patients without airflow obstruction (not mutually exclusive). The final study cohort consisted of 31,551 patients (Figure 1). Of the final cohort, 9,742 patients were prescribed low-value ICS and 21,809 patients were not prescribed low-value ICS. Most baseline characteristics

of the study population were similar among low-value ICS and control groups (Table 1). Compared to the control group, patients receiving low-value ICS were less likely to be a current smoker (46% vs 53%, SMD=0.14), but more likely to have lower FEV1 (1.56 liters vs 1.87 liters, SMD=0.48) and higher baseline costs ($3210.69 vs. $2623.76, SMD=-0.20).

Differences between treatment groups

The mean 1-year outpatient health care utilization was 12.6 (SD=11.0) encounters for patients exposed to low-value ICS, compared to 11.9 (SD=11.3) encounters in the control group. Patients who used ICS had more primary care, pulmonary, and telephone encounters compared with those who did not (Table 2). The mean 1-year outpatient cost was $4378.92 (SD=$4415.65) per patient in the ICS group, compared to $3820.81 (SD=$7823.60) per patient in the control group. In both subcomponents (encounter cost and medication cost), outpatient costs were higher among patients exposed to ICS than those not exposed.

Multivariable analyses

In adjusted analysis, ICS prescription was associated with higher 1-year outpatient health care utilization (AME=0.53 encounters; 95% CI, 0.23-0.83) than no ICS, primarily due to more frequent primary care (AME=0.07; 95% CI, 0.03-0.12) and pulmonary medicine (AME=0.28; 95% CI, 0.24-0.32) encounters (Table 2). Low-value ICS exposure was associated with higher 1-year outpatient costs (AME=$154.72; 95% CI, $45.58-$263.86) than controls.

Subgroup analyses

Incident ICS prescription was associated with greater utilization (AME=1.18 encounters; 95% CI, 0.59-1.77), compared to prevalent ICS prescription (AME=0.32 encounters; 95% CI, -0.004-0.64) (Table 3). Incident ICS prescription was also associated with higher cost (AME=$391.75; 95% CI $205.13-$578.37) compared to prevalent ICS prescription (AME=$70.38; 95% CI, -40.44-181.19).

Secondary Analyses

Logistic regression models demonstrated that ICS exposure was not associated with a higher odds of death in 1-year follow-up (OR=0.95; 95% CI 0.86-1.05), a higher odds of the composite outcome of pneumonia/death (OR=1.03; 95% CI 0.96-1.11), nor a higher odds of hospitalization for either COPD exacerbation or pneumonia (OR=1.08; 95% CI 0.98-1.19) (Table 4). However, ICS use was associated with a higher odds of the composite outcome of COPD exacerbation/death occurring in 1-year of follow-up (OR = 1.47; 95% CI 1.39-1.55).

Discussion

Among a nationwide cohort of veterans with spirometrically confirmed COPD and low-exacerbation risk, we demonstrated that exposure to low-value ICS is associated with higher downstream outpatient health care utilization and outpatient costs in the subsequent year. Our findings are unique in that we studied downstream utilization and costs in real world settings and have taken an approach that can inform other healthcare systems. Our work expands on prior studies that were conducted outside of the US with smaller cohorts. Our results are in general agreement, as these studies also found low-value ICS use potentially led to higher health care costs (35,36). Other cost analyses related to ICS have been conducted in the clinical trial setting

designed to address cost-effectiveness and therefore are not directly comparable (37). The greater utilization and cost identified in our study suggest that targeting this low-value prescription practice may be a way to improve value-based care and reduce waste.

Although not designed as a causal analysis, the identified association warrants further investigation into the factors that influence provider behavior and drive the observed higher utilization and cost. Based on our findings, there are a number of potential mechanisms underlying the association of low-value ICS with higher utilization and costs. First, it is possible that low-value ICS represents a marker of patients with high utilization, high costs and poor symptom control. That is, complex patients are more likely to receive low-value ICS when presenting with respiratory symptoms, even if their symptoms may be related to other comorbidities. This potential mechanism is supported by previous studies that have found a higher likelihood of being prescribed ICS with increased disease complexity and baseline primary care utilization (38,39).

A second potential mechanism is that the ICS prescriptions were appropriate in some cases, and the observed association is due to confounding by indication. It is possible that clinicians prescribed ICS due to an understanding, not captured in our administrative dataset, that patients were at high risk of exacerbation. Alternatively, it is possible that patients in the low-value ICS group had no exacerbations in the year prior to the index date because they appropriately initiated ICS two years prior to the index date. Though in such circumstances, GOLD recommendations suggest considering de-escalation of ICS after a period of stability based on clinical trial evidence (9,40). Due to dataset limitations, we were unable to conduct a two-year

lookback to evaluate for this potential mechanism. The observation that the ICS group had worse FEV1 and health care utilization at baseline supports the possibility of confounding by indication. We addressed this issue by (1) adjusting for severity of illness and (2) conducting a subgroup analysis of incident and prevalent users of ICS. The fact that our secondary outcome analysis showed that there was a higher risk of subsequent COPD exacerbation in the low-value ICS group suggests that there may be residual confounding by indication, despite adjusting for severity of illness, airflow obstruction and baseline utilization.

Third, it is possible that the prescription of low-value ICS increases utilization and costs, through either (1) the cost of the drug itself, (2) adverse effects or (3) increased care needs, such as additional visits related to refills, medication reconciliation and medication teaching. Results from the subgroup analysis support the first mechanism, which showed the association was more pronounced after incident ICS prescriptions, suggesting that new prescriptions may represent an important driver. The observed effect of incident ICS was almost 4 times that of prevalent ICS for utilization, and $321 more than prevalent ICS for costs. While low-value ICS was not associated with pneumonia, other potential adverse effects that were not directly evaluated may account for increased utilization, such as hyperglycemia (41). Most likely, the relationship is complex and all mechanisms are occurring simultaneously.

Regardless of the directionality of the underlying mechanism, the observed higher associated costs and utilization remain important findings, especially if the magnitude of these estimates are applied across a large health care system like the VA. Previous literature suggests that within the VA, there are over a million patients with COPD, of which 40% are on ICS therapy (17). Up to

84% of these ICS prescriptions may be discordant from the 2017 GOLD recommendations (18). This corresponds to roughly 340,000 patients with COPD that could be receiving low-value ICS in the VA. In our study, we found an additional 0.5 encounters per patient per year (about a 4% increase in utilization) and $155 additional cost per patient were associated with receiving low-value ICS. The estimated cost corresponds to roughly $53 million for the health system. If similar patterns of low-value prescribing are occurring in other health care systems outside of the VA, the magnitude of potential waste from this single practice could be far greater at a national level.

The findings from our study can guide health care systems and payers to improve value-based prescribing in a number of ways, as has been proposed by Kesselheim et al (6). First, at the provider level, knowledge of drug costs and the consequences of low-value prescribing should be disseminated to providers as part of medical training and continuing education. Second, at the health system level, the downstream costs and utilization of low-value ICS should motivate health system leaders to devote resources towards change. Such changes could include decision aids to prevent new low-value ICS prescriptions and interventions to de-prescribe existing low-value ICS. Finally, at the health policy level, reimbursement policies can be structured to disincentivize low-value prescriptions.

There are several limitations to this study. First, there are a higher number of patients in the low-value ICS group that have more severe airflow obstruction. This imbalance may be because they were placed on therapy at a time when severe airflow obstruction was a recommended indication for ICS, and thus was an appropriate management decision. Prior to 2017, ICS was

recommended for patients with an FEV1 <50% (42). As more evidence emerged about the limitations of FEV1 as a predictor of future outcomes, GOLD began recommending ICS only for those patients at high risk of exacerbation starting in 2017, during our study period (9,43). While the recommendation change does not alter the low-value nature of these ICS prescriptions based on most recent evidence, there may be unmeasured confounding that biases the results even after accounting for these difference in multivariable analysis. Second, the combination of dose and duration of low-value ICS exposure may be an important factor in understanding the relationship between the cost and utilization. Unfortunately, this level of detail was not available for our study cohort. Third, as we learn more about appropriate indications for ICS, such as the use of blood eosinophils in selecting therapies, it is possible that part of our study cohort is a population that benefits from ICS (44). Fourth, we identified receipt of ICS using VA pharmacy records. It is possible that patients were receiving medications outside the VA. However, Veterans have a strong incentive to obtain medications within the VA due to lower copayments, which mitigates the likelihood that unaccounted non-VA medications use could bias our results (45). Fifth, detailed inpatient utilization and costs were not available in our dataset, which would have further characterized the association with low-value ICS. However, we were able to study a binary inpatient utilization outcome of hospitalization for COPD exacerbation or pneumonia, which serves as a surrogate for inpatient costs. We found no difference in the adjusted odds of hospitalization between the groups, suggesting that much of the observed association could be driven by outpatient factors. Finally, this study was conducted amongst a group of Veterans within the VA, and additional studies are needed to confirm if similar associations exist in other health care systems. Despite these limitations, this study has substantial strengths, including a large number of participants, a unique VA dataset with detailed utilization and cost data with 1-

year of follow-up, and multivariable analysis to adjust for potential confounders, including severity of illness.

Conclusions

This study suggests that low-value ICS prescription for patients with COPD at low risk of exacerbation is associated with higher subsequent outpatient utilization and costs, an observation primarily driven by incident ICS prescriptions. Low-value ICS prescription is wasteful and costly to the health care system and should be a target of de-implementation. Other payers outside of the VA likely suffer from waste related to low-value ICS as well and should be an area of future investigation.

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Table 1: Baseline cohort characteristics, by ICS prescription status

Characteristic	Control group (n=21,809)	Low-value ICS (n=9,742)	Standardized Mean Difference*
Age at PFTs (years), mean (SD)	68 (9)	69 (9)	-0.09
Female sex, n (%)	552 (3%)	191 (2%)	0.04
Race, n (%)			0.08
Black/African American	2,096 (10%)	741 (8%)	
American Indian/Alaska Native	169 (1%)	64 (1%)	
Native Hawaiian/Pacific Islander	158 (1%)	86 (1%)	
Asian	69 (0%)	31 (0%)	
White	18,159 (88%)	8,276 (90%)	
VA service connected, n (%)	9,458 (43%)	4,311 (44%)	-0.02
Drive distance to VA (miles), mean (SD)	17.0 (21.9)	17.5 (18.8)	-0.03
Body mass index, n (%)			0.04
Underweight	806 (4%)	351 (4%)	
Normal	7,133 (33%)	3,038 (31%)	
Overweight	7,067 (32%)	3,130 (32%)	
Obese	6,799 (31%)	3,223 (33%)	
Current smoker, n (%)	11,539 (53%)	4,470 (46%)	0.14
FEV1<50% predicted, n (%)	6,350 (29%)	4,725 (49%)	-0.41
FEV1 (liters), mean (SD)	1.87 (0.68)	1.56 (0.62)	0.48
Elixhauser Comorbidity Index	5.9 (7.2)	5.7 (6.6)	0.04
Baseline outpatient utilization (encounters), mean (SD)	8.97 (9.52)	9.54 (9.53)	-0.06
Baseline outpatient costs (2018 dollars), mean (SD)	2623.76 (3017.94)	3210.69 (2780.48)	-0.20
Number of distinct inhaler classes prescribed, mean (SD)	0.73 (0.93)	1.81 (1.22)	-0.99

Abbreviations: ICS=inhaled corticosteroids; PFTs=pulmonary function test; FEV1 = forced expiratory volume in 1 second; VA=Veterans Affairs
* A cutoff of 0.1 indicates negligible differences between the groups(32)

Table 2: Association of Low-value ICS Prescription with Primary Outcomes

Outcome	Control group (n=21,809)	Low-value ICS (n=9,742)	Average Marginal Effects (95% CI)*	
			Unadjusted	Adjusted†
1-year outpatient utilization (encounters), mean (SD)	11.88 (11.27)	12.55 (11.01)	0.69 (0.37, 1.01)	0.53 (0.23, 0.83)
Primary care	2.23 (1.89)	2.31 (1.84)	0.08 (0.04, 0.13)	0.07 (0.03, 0.12)
Pulmonary	1.69 (1.55)	2.08 (1.65)	0.37 (0.33, 0.42)	0.28 (0.24, 0.32)
Cardiology	0.69 (1.86)	0.66 (1.75)	-0.03 (-0.09, 0.02)	-0.02 (-0.08, 0.03)
Telephone	5.40 (7.98)	5.77 (7.83)	0.39 (0.15, 0.63)	0.39 (0.07, 0.70)
Mental health	1.01 (3.46)	0.94 (3.33)	-0.07 (-0.16, 0.01)	-0.34 (-1.23, 0.56)
Emergency department	0.79 (1.82)	0.73 (1.70)	-0.06 (-0.09, -0.02)	-0.05 (-0.09, 0.01)
Urgent care	0.08 (0.45)	0.07 (0.42)	-0.01 (-0.02, 0.00)	-0.01 (-0.03, 0.01)
1-year outpatient costs (2018 dollars), mean (SD)	3820.81 (7823.60)	4378.92 (4415.65)	$544.43 (380.42, 708.44)	$154.72 (45.58, 263.86)
Outpatient encounter costs	3471.40 (7781.86)	3607.41 (4318.19)	$135.03 (-30.74, 300.80)	-$193.95 (-316.09, -71.81)
COPD-related medication costs	349.01 (464.85)	771.35 (619.32)	$380.20 (331.19, 429.20)	$329.92 (286.78, 373.05)

Abbreviations: ICS=inhaled corticosteroids; COPD=chronic obstructive pulmonary disease
* Average Marginal Effect are the change in the primary outcome associated with exposure to low-value ICS after adjustment for confounders
† Adjusted for age, sex, race, VA service connected status, body mass index, smoking status, Elixhauser Comorbidity Index, FEV1 less than 50% and drive distance to the closest VA primary care. Utilization models also adjusted for baseline utilization. Cost models also adjusted for baseline costs.

Table 3: Subgroup Analysis of the Primary Outcomes by Prevalent and Incident Low-value ICS Prescription

Outcomes	Average Marginal Effects (95% CI)*			
	Prevalent low-value ICS (n=7,328)		Incident low-value ICS (n=2,414)	
	Unadjusted	Adjusted†	Unadjusted	Adjusted†
1-year outpatient utilization (encounters), mean (SD)	0.86 (0.49, 1.24)	0.32 (-0.004, 0.64)	0.21 (-0.48, 0.90)	1.18 (0.59, 1.77)
1-year outpatient costs (2018 dollars), mean (SD)	$651.28 (473.58, 828.98)	$70.38 (-40.44, 181.19)	$275.33 (41.73, 508.93)	$391.75 (205.13, 578.37)
Outpatient encounter costs	$163.99 (-16.11, 344.10)	-$321.96 (-446.43, -197.50)	$51.08 (-165.27, 267.43)	$163.83 (2.34, 325.32)
COPD-related medication costs	$487.46 (430.93, 543.99)	$401.28 (351.86, 450.70)	$224.65 (177.71, 271.60)	$218.23 (169.41, 267.04)

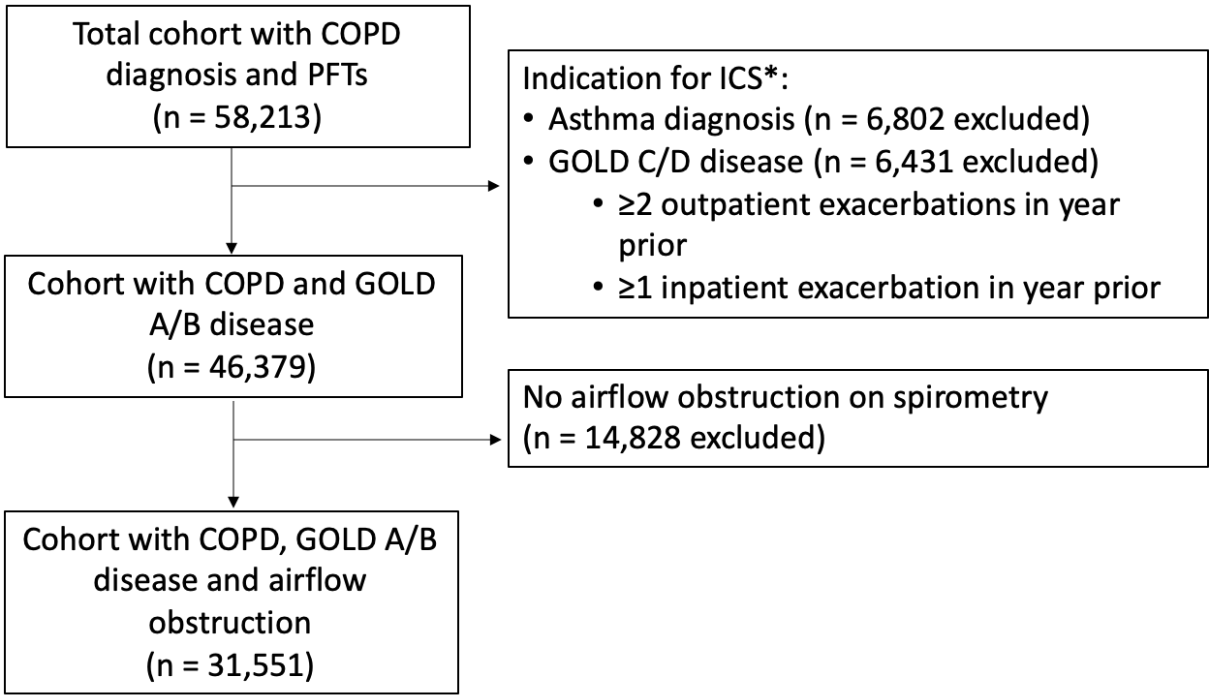
Abbreviations: ICS=inhaled corticosteroids; COPD=chronic obstructive pulmonary disease
* Average Marginal Effect are the change in the primary outcome associated with exposure to low-value ICS after adjustment for confounders
† Adjusted for age, sex, race, VA service connected status, body mass index, smoking status, Elixhauser Comorbidity Index, FEV1 less than 50% and drive distance to the closest VA primary care. Utilization models also adjusted for baseline utilization. Cost models also adjusted for baseline costs.

Table 4: Association of Low-value ICS Prescription with Secondary Outcomes

Outcome	Odds Ratio (95% CI)		
	Control group	Low-value ICS	
		Unadjusted	Adjusted*
Composite pneumonia or death in 1-year follow-up	Referent	1.14 (1.06, 1.22)	1.03 (0.96, 1.11)
Composite COPD exacerbation or death in 1-year follow-up	Referent	1.65 (1.56, 1.74)	1.47 (1.39, 1.55)
Death in 1-year follow-up	Referent	1.06 (0.97, 1.16)	0.95 (0.86, 1.05)
Hospitalizations for pneumonia or COPD exacerbation	Referent	1.23 (1.13, 1.35)	1.08 (0.98, 1.19)

Abbreviations: ICS=inhaled corticosteroids; COPD=chronic obstructive pulmonary disease
* Adjusted for age, sex, race, VA service connected status, body mass index, smoking status, Elixhauser Comorbidity Index, FEV1 less than 50%, drive distance to the closest VA primary care and baseline utilization.

Figure 1: Cohort selection



Abbreviations: COPD=chronic obstructive pulmonary disease; ICS=inhaled corticosteroids; GOLD=Global Initiative for Chronic Obstructive Lung Disease
* Not mutually exclusive

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