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A Cross-Sectional Analysis of Bronchodilator Prescribing in COPD and Cardiovascular Comorbidity

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A CROSS-SECTIONAL ANALYSIS OF BRONCHODILATOR PRESCRIBING IN COPD AND CARDIOVASCULAR COMORBIDITY

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ABSTRACT

Background: Bronchodilators used to treat Chronic Obstructive Pulmonary disease have been associated with adverse cardiovascular events. Moreover, the high prevalence of cardiovascular diseases (CVD) in COPD (8-40%) requires an evaluation of treatment differences between comorbid groups in order to understand the appropriateness of drug prescribing.

Objective: To determine whether COPD patients with concurrent CVD are less likely to be prescribed bronchodilators compared to those without CVD.

Methods: A retrospective cross-sectional study was conducted using the 2010 National Ambulatory Medical Care Survey (NAMCS) to quantify the association between concurrent CVD morbidity and the probability of receiving a bronchodilator prescription. Visits included patients ≥40 years who had COPD diagnosis. Survey-weighted data were analyzed through descriptive analysis, univariate (unadjusted) and multivariate (adjusted) logistic regression models. Demographics, patient, physician and visit characteristics were assessed as covariates in the models.

Results: Out of 11,627,061 ambulatory visits recorded by patients ≥40 years with COPD diagnosis, majority was male (57%), non-Hispanic White (80%) and used at least one bronchodilator (55.5%). We found that a significantly lower proportion of the COPD-CVD group (32.3%) was treated with bronchodilators versus 57.6% for the non-comorbid group. The effect of CVD on bronchodilator prescribing was modified by gender, beta-blockers and asthma. CVD patients who were female, not prescribed beta-blockers and not having concomitant asthma were 94% less likely to be prescribed bronchodilators compared the non-CVD females with the same

characteristics. On the other hand, males not prescribed beta-blockers and not having concomitant asthma had 68% lower probability when CVD coexisted with COPD. Female CVD patients prescribed beta-blockers and not living with asthma had only a 20% chance of being a bronchodilator user than those without CVD. Cardiovascular disease did not affect the utilization of bronchodilators in males taking beta-blockers who either had or did not have asthma.

Conclusion: Concurrent CVD diagnosis is a significant factor for reducing the probability of prescribing bronchodilators for COPD and our findings provide evidence of variations in bronchodilator prescribing for stratified groups of COPD-CVD patients. Most patients with COPD and CVD are less likely to be prescribed bronchodilators, with the exception of males who were also prescribed beta-blockers. Thus, this study highlights a specific patient subgroup for whom the guidelines are less likely to be observed.

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CHAPTER 1

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is defined as a "preventable and treatable disease characterized by persistent airflow limitation that is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients."[1] The disease is clinically diagnosed as one or more of 3 subtypes – chronic bronchitis, emphysema and chronic airway obstruction.[2]

COPD is the fourth leading cause of chronic morbidity and mortality in the United States affecting 6.5% of adults (13.7 million diagnosed cases) and leading to 133,575 deaths.[2] In 2010, there were 10.3 million physician office visits, 1.5 million emergency department visits, and 699,000 hospital discharges for COPD.[2] Globally, COPD ranked fifth cause of years lived with disability (YLDs) in the 2010 global burden of disease study.[3] The World Health Organization predicts that COPD will become the third leading cause of death worldwide by 2030.[4] Inevitably, COPD is and will continue to be a major global health problem.[5]

Bronchodilators are the mainstay for symptomatic treatment of COPD due to their ability to relieve bronchial obstruction and airflow limitation, improve emptying of the lungs and reduce hyperinflation during rest and exercise.[6,7] Three major classes are recommended as first-line agents - beta-(β) 2-agonists, anticholinergics (AC), and methylxanthines, used alone or in combination or as single or combination drugs.[7]

Despite the benefits of bronchodilator agents in the treatment of COPD, patients may be at an increased risk of cardiovascular (CV) toxicity due to beta-adrenergic stimulation. Previous studies showing an association between bronchodilators and adverse cardiovascular events such as arrhythmias, myocardial ischemia, heart failure and sudden cardiac death, will be discussed in detail in the literature review section.[8-13]

The potential cardiovascular risk of bronchodilators in COPD has important therapeutic implications for two main reasons: First of all, the prevalence of cardiovascular-related diseases (CVD) in COPD is estimated to range from 8% to as high as 40%[1,14-16] making it the most frequent and most important disease group coexisting with COPD. Secondly, the exclusion of comorbid subjects from clinical trials often limits the use of trial data in providing practical treatment recommendations for the real world COPD patient population where multiple morbidities are highly prevalent.

We hypothesize that cardiac disorders play an independent role in the lesser probability of receiving a bronchodilator prescription for COPD. The objective of this study is to provide descriptive data on the classes of bronchodilator medications prescribed to ambulatory patients with diagnosed COPD in the United States and examine whether COPD patients with CVD are less likely to be prescribed bronchodilators compared to COPD patients without CVD.

CHAPTER 2

REVIEW OF LITERATURE

Etiology and Epidemiology of COPD and its Comorbidities

Cigarette smoking is the dominant and best-studied risk factor for COPD, though a substantial burden of disease occurs in nonsmokers.[17-19] Other etiologic factors such as advanced age, occupational exposure to dust, fumes and gases, indoor and outdoor air pollution, airway hyper-responsiveness, asthma, infections and genetic predisposition (α-antitrypsin deficiency) are also important.[1] Furthermore, it has been increasingly recognized that COPD is more than just a lung disease: it is a complex heterogeneous systemic disease, frequently associated with other chronic diseases including coronary heart disease, cardiovascular, respiratory tract, metabolic, hematological, musculoskeletal, gastrointestinal, renal diseases, psychiatric disorders and neoplasias.[14,15,20-23]

The prevalence of comorbidity in COPD has been studied using nationally-representative data, National Health and Nutrition Examination Survey (NHANES) 1999-2008.[24] Using a ten-year analytic sample of 14,828 subjects (995 COPD cases) aged ≥45, subjects with self-reported physician diagnosis of COPD were more likely than subjects without physician-diagnosed COPD to have coexisting arthritis (54.6% vs. 36.9%), depression (20.6% vs. 12.5%), osteoporosis (16.9% vs. 8.5%), cancer (16.5% vs. 9.9%), coronary heart disease (12.7% vs. 6.1%), congestive heart failure (12.1% vs. 3.9%), and stroke (8.9% vs. 4.6%).[24]

Vanfleteren and colleagues used a cluster analysis approach to assess the prevalence and severity of objectively identified chronic concomitant disorders in a cohort of 213 patients with moderate to very severe COPD.[25] The CIRO CO-morbidity (CIROCO) study was an observational single-center study and almost all subjects (97.7%) had one or more comorbidities. More than half (53.5%) of the patients had at least four comorbidities.

Another study in a sample of COPD patients referred to an Australian outpatient hospital-based pulmonary rehabilitation program reported that 96% of patients had at least 1 other chronic conditions and 29% had 5 or more comorbidities.[26] Data were available on 70 patients and 64% of patients had multiple morbidities associated with cardiovascular disease.

While it is likely that the prevalence of comorbidities in people with COPD is influenced by common risk factors, such as smoking, advanced age, chronic systemic inflammation, physical inactivity and low socioeconomic status, studies have confirmed that concurrent conditions worsen health outcomes independent of pre-existing risk factors.[26] Comorbidities in COPD lead to lower health-related quality of life,[27,28] more hospitalizations, severe disabilities[5] and higher rates of mortality[29,30] compared to those without comorbidities.

Burden of comorbid COPD and Cardiovascular disease (CVD)

Observational studies indicate that COPD is associated with a high prevalence of coronary artery disease, cardiac arrhythmias, cerebrovascular disease, peripheral vascular disease and congestive heart failure.[31-33] In addition, COPD patients with

CVD pose significantly higher clinical and economic burden on patients and healthcare system than COPD patients without CVD.

One large retrospective cross-sectional survey involving 618,090 subjects quantified the association between COPD and diagnosis of CVD and stroke and revealed that COPD was associated with a fivefold increase in the odds of having had CVD (OR 4.98, 95% CI 4.85 to 5.81; $p<0.001$), and a threefold increase in the odds of having had a stroke (OR 3.34, 95% CI 3.21 to 3.48; $p <0.001$).[34]

Curkendall and colleagues found that the prevalence of all cardiovascular diseases was higher in the COPD group than in the comparison group subjects(n=11,493) in a retrospective cohort study in Saskatchewan longitudinal health care databases in Canada.[35] After adjusting for cardiovascular risk, odds ratios of prevalence were: arrhythmia 1.76 (CI: 1.64–1.89), angina 1.61 (CI: 1.47–1.76), acute myocardial infarction 1.61 (CI: 1.43–1.81), congestive heart failure 3.84 (CI: 3.56–4.14), stroke 1.11 (CI: 1.02–1.21), pulmonary embolism 5.46 (CI: 4.25–7.02). COPD patients also had an elevated risk of hospitalization and death (OR 2.7 CI: 1.82–2.36) due to cardiovascular causes.[35] One limitation of the study was the lack of baseline smoking data which made it difficult to separate the cardiovascular effects of smoking, a major risk factor for both COPD and CVD, from the effects of COPD.

Similar results on the impact of comorbid COPD-CVD on healthcare utilization were obtained in a retrospective matched-cohort of 4594 patients each with COPD and CVD $\geq$ 40 years of age using administrative claims data and propensity score technique for matching.[36] The data source for this study was the IMS Lifelink Database containing medical and pharmacy claims data from over 100 different

managed healthcare plans (encompassing over 60 million patients) in the United States. The COPD-CVD cohort was about twice as likely than the COPD-only cohort to require COPD-related hospitalization (OR 1.95; $p < 0.001$), 47% more likely to have an ER visit (OR 1.47; $p < 0.001$) and 62% more likely to require hospitalization and/or ER visit (OR, 1.62; $p < 0.001$).[36] Significant differences in healthcare costs were found as the average annual all-cause medical costs per patient were $22,755 vs $8,036 ($p<0.001$), and total costs were $27,032 vs $11,506 ($p<0.001$), for COPD-CVD and for COPD-only groups respectively.[36] Corresponding average COPD-related annual medical costs were $1891 vs $1060 ($p<0.001$) and total costs were $3295 vs $2379 ($p < 0.001$).

COPD Treatment

The most widely applied guideline for treatment is the Global Strategy for the Diagnosis, Management, and Prevention of COPD (GOLD strategy), revised in 2014 containing summaries of current evidence on management and prevention strategies.[1] Four grades of disease are defined according to severity of airflow obstruction; mild disease A (FEV1 ≥80% predicted), moderate disease B (50% ≤ FEV1 <80% predicted), C severe disease (30% ≤ FEV1 <50%), and very severe disease D (FEV1 <30% predicted); and the result of this classification leads to treatment choice.

Pharmacotherapy constitutes the major intervention used in COPD patients. Medications commonly used for COPD are bronchodilators, corticosteroids and phosphodiesterase-4 inhibitors.[37] None of the existing medications have been proven to change long-term decline in lung function, as such, the main goal of

pharmacological therapy is to reduce symptoms, decrease the frequency and severity of exacerbations, improve quality of life and exercise tolerance.[1]

Non-pharmacological treatment modalities include pulmonary rehabilitation, oxygen therapy, ventilation support and surgical treatments.[1] Regardless of disease stage, the identification and reduction of risk factors are important in COPD prevention and treatment. Smoking cessation is the first and most crucial step in COPD therapy for all COPD patients who smoke, and has greatly influenced the natural history of COPD and lowered mortality with long-term quit rates as high as 25%.[1] Use of smoking cessation products (Bupropion, Varenicline and Nortriptyline) combined with behavioral support is reported to increase successful smoking cessation compared with either intervention alone.[1,37]

Safety of Bronchodilators in COPD

Bronchodilators are the mainstay for symptomatic treatment of COPD due to their ability to relieve bronchial obstruction and airflow limitation, improve emptying of the lungs and reduce hyperinflation during rest and exercise.[6,7] Bronchodilator treatments include beta-(β) 2-agonists, anticholinergics (AC), and methylxanthines, used alone or in combination. They are recommended as first-line agents useful to prevent or reduce symptoms as-needed or on a regular basis.[7] Short-acting bronchodilators are typically used as rescue medication for immediate symptom relief, routinely in the early disease stages or in COPD patients with a low symptom burden whereas long-acting bronchodilators are used as regular maintenance therapy and are generally more effective and convenient.[7] Combinations of bronchodilators may improve efficacy and

reduce risk of adverse effects rather than increasing the dose of a single agent.[7] Inhaled bronchodilators are preferred over oral preparations based on favorable efficacy and side effect profile.[1]

Despite the benefits of bronchodilator agents in the treatment of COPD, patients may be at an increased risk of cardiovascular (CV) toxicity due to beta-adrenergic stimulation. Evidence on the safety of bronchodilator therapy in COPD is mixed. There have been reports on the relative safety of bronchodilator use in COPD [38] whereas some researchers have found clinically significant higher risks in the incidence of cardiovascular events in patients on selected bronchodilator agents than control groups.[8,11,12,39,40]

In 2003, Ferguson and coworkers[38] evaluated the cardiovascular safety of salmeterol (a beta-2-agonist), in COPD patients by reviewing safety data from randomized, double-blind, parallel group, multiple-dose studies. Pooling results from 7 clinical trials, the authors concluded that though both salmeterol and placebo groups had an increased incidence of adverse CV events with age, concurrent cardiovascular conditions, and treatment with antiarrhythmic/bradycardic agents, the incidence of cardiovascular events (8%), including cardiovascular deaths, was similar in both groups.

However, a meta-analysis of randomized placebo-controlled trials of beta-2 agonists in patients with obstructive airway disease (asthma and COPD) performed a year later, revealed opposite results.[39] This study included longer duration trials in the analysis to evaluate both the short-term effect on heart rate and potassium concentrations, and the long-term outcome of adverse cardiovascular events. Adverse

events included sinus and ventricular tachycardia, syncope, atrial fibrillation, congestive heart failure, myocardial infarction, cardiac arrest, or sudden death. From among 33 trials, the conclusion was that beta-2 agonist treatment significantly increased the risk for a cardiovascular event (relative risk RR 2.54; 95% CI, 1.59 to 4.05) compared to placebo mainly because of the short term effects of tachycardia and hypokalemia.

In 2008, Macie et al[8] examined the relationship between use of inhaled respiratory drugs in people with chronic obstructive respiratory diseases and cardiovascular hospitalizations for 5years from 1996 through 2000 using the Manitoba Health Database. The nested case control study included exposure to beta agonists, anticholinergic (ipratropium bromide), and inhaled corticosteroids (ICS) and outcomes were first hospitalizations for supraventricular tachycardia, myocardial infarction, heart failure or stroke. The likelihood of a hospitalization for SVT, MI, and HF was significantly increased for those to whom beta agonists [OR 1.68, 95% CI 1.41–2.00], ipratropium [OR 1.48, 95% CI 1.29–1.70] but not ICS [OR 1.13, 95% CI 0.95–1.35] were dispensed within 60 days prior to the hospitalization. While it is likely that bronchodilator use was simply a marker of disease severity and this accounted for their association with cardiovascular disease, the authors note that ICS was not associated with these outcomes. The findings on specific drug interactions were that each case the receipt of cardiac drugs decreased the likelihood of hospitalizations associated with bronchodilator. For example, bronchodilators increased the risk of stroke in patients who were not taking cardiac drugs but did not increase the risk of arrhythmia in the presence of anti-arrhythmic agents.

In 2012, another nested case-control study involving 6018 subjects with COPD from the Saskatchewan Cohort Study [9] found that the rate of arrhythmia was elevated with the new use of ipratropium, a short-acting anticholinergic agent (RR 2.4; 95% CI, 1.4–4.0) and of long-acting β-agonists (RR, 4.5; 95% CI, 1.4–14.4). The researchers did not find an elevated risk with short-acting beta-2-agonists or methylxanthines and proceeded to ascertain the results in a larger patient pool. For the reassessment, the larger Quebec cohort of 76,661 subjects was analyzed.[10] They found that the rate of arrhythmias increased with the new use of short-acting beta-2-agonists (RR, 1.27, 95% CI, 1.03–1.57) and long-acting beta-2-agonists (RR 1.47; 95% CI, 1.01–2.15), but not with ipratropium and methylxanthines. This slightly increased risk for short-acting beta-2 agonists and ipratropium corroborates evidence earlier obtained from the Manitoba Health Database.[8]

Tiotropium, a once daily long-acting anticholinergic bronchodilator has also been reported for safety concerns regarding its use in the COPD patient population. In 2013, Singh *et al* [13] reported that an increased risk of all-cause mortality (RR 1.52; 95% CI, 1.06–2.16) and CVD mortality (RR 2.05; 95% CI, 1.06–3.99) was associated with tiotropium use. Patients with known cardiac disease were also reported to have significantly high risk of dying from cardiac causes though the risk estimates largely varied among patients (RR 8.6; 95% CI, 1.1–67.2).

In 2011, a retrospective cohort study of patients attending a Heart Failure (HF) Disease Management Programme was done by Bermingham and colleagues.[11] The cohort size was 1294 patients (age 70.6+11.5 years) of whom 64% were male and 22.2% were taking β2 agonists. The mean follow-up was 2.9+2.4 years. The study

intended to address gaps in literature that did not consider the influence of factors such as the dose, duration, or type of bronchodilator therapy (long acting vs. short acting) on outcomes. The primary endpoint was the effect of β2 agonist use compared with no β2 agonist use on mortality using unadjusted and adjusted Kaplan2Meier survival curves. Beta-agonist users were older, more likely to be male, to have smoked, to have chronic obstructive pulmonary disease (COPD) and asthma, and less likely to take beta-blockers. Unadjusted mortality rates for β2 agonist users were found to be significantly higher than non-β2 agonist users [hazard ratio (HR) 1.304, 95% CI 1.030–1.652, P= 0.028]. Overall mortality rates were similar [HR 1.043, 95% CI (0.771–1.412), P=0.783] after adjusting for covariates like age, sex, beta-blocker use, co-morbidity, smoking, COPD, and differences in B-type natriuretic peptide (BNP). There was no influence of β2 agonist duration of use, dose, or type on outcome in fully adjusted models.

The possible role of the mode of administration of bronchodilators in observed differences in treatment effects has also been explored. Available formulations include metered dose inhalers (MDI), dry powder inhalers (DPI) and soft mist inhalers (SMI). Using a retrospective study, Verhamme and colleagues[12] investigated the risk of mortality between tiotropium Respimat (an SMI) vs Handihaler (DPI) and showed that the use of Respimat was associated with about 30% increased mortality (adjusted HR 1.27; 95% CI, 1.03–1.57) compared with Handihaler and the association was strongest for cardiovascular /cerebrovascular death (adjusted HR 1.56, 95% CI 1.08-2.25). The reason for this apparent elevated risk is not clear, though it may be related to rapid peak drug concentrations achieved after mist inhalation.[40]

The publications on safety of bronchodilators reveal the likelihood of different study designs to bias and confounding. Smoking status, non-respiratory drugs with known arrhythmogenic properties taken concomitantly may bias the study results. The adverse cardiovascular outcomes may reflect COPD severity or confounding by indication rather than an adverse effect of bronchodilator therapy. It is also possible that bronchodilators impose a larger relative risk in people with undiagnosed cardiovascular disease than in people with known disorders since bronchodilators did not increase the risk of arrhythmia in the presence of anti-arrhythmic agents.

Utilization of Bronchodilators

Although, long-term decline in lung function is irreversible in COPD, bronchodilators are recommended to reduce airflow obstruction, reduce the frequency of exacerbations, improve health status and decrease mortality.[1] Therapy usually includes a short-acting bronchodilator or a long-acting bronchodilator (either a Beta-2-agonist or an anticholinergic drug or a methylxanthine) or combination products for adequate clinical response and tolerance of side effects. [1]

A case-control study was conducted on the use of bronchodilators and arrhythmias in COPD in 2012.[9] Out of 469 cases of arrhythmias, the proportion taking at least one short-acting β-agonist was 37.9%, long-acting β-agonists 1.9%, Ipratropium bromide 29.4% and Methylxanthine 10.2% compared to the controls where use was short-acting β-agonist was 35.2%, long-acting β-agonists 1.6%, Ipratropium bromide 22.2% and Methylxanthine 8.7%. The percentage of β-blocker users in the study sample was 11.6% and overall cardiovascular medication prescribed

is 22.4%. Groenwold and colleagues described the characteristics of a cohort of 3376 COPD/ asthma patients that were beta-agonist users and non-users.[41] 47.5% were female, 16.7% of the medication users had diagnosed cardiovascular disease, 29.1% utilized beta-agonist and 16.7% had prescriptions for anticholinergic drugs.

In addition to the relationship between bronchodilators and cardiovascular disease in COPD, evidence that medication prescribing may differ by patient demographic characteristics exists. Treatment differences by sex in the utilization of bronchodilators and other COPD medications were investigated in a cross-sectional analysis based on 10 year data from two national datasets - National Ambulatory Medical Care Survey (NAMCS) and the National Hospital Ambulatory Medical Care Survey (NHAMCS).[42] Women had a consistently higher proportion of visits with COPD medication prescriptions than visits by men. The frequency of COPD medications prescribed to women decreased by 7% (from 73% to 67%) during the study period (1995-2004). The average number of COPD drug mentions per visit decreased for both women and men and trends were significantly different between men and women ($P < 0.001$). Prescription of methylxanthines decreased in visits by women and men, whereas prescription of anticholinergics increased continuously in the recent years.

Certainly, the high prevalence of COPD and cardiovascular disease warrant further study of prescribing patterns in COPD patients with cardiac conditions. Thus, the purpose of the present study is to determine whether COPD patients in ambulatory care in the United States have a lower likelihood of being prescribed bronchodilators if they have concurrent CVD compared to those without CVD.

CHAPTER 3

METHODOLOGY

Data Source

The 2010 National Ambulatory Medical Care Survey (NAMCS) [43] was the source of data used to assess COPD patient visits. The NAMCS is designed to collect data on outpatient visits from non-federally employed office-based physicians in the United States and it is conducted annually by the National Center for Health Statistics (NCHS), a division of the Centers for Disease Control and Prevention (CDC). The survey employs multistage probability sampling design to generate unbiased national estimates. These data are weighted to be nationally representative of outpatient doctor visits throughout the United States.

The unit of data collection is the visit or encounter not patient-level. NAMCS data contains variables on reason for visit, diagnoses, diagnostic/screening services provided, medication therapy, demographic characteristics of patients, specialty of physician seen, and certain characteristics of the facility, such as geographic region and metropolitan status for a randomized sample of patient visits during a randomly selected 1-week time period. The NAMCS has gained enormous popularity as a choice dataset to assess national trends in ambulatory medical care utilization and examine concordance of prescribing patterns with evidence-based treatment guidelines. Therefore, we consider the dataset suitable for this analysis. The 2010 NAMCS data were used because they were the most recently available.

The Institutional Review Board of the University of Rhode Island recognizes that studies using de-identified, publicly available data do not constitute human subjects research and granted exempt status for this study.

Analytic sample

The study population consisted of patients aged 40 years and over, who had visits where chronic obstructive pulmonary disease (COPD) was diagnosed. A patient visit was included if the COPD International Classification of Diseases, 9th revision, Clinical Modification ICD-9-CM codes 491, 492 and 496 were listed as 1 of 3 diagnoses for that visit. COPD visits were compared to number of 'Yes' responses to the question "Does the patient now have COPD (Yes/No)" captured on the patient record form. Figure 1 depicts the inclusion and exclusion criteria.

Further stratification of COPD sub-groups was done by presence or absence of concurrent diagnosis of cardiovascular conditions of interest. Based on previous studies, the following cardiovascular diseases were selected: myocardial infarction, angina, coronary artery disease, cardiac arrhythmias (including tachycardia, atrial fibrillation, and cardiac arrest), and congestive heart failure. The ICD-9 diagnosis codes are presented in Table 2.

Variables Specification

The dependent variable is defined as the prescription of a bronchodilator at a visit (Rx =1 or 0). New or continued bronchodilators recorded in any of the 32 therapeutic class fields were identified using the therapeutic class codes extracted from

NCHS's Ambulatory Care Drug Database. Table 3 shows the relevant drug codes. The drug visits strategy was used instead of drug mentions because we are interested in a binary response per visit (any bronchodilator treatment Rx=1 *vs* no bronchodilator treatment Rx=0) not the total number of times bronchodilators are mentioned in the entire study population, which was more than one bronchodilator medication for each ambulatory medical care visit, on the average.

Bronchodilator users were stratified into 4 therapeutic categories (beta-(β) 2-agonists, anticholinergics (AC), methylxanthines and combination bronchodilators) to estimate the proportion of users in each subclass and compare bronchodilator therapy across CVD exposure variable and other visit characteristics. Table 3 outlines the commercially available bronchodilator medications according to pharmacological classes. It should be noted that all bronchodilator-containing drugs whether single agents or in combination with corticosteroids were included in the outcome variable definition.

The independent variable of interest is CVD status (Dx =1 or No Dx=0). Age was modeled as a continuous variable. All other explanatory variables (confounders/effect modifiers): tobacco smoking, physician specialty, type of healthcare insurance, use of inhaled corticosteroids, cardiac medications (antiarrhythmic and beta-blockers) and asthma were measured as categorical variables.

Some study covariates had to be re-coded by removing unknown or missing responses, collapsing/combining categories and dummy coding. Categorical independent variables were dummy coded as follows: Race/ethnicity was recoded into 4 groups as Non-Hispanic White (0), Non-Hispanic Black (1), Hispanic (2) and Non-

Hispanic Other (3). Tobacco use was recoded into Non-current (0) and Current (1). Use of selected medications including inhaled corticosteroids, antiarrhythmic drugs and beta-blockers were recoded into No (0) and Yes (1) values. Health insurance coverage was collapsed into 4 categories and dummy coded - Medicare (0), Private insurance (1), Medicaid (2) and Other (3). The last group combined other sources of payment like self-pay, worker's compensation, no Charge/Charity. Similarly, physician specialty initially presented as 15 groups was collapsed into 4 groups since some specialties had no or very few COPD patient visit to have meaningful interpretation. General/Family Practice, Internal Medicine, Cardiology and Other were the 4 dummy variables created.

Parametric Assessment

A parametric assessment was done to determine if continuous independent variables satisfied the assumption of linearity in the logit. Age was the only continuous variable and was categorized into 3 groups 40-54, 55-74 and 75 & over for the univariate logistic regression analysis. In the results obtained, the Odds Ratios followed a positive linear relationship with bronchodilator prescription across the different age groups (Appendix - Figure 3) and implies it can be coded as either a continuous or categorical variable. Age was modeled as a continuous variable for the purpose of this study.

Descriptive Statistics and Modeling Strategy

Descriptive statistics, univariate and multivariate techniques were used. All analyses were performed on weighted data as recommended by the NCHS. The patient visit weighting, as provided, uses the most recently available census data to provide a stratified representation of the nation's patient population. All statistical analyses were done using SAS version 9.3 and the results report weighted information.

For descriptive analysis, the means (with standard error) and proportions of demographic, clinical and medication utilization characteristics for the study population were calculated. Rates of drug visits were computed for the sub-categories of bronchodilator medications. Bivariate associations between the dependent variable (prescription of one or more bronchodilators) and each independent variable were separately estimated using univariate logistic regression to obtain unadjusted Odds Ratios and 95% confidence intervals. This will enable inferences to be deduced about the true population parameter lies between the confidence limits with 95% certainty.

Confounding and interaction were assessed given that they may bias the relationship between CVD morbidity and treatment with bronchodilators. Two multivariate logistic regression (LR) models were developed - one containing interaction terms plus confounding variables and the other without interaction (confounders only). First of all, interaction was tested by applying the hierarchy principle to combinations of variables. This implies that if certain interaction terms are significant, all lower order components of such terms cannot be deleted and will remain in any further models considered. Two-way interaction analysis was performed for the following pairs of variables: CVD and gender, CVD and beta-blockers, CVD and asthma. Here, the Odds Ratios of prescribing a bronchodilator for COPD in a

CVD patient is described in terms of the modifying variable, either gender, beta-blockers or asthma. The multivariate logistic regression (LR) model without interaction terms was developed.

Both multivariate models included a number of confounders - Age, gender, race, insurance coverage, asthma, concomitant antiarrhythmic and beta-blocker use, and physician specialty. Therefore, the multiple regression analysis presented adjusted models and allowed us to quantify the true association between concurrent COPD-CVD morbidity and the probability of receiving a bronchodilator prescription, while controlling for the effects of other explanatory variables.

Model fit

The next step in the model building procedure was to verify whether or not the model fitted the data well. Hosmer and Lemeshow goodness-of-fit test and a likelihood ratio test were conducted on the two multivariate logistic models - full model with interaction and reduced model without interaction. A final model was selected based on the adequacy of the fit.

In interpreting the results of the likelihood of prescribing a bronchodilator for COPD visit of a patient with cardiovascular comorbidity, the Adjusted Odds Ratios derived from the selected multivariate logistic regression model were used. The 95% confidence intervals were also calculated for each Odds Ratio.

CHAPTER 4

FINDINGS

Study Sample Characteristics

An estimated 13,799,072 visits of patients above 40 years had a diagnosis of COPD occurred in 2010 in the US. This is approximately 1.4% of 1billion annual office visits. Missing or unknown data were removed leaving 11,627,061 visits in the analytic sample (Table 4).

The majority of the population (57%) was male, between 55 and 74 years (mean age, 69 years). Over 80% were Non-Hispanic White and only 8.3% had the cardiac comorbidities of interest. In terms of the dependent variable, 55.5% of the COPD visits had a bronchodilator prescription. Source of payment for most visits was reported to be Medicare (67.5%) which is consistent with the average age ≥ 65 years eligible for Medicare benefits. 14.4% had a concurrent diagnosis of asthma showing that some patients may be suffering from the asthma-COPD overlap syndrome. A small proportion of visits received a prescription for inhaled corticosteroids. Concomitant use of cardiac medications like anti-arrhythmic agents and beta-blockers occurred in 14.3% and 23.4%. Cardiologists had a lower percentage of the office visits compared to Internal Medicine doctors (22.5%), Family physicians (29.4%) and other specialties (44%).

Univariate Logistic Regression

The univariate logistic regression analysis performed indicated that most of the independent variables were significantly associated with the dependent variable (Table 5). Of the 11,672,061 COPD visits, 55.5% had a bronchodilator (BD) prescribed. CVD visits had lesser odds (OR = 0.35, 95% CI 0.31 - 0.4) than non-CVD visits of receiving a prescription for a bronchodilator. Females had a lower chance of being prescribed a bronchodilator compared to males OR= 0.51 95%CI 0.47 - 0.55). In terms of patient ethnicity, Hispanics and non-Hispanics blacks were about 24% and 78% less likely to have a bronchodilator medication than Non-Hispanic Whites because they had lower OR of 0.76 (95%CI 0.62, 0.92) and 0.22 (95%CI 0.2, 0.26) respectively. There was no significant treatment difference between non-Hispanic whites and non-Hispanics persons that were neither white nor black (OR = 0.94, 95% CI 0.74 -1.19).

The effect of age on the likelihood of bronchodilator use was significant in the univariate regression analysis (OR = 1.01, 95% CI 1.01 - 1.02 p= <0.0001). Odds Ratio of 1.01 implies that the chance of being prescribed the medication increases by 10% with every 10 years of increasing age. Surprisingly, current smokers were half as likely to be prescribed one or more bronchodilators compared to those who did not currently smoke (OR = 0.55 95% CI 0.51 - 0.59). The most likely reason is that those who eventually developed COPD and were taking medications may have quit smoking and be in the ‘not current’ category. Again, the implication of the broad categorization of the tobacco use variable into ‘Current’ and ‘Not current’ smokers is that it excludes smoking behaviors like ex-smokers, never smokers, heavy or light smokers and we

cannot compare treatment differences. There was a strong association between asthma and bronchodilator utilization as revealed by the odds ratio of 4.64, 95% CI 4.07 - 5.3.

The use of inhaled corticosteroids appears to increase the chance that patient is also taking a bronchodilator (OR=2.84, 95% CI 2.23 - 3.63) while beta-blocker utilization decreased the probability of concomitant bronchodilator treatment (OR=0.88, 95% CI 0.80 - 0.95). Antiarrhythmic drugs were not associated with prevalent BD use (OR = 1.02, 95% CI 0.92 - 1.13).

Physician specialty and type of insurance were associated with increased odds of receiving a bronchodilator during a doctor visit (p-value < 0.001). A patient who had private insurance (OR=1.12, 95%CI 1.02 - 1.21) or was seen by a cardiologist (OR= 1.32, 95%CI 1.09 - 1.59) or other specialty (OR=2.13, 95%CI 1.95 - 2.33) was more likely to get a BD prescription compared to those in the reference category who had Medicare coverage or were seen by a family doctor or internal medicine specialist (OR=1.00). Medicaid enrollees did not differ in their treatment with bronchodilators for COPD diagnosis (OR=1.09, 95%CI 0.91 -1.31).

Multivariate Logistic Regression

Two multivariate logistic regression (LR) models were developed - one containing interaction terms, exposure and other independent variables and the other without interaction (exposure plus independent variables only).

In the interaction model, the effects were significant between CVD and each of three possible modifying variables tested - gender, beta blockers (BB) and asthma since

all p-values < 0.05. All three modifiers and their product terms with CVD were retained in the model according to the hierarchy principle.

The reduced model without interaction terms contained the exposure variable (CVD), and potential confounding variables yielded the results in Table 8. A likelihood ratio test was conducted based on the null hypothesis of 'no interaction' versus 'interaction' as alternative hypothesis. The test statistic was 134.4, p-value < 0.0001 produced evidence that the 'interaction' model is a significantly better fitting model. Therefore, the interaction model was selected as the best model and this final choice guided the interpretation of the parameter estimates and odds ratios. Table 7 displays the Odds Ratio for the modifying effect of gender, asthma and β-blockers on the association between CVD and bronchodilator prescribing in COPD.

For effect modification by gender, CVD had a greater effect on bronchodilator prescribing compared to the non-CVD group in females with neither asthma nor beta-blocker medication. OR=0.06, 95%CI 0.04-0.09 implies a 94% reduction in the probability of receiving bronchodilator. In males with no asthma and no beta-blocker utilization, the effect of CVD was 68% since OR=0.32, 95%CI 0.25-0.40. The highest difference in the odds of bronchodilator use between CVD and non-CVD groups was observed in females who had asthma and did not use beta-blockers (OR=0.03, 95%CI 0.02-0.06). Thus, this patient group had the least chance of taking bronchodilators.

CVD was not associated with bronchodilator prescribing in male beta-blocker users, regardless of asthma status (for male, BB users with asthma OR=0.62 95%CI 0.33-1.16; for male BB users without asthma OR=1.11 95%CI 0.82 - 1.51). Therefore, cardiovascular disease did not affect the outcome in this category of patients. On the

contrary, CVD female beta-blocker users without asthma had 79% less probability of receiving a bronchodilator than similar patients without CVD.

The effect of cardiovascular disease was also modified by concomitant asthma to different degrees. CVD asthma patients who were males and not taking BB were only 17% as likely to be prescribed bronchodilators compared to those without CVD, that is, 83% less chance of receiving the drug. The effect of CVD was stronger for female asthma patients taking BBs with 89% lower likelihood, and strongest for female asthma patients who did not use BB (97% lower likelihood).

CHAPTER 5

DISCUSSION

Our study revealed that ***β***-agonists were the most frequently prescribed class of bronchodilators and were prescribed at 56.4% of COPD visits. This fact supports previous studies.[44] We conducted this cross-sectional study to determine whether prescribing rates of bronchodilators in COPD patients were different in cardiovascular comorbidities and if so, to what extent patient characteristics modified the prescribing pattern in ambulatory care in the United States.

We found that most COPD patients, who had been diagnosed with cardiovascular disease, were prescribed bronchodilators less frequently than were those who had COPD without cardiovascular diagnosis, but that this relationship was modified by patient characteristics. This pattern was more evident for females, whereas males had less pronounced differences between CVD and non-CVD groups. Our finding was consistent with literature on treatment differences in bronchodilator utilization for comorbid groups. [45]

There were significant interactions between cardiovascular disease and gender, β-blocker and asthma, shown in Table 7. The presence of cardiovascular diagnosis significantly decreased the likelihood of bronchodilator prescription by 97% for females who were not taking beta-blockers but had asthma (OR=0.03, 95% CI 0.02-0.06). Males with similar characteristics had 83% reduced odds of taking bronchodilators. This was not entirely suspected as a previous cross-sectional study by

Suh *et al* based on 10 years data from the NAMCS and hospital files (NHAMCS) [42] found that women had a consistently higher proportion of visits with COPD medication prescriptions than visits by men.

No significant difference in bronchodilator utilization between CVD and non-CVD groups was observed with the use of beta-blockers in males who were either asthma (OR=0.62 95% CI 0.33-1.16) or non-asthma patients (OR=1.11 95%CI 0.82-1.51). A possible explanation may be that the concurrent use of beta-blockers for cardiac conditions and bronchodilators (which are majorly beta-agonists) in patients with multiple morbidities, leads to opposing pharmacological activity due to interaction between these medications. Other studies have found that the effects of β-agonists may be diminished by β-blockers and vice-versa.[46] In the Cooperative Cardiovascular Project[47], β-blocker use was not associated with lower mortality among patients receiving concurrent beta-agonists. Subjects enrolled in the Veterans Administration's ACQUIP trial who received both beta-blockers and beta-agonists had no increase in risk of acute coronary syndromes.[48] However, we did not observe this nullifying effect among females with comparable characteristics. The effect of CVD on bronchodilator prescribing in females taking beta-blockers with coexisting asthma was about 79% less than those without CVD (OR=0.21 95%CI 0.14 - 0.30). These results point to the fact that the effect of CVD on prescribing differs between males and females who concurrently use beta-blockers and bronchodilators (mainly beta-agonists) and suggest more conservative prescribing practices for females than for males.

Strengths and Limitations

One of the strengths of the current study is the dataset. The NAMCS provides a national perspective on drug utilization in ambulatory medical care. We included patients with COPD diagnosis, race and ethnicity data, sources of payment, all regions and physician categories across the United States. Standard ICD-(-CM coding used for all the diagnoses aided identification of the COPD and cardiovascular conditions of interest. Apart from the ICD-9 codes, the survey included separate physician-defined variables for chronic conditions like COPD, Congestive heart failure, Ischemic heart disease. For example, the questions on the patient record form came in form of "Does the patient now have COPD (Yes/No)". We could compare responses from both approaches to increase the reliability of patients' diagnosis. The Ambulatory Drug database had specific drug codes for each therapeutic class which were employed for easy analysis of medication utilization for bronchodilators, cardiovascular drugs and their therapeutic subcategories. The inclusion of these details helped to evaluate differences in the use of bronchodilators across patient characteristics.

This study has limitations related to the study design and datasource. Because of the cross-sectional nature of the study design, the disease diagnosis and use of medications prescribed were collected at a single point in time, precluding the researcher from establishing the temporal relationship between onset of cardiovascular disease and initiation of bronchodilator treatment.

Bronchodilator prescriptions were assumed to be directly indicated for COPD treatment which may not be accurate. The NAMCS data has a comprehensive list of medications and diagnosis codes documented for each patient encounter but since there

is no clear match between the prescribed medications and ICD-9 diagnosis codes, we could not verify the specific diagnosis for which bronchodilators are being prescribed. Future improvements to the survey design to establish a link between these disease condition and medications prescribed would be helpful to researchers. The dataset did not contain specific information that would indicate that patients may have a contraindication or past drug-related adverse event, thereby preventing the use of one or more bronchodilator medication.

Another limitation is the type of drug formulation. 17.4% of the prescribed products per visit were fixed combinations of different classes of bronchodilators or a bronchodilator in addition to an inhaled corticosteroid. However, we categorized and assessed them like any other bronchodilator in the study because evidence suggests inhaled corticosteroid present less cardiovascular risk unlike oral corticosteroids that may cause sodium and fluid retention leading to elevated blood pressure and adverse cardiovascular effects.[49,50] Combination regimens are substantially utilized in COPD due to the increased effectiveness, reduced burden of medication use and increased adherence that can potentially achieved with this agents. Therefore, all bronchodilator-containing drugs whether single agents or in combination with corticosteroids were included in the definition of the outcome variable.

We considered including disease severity measures as covariates in this study but were unable to because the cross-sectional data did not contain clinical outcomes or follow-up information. Prescribing practices often differ from provider to provider and it may be worth investigating predictors of bronchodilator prescribing among physicians. Future research should attempt documenting the physician characteristics

influencing bronchodilator prescribing for COPD patients. The outcome of this type of analysis can provide inputs for shaping integrated disease management programs for concurrent COPD and CVD conditions.

CHAPTER 6

CONCLUSION

Despite considerable research interest in the potential risk of cardiac events associated with use of bronchodilators in COPD patients, few studies have analyzed the real-world prescribing rates of this highly utilized COPD therapy in cardiovascular disease. This study presents a unique national perspective to understand the effect of CVD on prescribing practices of bronchodilators in the United States.

Concurrent CVD diagnosis is a significant factor for reducing the probability of prescribing bronchodilators for COPD and the odds of prescribing were further decreased due to differences in gender, asthma and beta-blocker use. CVD patients who were female, not taking beta-blockers and not having concomitant asthma were 94% less likely to be taking bronchodilators compared the non-CVD females with same characteristics. On the other hand, males not taking beta-blockers and not having concomitant asthma had 68% lower probability when CVD coexisted with COPD. Female CVD patients taking beta-blockers and not living with asthma had only 20% chance of being a bronchodilator user than those without CVD. It is noteworthy that the general pattern observed in these national data is consistent with treatment guidelines that advise using bronchodilators with caution in the comorbid COPD-CVD patient population, however cardiovascular disease did not affect the utilization of bronchodilators in males taking beta-blockers.

Our findings provide evidence that most patients with COPD and CVD are less likely to be prescribed bronchodilators, with the exception of males who were also prescribed beta-blockers. Thus this study highlights a specific patient subgroup for whom the guidelines are less likely to be observed.

APPENDICES

Appendix A: University of Rhode Island IRB Exemption Letter

THE UNIVERSITY OF RHODE ISLAND
DIVISION OF RESEARCH AND ECONOMIC DEVELOPMENT

THINK BIG WE DO

OFFICE OF RESEARCH INTEGRITY
70 Lower College Road, Suite 2, Kingston, RI 02881 USA
p: 401.874.4328 f: 401.874.4814 uri.edu/research/ori/offices/research/integrity

FWA:	00003132
IRB:	00000599
DATE:	April 6, 2015
TO:	Cynthia Willey, PhD
FROM:	University of Rhode Island IRB
STUDY TITLE:	A cross-sectional analysis of bronchodilator utilization in COPD and cardiovascular comorbidity
IRB REFERENCE #:	736637-1
LOCAL REFERENCE #:	HU1415-137
SUBMISSION TYPE:	New Project
ACTION:	DETERMINATION OF NOT HUMAN SUBJECT RESEARCH
EFFECTIVE DATE:	April 6, 2015

Thank you for your submission of New Project materials for this research study. The University of Rhode Island IRB has determined this project does not meet the definition of human subject research under the purview of federal regulation 45 CFR 46 regarding human subject research at this time. Therefore, your project does not require Institutional Review Board (IRB) oversight. Any changes in focus of this project will require further review of the IRB.

If you have any questions, please contact us by email at researchintegrity@uri.edu. Please include your study title and reference number in all correspondence with this office.

Andrea Rusnock, Ph.D
IRB Chair

Table 1: Selected Information on the 2010 NAMCS Data and Analytic Sample

Survey Item	Data	Result
Unweighted number of office visits recorded by participating physicians	2010 NAMCS	31, 229
Weighted number of representative ambulatory-based medical care office visits in the United States		1,008,802,005
Unweighted number of office visit records for COPD patients 40 years and over, without missing/unknown values	Analytic sample	263
Weighted number of representative COPD office visits for patients 40+years in the United States		11,627,061

Table 2: ICD-9-CM diagnosis codes for COPD and cardiovascular diseases

Description of Diagnosis	Diagnosis code	Study variable
Chronic bronchitis	491.xx	COPD
Emphysema	492.xx	COPD
Chronic airway obstruction	496.xx	COPD
Acute myocardial infarction	410.xx	CVD
Angina pectoris	413.xx	CVD
Coronary artery disease	414.xx	CVD
Cardiac arrhythmias (including tachycardia, atrial fibrillation)	427.xx	CVD
Congestive heart failure	428.xx	CVD

Table 3: List of NAMCS 2010 Pharmacologic classes and codes of bronchodilator medications

Drug therapeutic category Level 2	Drug therapeutic category Level 3	Sub-class	Generic names	Brand names available in 2010
Bronchodilators (code 125)	Beta-2-agonists (code 180)	Short-acting Beta-2-agonists (SABA)	Albuterol, levalbuterol, metaprotenerol	Ventolin, Proair, Proventil, VoSpire, Xopenex,
		Long-acting Beta-2-agonists (LABA)	Arformoterol, formoterol, salmeterol,	Brovana, Foradil, Perforomist, Serevent,
	Anticholinergics (code 299)	Short-acting Anticholinergics	Ipratropium	Atrovent
		Long-acting Anticholinergics	Aclidinium, tiotropium	Tudorza Pressair, Spiriva
	Methylxanthines (code 126)	Methylxanthines	Aminophylline, dyphylline, theophylline	Lufyllin, Jay-Phyl, Theo-24, Elixophyllin, Uniphyl,
	Combination bronchodilators (code 181)	Beta-2-agonists plus anticholinergic	Albuterol/ipratropium,	Combivent,
		Beta-2-agonists plus corticosteroid	Salmeterol/Fluticasone	Advair

Table 4: Demographic and Clinical characteristics of COPD visits (N=11,627,061)

Characteristic		Weighted Estimates ┼	
		No. ('000s)	%
Age	Mean age *	69.2 (0.9)	
	40 – 54	1331	11.4
	55 – 74	6296	54.1
	≥ 75	4000	34.4
Gender	Female	4999	43.0
	Male	6628	57.0
Race/ethnicity	Non-Hispanic White	9545	82.1
	Non-Hispanic Black	1376	11.8
	Hispanic	418	3.6
	Non-Hispanic Other	289	2.5
Region	Northeast	1556	13.4
	Midwest	1928	16.6
	South	6097	52.4
	West	2046	17.6
Tobacco Use	Current	7392	63.6
	Not current	4235	36.4
Cardiovascular disease CVD**	Yes	960	8.3
	No	10667	91.7
Bronchodilator prescription	Yes	6456	55.5
	No	5171	44.5
Type of Bronchodilator prescribed	Beta-2- agonist	3638	56.4
	Anticholinergics	1604	24.8
	Methylxanthines	89	1.4
	Combination bronchodilators	1126	17.4
Concomitant Asthma	Yes	1677	14.4
	No	9950	85.6
Inhaled corticosteroid use	Yes	379	3.3
	No	11248	96.7
Antiarrhythmic drugs	Yes	1658	14.3
	No	9969	85.7
Beta-blockers	Yes	2726	23.4
	No	8901	76.6
Payment Source	Private Insurance	2996	25.8
	Medicare	7848	67.5
	Medicaid	505	4.3
	Other	277	2.4
Physician specialty	General/Family Practice	3424	29.4
	Internal Medicine	2620	22.5
	Cardiology	489	4.2
	Other specialty	5094	44

* Mean age and standard error in years

** CVD includes myocardial infarction (0.05%), angina (0.3%), coronary artery disease (5.15%), cardiac arrhythmias 2.0% (including tachycardia, atrial fibrillation), congestive heart failure (0.7%)

┼ Weighted values represent the sample adjusted to represent national visit characteristics

Table 5: Utilization of bronchodilator by CVD status

Type of bronchodilator (Yes)	% CVD	% No CVD	p-value
Beta-2- agonist	5.1	94.9	< 0.0001
Anticholinergics	6.9	93.1	
Methylxanthines	0	100	
Combination bronchodilators	1.1	98.9	

Table 6: Univariate Logistic Regression Analysis of NAMCS 2010 COPD visits of patients ≥ 40years with bronchodilator prescription by covariates

Characteristic		% of COPD visits receiving Bronchodilator prescription	Unadjusted Odds Ratio (95% CI)	
Cardiovascular disease	Yes	32.3	0.35 (0.31, 0.4)	<0.0001
	No	57.6	1.00 (reference)	
Gender	Female	46.1	0.51 (0.47,0.55)	<0.0001
	Male	62.7	1.00 (reference)	
Age		55.5	1.01 (1.01,1.02)	
Race/ethnicity	Non-Hispanic White	59.9	1.00 (reference)	<0.0001
	Non-Hispanic Black	25.1	0.22 (0.2,0.26)	
	Hispanic	53.1	0.76 (0.62,0.92)	
	Non-Hispanic Other	58.4	0.94 (0.74,1.19)	
Tobacco Use	Current	46.1	0.55 (0.51,0.59)	<0.0001
	Not current	60.9	1.00 (reference)	
Patients with Asthma	Yes	82.8	4.64 (4.07,5.3)	<0.0001
	No	50.9	1.00 (reference)	
Inhaled corticosteroid use	Yes	77.5	2.84 (2.23,3.63)	<0.0001
	No	54.8	1.00 (reference)	
Antiarrhythmic drugs	Yes	55.9	1.02 (0.92,1.13)	0.7159
	No	55.5	1.00 (reference)	
Beta blockers	Yes	53.0	0.88 (0.8,0.95)	0.0023
	No	56.3	1.00 (reference)	
Health Insurance type	Private Insurance	57.6	1.12 (1.02,1.21)	
	Medicare	55.0	1.00 (reference)	0.0005
	Medicaid	57.1	1.09 (0.91,1.31)	
	Other	45.6	0.69 (0.54,0.88)	
Physician specialty	General/Family Practice	48.8	1.00 (reference)	<0.0001
	Internal Medicine	42.1	0.76 (0.69,0.85)	
	Cardiology	55.6	1.32 (1.09,1.59)	
	Other specialty	67.0	2.13 (1.95,2.33)	

Table 7: Modification of the effect of cardiovascular disease comorbidity on bronchodilator prescription in COPD

Exposure (CVD)	Effect modifier (s) *	Adjusted Odds Ratio	95% confidence limits	Effect measure modification **
Yes	Male, no Asthma, no β-blocker	0.32	0.25 - 0.40	68%
No	Male, no Asthma, no β-blocker	1.00	reference	
Yes	Male, Asthma, no β-blocker	0.17	0.10 - 0.31	83%
No	Male, Asthma, no β-blocker	1.00	reference	
Yes	Male, no Asthma, β-blocker	1.11	0.82 - 1.51	None
No	Male, no Asthma, β-blocker	1.00	reference	
Yes	Male, Asthma, β-blocker	0.62	0.33 - 1.16	None
No	Male, Asthma, β-blocker	1.00	reference	
Yes	Female, no Asthma, no β-blocker	0.06	0.04 -0.09	94%
No	Female, no Asthma, no β-blocker	1.00	reference	
Yes	Female, Asthma, no β-blocker	0.03	0.02 - 0.06	97%
No	Female, Asthma, no β-blocker	1.00	reference	
Yes	Female, no Asthma, β-blocker	0.21	0.14 - 0.30	79%
No	Female, no Asthma, β-blocker	1.00	reference	
Yes	Female, Asthma, β-blocker	0.11	0.07 - 0.19	89%
No	Female, Asthma, β-blocker	1.00	reference	

* Effect modifiers are gender, asthma and β-blockers
** Effect measure modification was calculated by the difference between the odds in the CVD group and the non-CVD comparison group, on a percent-scale

Table 8: Multivariate Logistic Regression Analysis of bronchodilator prescription in COPD without effect modification

Characteristic	Factor	Adjusted Odds Ratio (95% CI)
Main effects		
CVD	Yes	0.30 (0.25 - 0.35)
	No	1.00 (reference)
Gender	Female	0.50 (0.46 - 0.55)
	Male	1.00 (reference)
Beta blockers	Yes	0.90 (0.82 - 1.00)
	No	1.00 (reference)
Asthma	Yes	4.85 (4.17 - 5.63)
	No	1.00 (reference)
Race/ethnicity	Non-Hispanic White	1.00 (reference)
	Non-Hispanic Black	0.24 (0.21 - 0.28)
	Hispanic	0.39 (0.32 - 0.49)
	Non-Hispanic Other	1.49 (1.15 - 1.93)
Tobacco Use	Current	0.55 (0.50 - 0.61)
	Not current	1.00 (reference)
Inhaled corticosteroid use	Yes	1.52 (1.15 - 2.00)
	No	1.00 (reference)
Antiarrhythmic drugs	Yes	1.71 (1.50 - 1.94)
	No	1.00 (reference)
Health Insurance type	Private Insurance	1.47 (1.32 - 1.62)
	Medicare	1.00 (reference)
	Medicaid	1.68 (1.34 - 2.10)
	Other	1.15 (0.85 - 1.55)
Physician specialty	General/Family Practice	1.00 (reference)
	Internal Medicine	0.72 (0.64 - 0.81)
	Cardiology	1.94 (1.56 - 2.43)
	Other specialty	2.00 (1.81 - 2.22)

Figure 1: Flow Chart of application of study eligibility criteria

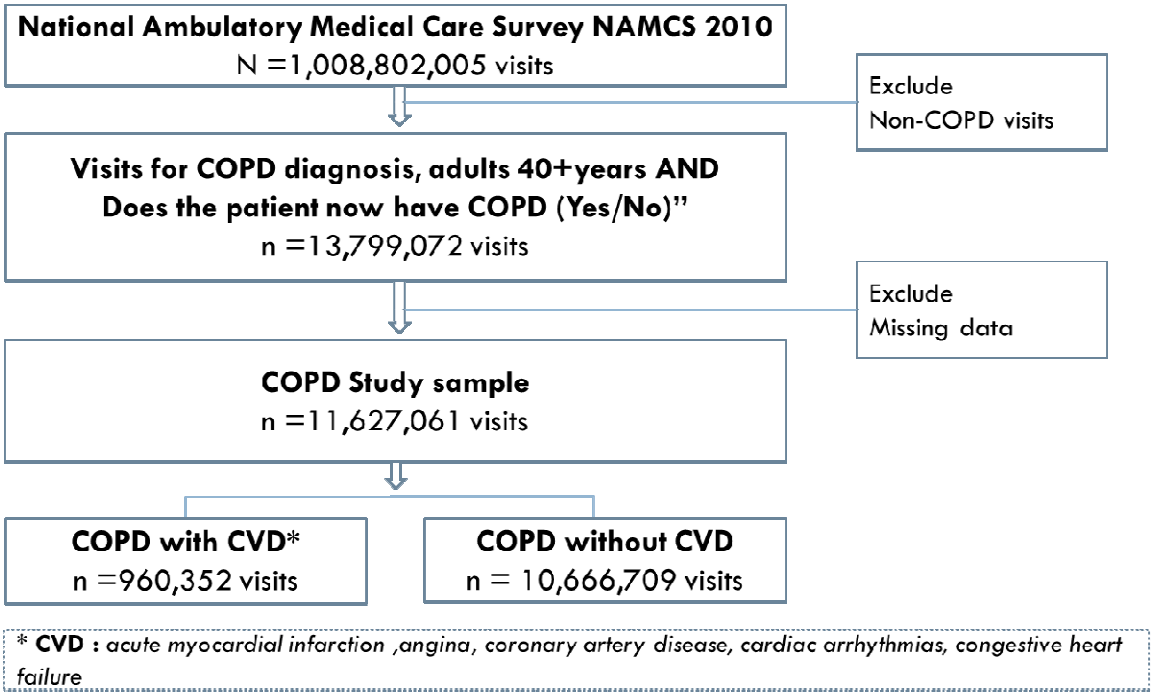


Figure 2: Two-way contingency table for Primary IV and DV

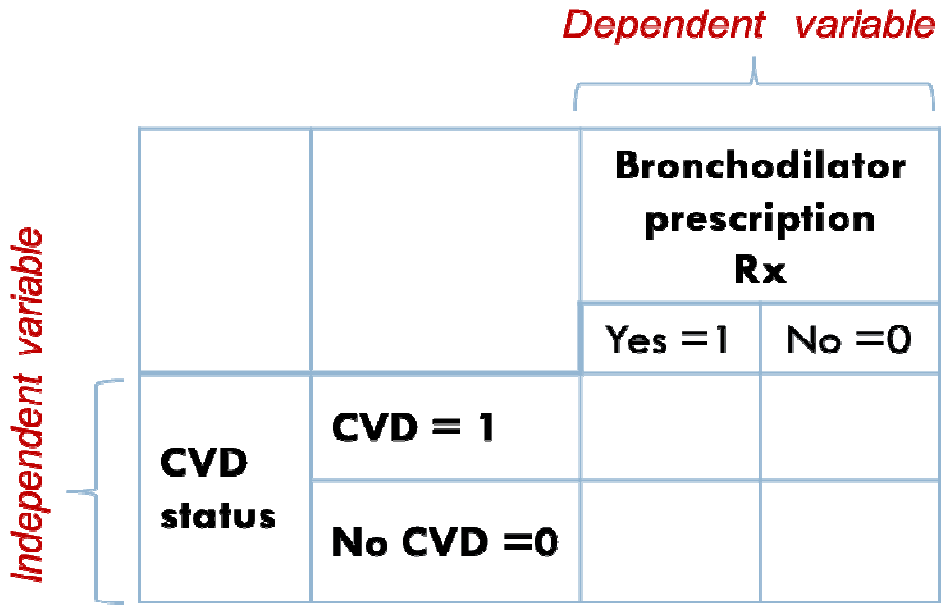
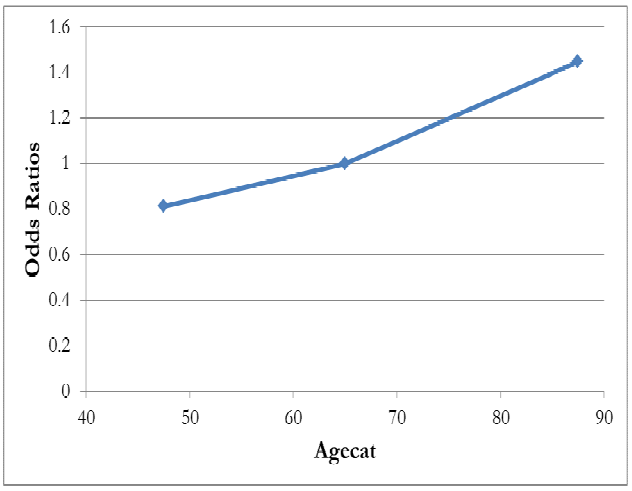


Figure 3: Parametric Assessment of Continuous Variables



Reference class= agecat2

Effect	Age category	Mid-point	% Frequency	Odds Ratio
agecat 1	40 - 54	47.5	11.4	0.709
agecat 2	55 - 74	65	54.1	1.00
agecat 3	75 & over	89.5	34.4	1.378

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