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Original article

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Comparative risks of chronic inhaled corticosteroids and macrolides for bronchiectasis

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Take home message

Macrolides are a better choice than ICS to prevent hospitalized respiratory infections in older bronchiectasis patients, but further evaluation of the safety and long term effects of chronic macrolide use needs to be conducted.

Abstract

Introduction

Non-cystic fibrosis bronchiectasis ("bronchiectasis") is a chronic airway disease for which little data exist to inform treatment decisions. We sought to compare the risks of respiratory infections in chronic users of inhaled corticosteroids (ICS) versus macrolide monotherapy.

Methods

We identified a cohort of U.S. Medicare enrollees with a bronchiectasis diagnosis (494.0/494.1) between 2006-2014, excluding cystic fibrosis. We defined chronic new use as the first 28+ day prescription of ICS or macrolide monotherapy. We compared characteristics of the exposure cohorts using standardized mean differences (SMD) and computed a propensity score (PS) to account for treatment differences. The risks of acute exacerbation, hospitalized respiratory infection, all-cause hospitalization, and mortality were compared using PS decile-adjusted Cox regression models.

Results

We identified 83,589 new users of ICS and 6,500 of macrolides from 285,043 included Medicare enrollees with bronchiectasis. The crude incidence of hospitalized respiratory infection was 12.6 (ICS) and 10.3 (macrolide) per 100 patient-years. The PS-adjusted hazard comparing ICS to macrolide new-users was 1.39 (95% CI 1.23-1.57) for hospitalized respiratory infection, 1.56 (1.49-1.64) for acute exacerbation, and 1.09 (0.95-1.25) for mortality.

Interpretation

Among patients with bronchiectasis, the use of ICS was associated with an increased risk of hospitalized respiratory infections compared to macrolide monotherapy.

Introduction

Non-cystic fibrosis bronchiectasis ("bronchiectasis") is an increasingly common, chronic airway disease.[1,2] The disease is characterized by bronchial inflammation and chronic cough, with frequent exacerbations, i.e. increased symptoms, occurring in the majority of patients.[3,4] Chronic infection with *Pseudomonas aeruginosa*, advanced disease severity, and multimorbidity all increase the risk for hospitalization and death among bronchiectasis patients.[5-7] Additional risk factors for frequent exacerbations include older age, smoking history, comorbidities such as chronic obstructive pulmonary disease (COPD) and heart disease, and bronchiectasis disease severity.[8]

At present, pharmacologic strategies are commonly employed to treat bronchiectasis, yet very little effectiveness or safety data exist to guide patient-centred decision making. One of the primary goals of bronchiectasis treatment is to reduce airway inflammation and prevent exacerbations that lead to hospitalization. In recent years several expert-based guidelines that describe pharmacotherapy options have been published. [9-11] Options that have been reviewed include oral or inhaled corticosteroids (ICS), oral or inhaled antibiotics, and techniques to promote airway hygiene/mucous clearance.

To our knowledge, there are no long-term studies specifically evaluating the risks or potential benefits of oral steroids or ICS in bronchiectasis patients, though the risk of pneumonia is increased in patients with COPD taking ICS.[12] ICS is also associated with an increased risk of nontuberculous mycobacterial (NTM) infection in patients with COPD.[13] Corticosteroids are often prescribed short-term to treat bronchiectasis exacerbations, but are also frequently prescribed chronically in an attempt to limit inflammation and slow bronchiectasis progression.[14] Despite common use of ICS in this patient population, none of the published bronchiectasis treatment guidelines have recommended the use of ICS in bronchiectasis patients due to the lack of evidence, except as indicated to treat concomitant asthma or COPD.[9-11]

In contrast, there is some limited evidence that long-term use of antibiotics benefits patients with bronchiectasis. One mechanism for improving outcomes is the reduction in bacterial load and associated inflammation. In addition, macrolides (erythromycin and azithromycin) are oral antibiotics that also exhibit immunomodulatory effects that may reduce the airway inflammation associated with bronchiectasis patients.[15] They have been tested in three small randomized trials that used exacerbations as a primary endpoint, with macrolide-treated groups experiencing fewer respiratory exacerbations over the 6-12 month study period.[16-18] The most recent bronchiectasis treatment guidelines recommend macrolides in patients with a recent history of multiple exacerbations, with the

European guidelines suggesting macrolides after inhaled antibiotics are contraindicated, not tolerated, or fail to reduce exacerbations in those with a *P. aeruginosa* infection.[10,11]

Accordingly, we compared outcomes of two anti-inflammatory therapies, ICS and macrolide monotherapy, in bronchiectasis patients using a robust new-user observational cohort design.[19] We evaluated the relative risks of hospitalized respiratory infection, all-cause hospitalization, and mortality in older bronchiectasis patients using a large cohort identified from U.S. Centers for Medicare and Medicaid Services (Medicare) enrollees.

Methods

Data source and cohort eligibility

Medicare provides insurance to all adults over age 65 and some people with disabilities in the U.S. We obtained a dataset of all patients with an ICD-9-CM code for bronchiectasis (494.0, 494.1) from Medicare Part A, B and D (but not C) during 2006-2014. Medicare Part A includes all inpatient claims, Part B includes all outpatient claims, and part D includes all prescription drug claims for patients who do not have Part C (Medicare Advantage). The bronchiectasis codes have not been previously validated, but have been used previously in epidemiologic studies in Medicare data.[20,21] Our bronchiectasis cohort was further restricted to those with the bronchiectasis diagnosis code from a pulmonologist, and excluded those who ever had a diagnosis of cystic fibrosis, human immunodeficiency virus (HIV) infection, or history of organ transplant.

Exposure

Our exposures were ICS or macrolide monotherapy. We used a new-user cohort design, with established methodology previously described.[19,22-24] New use was defined as the first prescription for a minimum 28 day ("chronic") supply of either of the exposures of interest, after a clean period of 12 months. The clean period was defined as without a prescription for 28+ days of either exposure of interest. ICS included ICS alone or in combination with long-acting beta agonists, and macrolide monotherapy was defined as oral azithromycin or erythromycin and no other chronic prescription within 30 days that could be associated with NTM therapy (ethambutol, a rifamycin, or a fluoroquinolone). Patients who did not start on macrolide monotherapy were excluded.

Outcomes

The primary outcome of interest was hospitalized respiratory infection, and secondary outcomes included all-cause (with and without respiratory infection) hospitalization, all-cause mortality, and acute exacerbation. We defined hospitalized respiratory infection as an inpatient visit with a principal diagnosis of 480-487.0[25,26] or a bronchiectasis exacerbation (494.1). We defined acute exacerbations as treatment presumed to be for an acute respiratory infection: a 7 to 28-day supply of erythromycin, clarithromycin, levofloxacin, moxifloxacin, ciprofloxacin, minocycline, trimethoprim/sulfamethoxazole, amoxicilin, amoxicilin/clavulanate, or doxycycline or a 3 to 28-day supply of azithromycin that was not associated with wound or stool culture or urinalysis. As a sensitivity analysis we also evaluated acute exacerbations with the above definition and 494.1 diagnostic code in any setting +/- 7 days from the diagnosis.

Statistical analysis

Exposure cohort characteristics were compared using standardized mean differences (SMDs). SMDs >0.10 were considered imbalanced.[27] Follow-up began at the time of drug initiation of either drug exposure group and ended at the first occurrence of the outcome of interest, loss of medical and pharmacy coverage, death, the end of the data or end of drug exposure plus a 30-day extension. Patients who added the comparison drug or switched exposure groups were censored at the time of new prescription. We calculated the crude incidence rate as incident events divided by the total person-years for each exposed group.

For each patient, we calculated a propensity score (PS) in a logistic regression model using the baseline demographic, comorbidity, and utilization history variables listed in Table 1. This model estimated the probability a patient receives therapy with ICS (vs. macrolide therapy). PS scores by exposure cohorts were reviewed for overlapping distributions, dropping patients with non-overlapping PS.[19] The PS score was grouped into deciles based on the PS in the macrolide monotherapy group.[28] Key covariates were plotted by decile to check for balance between exposure cohorts. We used Cox proportional hazard regression models to compare incidence of outcomes between new users of ICS and macrolides, adjusted for PS decile category and oral corticosteroid use category, a pre-specified potential confounder.[29] We conducted sensitivity analyses of the outcomes models using weighted and/or truncated PS and separately after trimming the tails to 2.5% on either end. Additional sensitivity analysis stratified results by sex, COPD, asthma diagnosis, and prior NTM history. We defined *a priori* that a 25%

increase (hazard ratio [HR] of 1.25) is a clinically meaningful increase in the risk of a given outcome (hospitalization, death, etc.). All analyses were done in SAS 9.4 (Cary, NC). The Oregon Health and Science University and University of Alabama at Birmingham institutional review boards approved the study protocol.

Results

We received data from Medicare for 618,303 patients with a bronchiectasis diagnosis. Of these, 285,043 (46.1%) met our eligibility criteria (Figure 1). We further identified and described 83,589 (29.3%) ICS and 6,500 (2.3%) macrolide monotherapy new users (Table 1). Patients in the two exposure cohorts were similar with regards to age (mean 74.4 years ICS vs. 74.8 macrolide, SMD 0.04) but patients taking ICS were less likely female (67.7% vs. 73.1%, SMD 0.12) and White (non-Hispanic) (82.0% vs. 89.5%, SMD 0.23) compared to those taking macrolides. Baseline history of inpatient admissions and hospitalized respiratory infections were similar (SMD 0.08 and 0.07, respectively) but notable differences in baseline healthcare utilization history were observed, e.g. fewer baseline pulmonologist encounters (SMD 0.44) and acute respiratory infections in the ICS cohort (SMD 0.33). The ICS cohort was less likely to have a prior diagnosis of *Pseudomonas* infection (6.1% vs. 12.5% of macrolide cohort, SMD 0.22) and NTM infection (3.8% vs. 20.1%, SMD 0.52), and more likely to have a COPD/emphysema diagnosis (84.4% vs. 77.7%, SMD 0.17).

The crude incidence rates of hospitalized respiratory infection (Table 2) were 12.6 (95% CI 12.3, 13.0) per 100 patient-years (py) for the ICS cohort and 10.3 (95% CI 9.2, 11.5) per 100 py for the macrolide cohort. The rates for other outcomes ranged from 6.2 (mortality) to 104.2 (acute exacerbation) per 100 py for the ICS cohort and 5.8 (mortality) to 72.9 (acute exacerbation) per 100 py for the macrolide cohort.

The PS model included all characteristics in Table 1. The overlap and decile cutpoints are shown in Supplemental Figure 1. The area under the ROC was 0.76. Key PS model covariates were balanced across treatment group within each decile (Supplemental Figures), indicating the PS model adequately controlled for treatment exposure differences. The one exception was prior NTM history (Supplemental Figure 2A), which exhibited imbalance in the lowest PS decile. We subsequently included this as a covariate in the Cox proportional hazards models for all outcomes.

The unadjusted and PS-adjusted HRs comparing the use of ICS to macrolide monotherapy is shown in Figure 2. All HRs were statistically significant, except for mortality. The aHRs were 1.39 (95% CI 1.23-1.57) for hospitalized respiratory infection and 1.56 (95% CI 1.49-1.65) for acute exacerbation. Mortality was not increased, aHR 1.09 (95% CI 0.96-1.25).

The primary diagnosis groups associated with hospitalization and death are listed in Table 3. For hospitalized respiratory infection, the ranking of the top 10 leading causes was very similar, but the proportion related to the top diagnoses varied: the ICS and macrolide cohorts were hospitalized due to pneumonia, organism NOS (60.0% and 45.3%), bronchiectasis exacerbation (13.5% and 26.8%), and pseudomonal pneumonia (9.8% and 12.4%). The leading cause of all-cause hospitalization except respiratory infection was COPD exacerbation (11.8% of ICS cohort and 9.4% of macrolide cohort) with septicaemia occurring as the second most common diagnosis (5.0% and 4.8%, respectively). The leading causes of death during or proximal to hospitalizations for the ICS cohort were septicaemia (8.5%), pneumonia (6.1%), and acute respiratory failure (4.7%) and for the macrolide cohort acute and chronic respiratory failure (7.0%), septicaemia (6.7%), and acute respiratory failure (5.6%).

Sensitivity analysis using weighted and/or truncated PS and trimming the tails by 2.5% produced similar results in both the direction and strength of effect (data not shown). Stratification by sex and COPD produced similar HR for hospitalized respiratory infection in each comparison group (Figure 3). Stratification by asthma suggested that patients with an asthma diagnosis taking ICS may have a lower risk of hospitalized respiratory infection, HR comparing ICS vs. macrolides 1.00 (95% CI 0.80-1.25) and aHR 1.20 (95% CI 0.96-1.49), compared to HR 1.33 (95% CI 1.2-1.5) and aHR 1.47 (95% CI 1.27-1.71) in those with no asthma diagnosis, p-value for interaction <0.001.

Discussion

In a Medicare population-based analysis, we found that chronic ICS use was associated with an increased risk of hospitalization due to respiratory infection compared to macrolide monotherapy in patients with bronchiectasis. Despite a lower rate of prior infections in the ICS cohort compared to the macrolide cohort, e.g. baseline acute respiratory infection and history of *Pseudomonas*, and similar rates of baseline hospitalized respiratory infections compared to the macrolide cohort, after initiating ICSs patients had a higher relative risk of hospitalization and death. The direction and magnitude of risk did not change in the subgroup of patients with an underlying COPD diagnosis.

The study cohort is typical of the older population (>=65 years) in the U.S., which includes around 75% all bronchiectasis patients, in contrast to Europe where 50% of all bronchiectasis patients are age 65 or older.[30,31] The proportion of female patients in each treatment group (67% ICS, 73% macrolides) was higher than reported in U.K. (58%), but similar to the overall population of adults with bronchiectasis in the U.S. (67%).[2,30] Treated patients included in our cohort were on average 1-2 years younger than the overall prevalent bronchiectasis population within Medicare, which is reasonable considering we included patients at "first new use".[32]

There is evidence that ICS therapy reduces exacerbations and slows the decline of quality of life in patients with advanced COPD.[33] To date, however, there is no evidence that long-term use of corticosteroids benefit patients with bronchiectasis, and no large clinical trials have looked at ICS use in bronchiectasis. Several small randomized trials in patients with multiple exacerbations in the prior year have suggested an improvement in symptoms in patients receiving ICS for 6-12 months, but no difference in other outcomes when compared to placebo.[34-36] The systematic review of therapies included in the 2010 British Thoracic Society guidelines and more recent 2017 European Respiratory Society guidelines concluded that there is a lack of evidence to support the chronic use of oral or ICS in bronchiectasis.[9,11] Despite these recommendations, the use of ICS among such patients is common in the U.S., even in patients without an indication for their use (asthma or COPD diagnoses).[14,37-39] Ongoing registry data and our finding that the risk of hospitalized respiratory infections was somewhat decreased in patients with bronchiectasis and an asthma diagnosis may reflect the benefit of appropriate use of ICS to treat asthma.

There are data in other types of chronic lung disease suggesting that oral steroid or ICS use increases the risk of infection, particularly pneumonia,[40] an outcome for which bronchiectasis patients are already at increased risk. In COPD patients, a population-based study identified a RR of 1.69 (95% CI 1.63-1.75) for serious pneumonia in current ICS users.[12] We observed an attenuated but clinically meaningful 39% increase in the relative risk of hospitalized respiratory infection which was based on a comparison to another active treatment (macrolide monotherapy). A recent meta-analysis concluded that budesonide and fluticasone, with or without long-acting bronchodilators, are associated with increased risk of serious adverse pneumonia events in COPD patients but not an increased risk of death.[41] We observed a similar pattern in our population of elderly bronchiectasis patients.

Antibiotics are used with the twin goals of reducing bacterial load in the airways, which in turn reduces airway inflammation, and, in the case of macrolides, exerting an immunomodulatory role independent of bacterial load reduction.[15,42] Two small randomized clinical trials published in 2012 and 2013 evaluated long term (6 months to 1 year) azithromycin and a third evaluated long term erythromycin use in bronchiectasis patients.[16-18] While macrolide-treated groups experienced fewer respiratory exacerbations, defined as increasing symptoms (requiring treatment in two studies), there was limited or no improvement in overall lung function. Treatment guidelines have recommended that macrolides be considered for the subset of patients with a history of repeated exacerbations. For example, the 2017 European Respiratory Society guidelines suggest considering macrolides in patients with 3 or more exacerbations, either in the absence of *P. aeruginosa* infection or in those with *P. aeruginosa* infection in whom inhaled antibiotics are not efficacious or not tolerated.[11] In contrast to ICS, we observed relatively low rates of chronic macrolide use in Medicare patients through 2014, similar to what was observed in the U.S. Bronchiectasis and NTM Research Registry.[39] These rates may reflect the high rates of NTM isolation in the registry, and may have increased after 2014 as time allows for practice change after the publication of the 2012/2013 randomized clinical trials.

Our results suggest that macrolides are associated with lower risks of common outcomes of treated acute infectious exacerbations and serious outcomes of hospitalized respiratory infection compared to ICS. In general, the risks of antibiotic therapy compared to benefits are not clear. Azithromycin use has been linked to sudden cardiac death in population-based studies[43], and it is known to cause QT prolongation with potential for causing other cardiac arrhythmias, particularly when used with other drugs that also cause QT prolongation.[44] Further, a significant risk of long-term azithromycin use could be the selection of macrolide-resistant NTM in patients with NTM isolated in respiratory specimens. Accordingly, macrolide monotherapy is not to be used in the treatment of pulmonary NTM disease (similar to tuberculosis where multiple drugs are used to diminish the evolution of drug resistance).[45] The top 10 causes of hospitalization or death within 30 days of discharge in our study population were similar between the two treatment cohorts, predominately related to respiratory failure and notably not cardiac arrest in either cohort.

Most therapies for bronchiectasis have received little research attention outside of CF populations, meaning the proposed benefits/risks of their use have been extrapolated from these and other settings of chronic lung disease such as COPD. However, the pathophysiology and natural history of

bronchiectasis is distinct from CF-associated bronchiectasis and other lung diseases, and therapies that benefit one do not necessarily benefit the other. For example, DNAse, which improves mucus clearance and outcomes in CF bronchiectasis patients, actually caused worsened lung function in other bronchiectasis patients.[46,47] This underscores the importance of evaluating therapies within diverse populations of patients with bronchiectasis, rather than extrapolating from studies performed in other chronic lung disease conditions or bronchiectasis associated with CF.

Strengths of the study include the fact that it a real-world, large population based evaluation of the comparative risks of inhaled corticosteroid and macrolide monotherapy use in older bronchiectasis patients. Although older bronchiectasis patients tend to have more comorbidities, at least one study has shown that the etiology and severity of bronchiectasis do not differ across age groups, except that the proportion of bronchiectasis due to COPD increased with age.[31] The analysis used established new-user methodology, propensity-score adjustment, an active control group, and limited to the first event of interest to account for channelling bias that otherwise limits our ability to determine causal association in observational studies. Although there were significant differences between the two exposure groups at treatment start, the proportion of COPD or *Pseudomonas* diagnoses was well-balanced within each PS decile.

The main limitations result from the use of claims-based data, which limited our ability to confirm the bronchiectasis diagnosis and include disease symptoms or severity in our models and acute exacerbation definition. Although the propensity score balances the cohorts across known characteristics, there are likely additional (unmeasured) factors that influence treatment decisions. We were able to balance for important risk factors for hospitalization and death of bronchiectasis patients, including acute respiratory infection history and comorbidities, in addition to utilization history. There is the possibility of a small amount of residual confounding, given the slightly elevated risk in non-respiratory infection hospitalizations, although that risk was predominantly driven by COPD exacerbations and other underlying lung disease. Further, the Medicare study population consists of adults over age 65, and results may not be applicable to younger bronchiectasis patients who a different comorbidity profile.[31] There may be additional limitations extrapolating to other healthcare systems.

Our results provide evidence that the widespread use of chronic ICS in older bronchiectasis patients without comorbid indications such as asthma and COPD is not supported. Future studies using registry

or electronic health record data may be able to better group patients by comorbidities that impact therapy choice and include younger patients. Macrolides may be a better choice than ICS to prevent hospitalized respiratory infections and acute respiratory infections in older bronchiectasis patients with frequent exacerbations. Further study of potential long-term risks and benefits of macrolide monotherapy is recommended.

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Author contributions –EH had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. EH drafted the manuscript. All other co-authors contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript.

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Table 1. Characteristics of U.S. Medicare bronchiectasis new users of inhaled corticosteroids or macrolide monotherapy

Variable		Inhaled steroid therapy	Macrolide monotherapy	SMD
Demographics at therapy start		**N=83589**	**N=6500**	
Age (mean (sd))		74.42 (10.18)	74.82 (10.11)	0.04
Year of therapy start	2006	7326 (8.8)	429 (6.6)	**0.19**
	2007	6374 (7.6)	339 (5.2)	
	2008	6753 (8.1)	483 (7.4)	
	2009	7949 (9.5)	523 (8.0)	
	2010	8260 (9.9)	570 (8.8)	
	2011	8976 (10.7)	782 (12.0)	
	2012	10721 (12.8)	978 (15.0)	
	2013	15991 (19.1)	1275 (19.6)	
	2014	11239 (13.4)	1121 (17.2)	
Sex	Female	56583 (67.7)	4750 (73.1)	**0.12**
Race/ethnicity	American Indian or Alaska native	362 (0.4)	17 (0.3)	**0.23**
	Asian/Pacific Islander	3353 (4.0)	160 (2.5)	
	Black or African-American	5338 (6.4)	236 (3.6)	
	Hispanic	5188 (6.2)	203 (3.1)	
	White (non-Hispanic)	68508 (82.0)	5820 (89.5)	
	Other/ unknown	840 (1.0)	64 (1.0)	
Region of residence	Midwest	17129 (20.5)	1612 (24.8)	**0.21**
	Northeast	18629 (22.3)	992 (15.3)	
	South	33289 (39.8)	2897 (44.6)	
	West	14542 (17.4)	999 (15.4)	
Rural or metropolitan residence	Metropolitan	65261 (78.1)	4798 (73.8)	0.10
Median household income, zip code of residence (mean (sd))		59,210 (25,500)	59,490 (25,220)	0.01
Nursing home residence		8408 (10.1)	470 (7.2)	0.1
Comorbidities (any history)				
Allergic bronchopulmonary aspergillosis		854 (1.0)	64 (1.0)	0
Alpha-1 antitrypsin deficiency		292 (0.3)	43 (0.7)	0.04
Asthma		33480 (40.1)	1795 (27.6)	**0.27**
COPD/emphysema		70548 (84.4)	5050 (77.7)	**0.17**
Interstitial lung disease		5526 (6.6)	507 (7.8)	0.05
Lung cancer		3497 (4.2)	196 (3.0)	0.06
NTM History		3164 (3.8)	1307 (20.1)	**0.52**
Primary ciliary dyskinesia		141 (0.2)	23 (0.4)	0.04
Primary immune deficiency		3857 (4.6)	466 (7.2)	**0.11**
Pseudomonas infection		5123 (6.1)	810 (12.5)	**0.22**
Silicosis		103 (0.1)	6 (0.1)	0.01
Charlson comorbidity index (prior 12 months)	0	20514 (24.5)	1534 (23.6)	**0.16**
	1	33959 (40.6)	3119 (48.0)	
	2+	29116 (34.8)	1847 (28.4)	
Medication and healthcare utilization (prior 12 months)				
Office visit (outpatient)		81073 (97.0)	6365 (97.9)	0.06
Physician encounters	0-7	24345 (29.1)	1482 (22.8)	**0.16**
	8-12	20027 (24.0)	1526 (23.5)	
	13-19	20549 (24.6)	1771 (27.2)	
	20+	18668 (22.3)	1721 (26.5)	
Pulmonologist encounters	0	19013 (22.7)	692 (10.6)	**0.44**
	1	15157 (18.1)	941 (14.5)	
	2	15437 (18.5)	1032 (15.9)	
	3	11025 (13.2)	1005 (15.5)	
	4	7232 (8.7)	724 (11.1)	
	5+	15725 (18.8)	2106 (32.4)	
Inpatient admissions	1	17943 (21.5)	1299 (20.0)	0.08
	2+	15851 (19.0)	1093 (16.8)	
Hospitalized respiratory infections	1+	9583 (11.5)	885 (13.6)	0.07
Number of acute respiratory infections	0	40746 (48.7)	2478 (38.1)	**0.33**
	1	20193 (24.2)	1384 (21.3)	

	2-3	15993 (19.1)	1499 (23.1)	
	4+	6657 (8.0)	1139 (17.5)	
Distinct medication classes	1-8	24768 (29.6)	2169 (33.4)	**0.12**
	9-12	18871 (22.6)	1540 (23.7)	
	13-17	19182 (22.9)	1478 (22.7)	
	18+	20768 (24.8)	1313 (20.2)	
Mean prednisone equivalent dose category	No oral corticosteroid	50227 (60.1)	4077 (62.7)	**0.16**
	Low (<2.5 mg/d)	25572 (30.6)	1614 (24.8)	
	Low (<2.5 mg/d)	25572 (30.6)	1614 (24.8)	
	Medium-Low (2.5-5 mg/d)	4226 (5.1)	358 (5.5)	
	Medium-High (5-10 mg/d)	2739 (3.3)	343 (5.3)	
	High (10+ mg/d)	825 (1.0)	108 (1.7)	
Nebulizer		31502 (37.7)	2681 (41.2)	0.07
Home oxygen		26810 (32.1)	1934 (29.8)	0.05

Table 2. Incident rates of acute exacerbation, hospitalized respiratory infection, all-cause (except respiratory infection), and mortality among new users of chronic inhaled corticosteroids and macrolide monotherapy with bronchiectasis.

	Inhaled corticosteroid			Macrolide monotherapy		
Outcome	Events	Patient-years	Incidence rate*	Events	Patient-years	Incidence rate*
Acute exacerbation	24,519	23,528	104.2 (102.9-105.5)	1,773	2,431	72.9 (69.6-76.4)
Hospitalized respiratory infection	4,213	33,328	12.6 (12.3–13.0)	317	3,068	10.3 (9.2–11.5)
All-cause (except respiratory infection) hospitalization	15,611	29,785	52.4 (51.6–53.2)	1,177	2,808	41.9 (39.6–44.4)
All-cause hospitalization	17,939	28,882	62.1 (61.2–63.0)	1,352	2,729	49.5 (46.9–52.3)
Mortality	2,152	34,912	6.2 (5.9–6.4)	186	3,193	5.8 (5.0–6.7)

*Incidence rate per 100 patient-years

Table 3. Ten most common primary diagnoses associated with inpatient hospitalization and hospital-associated deaths.

Hospitalized respiratory infection		All-cause hospitalization (except respiratory infection)		Death at hospital or within 30 days of discharge*	
Inhaled corticosteroids (n= 4,213)	**Macrolide monotherapy (n=317)**	**Inhaled corticosteroids (n= 15,611)**	**Macrolide monotherapy (n=1,177)**	**Inhaled corticosteroids (n= 2,235)**	**Macrolide monotherapy (n=185)**
486. Pneumonia (60.3%)	486. Pneumonia (44.5%)	491.21 COPD exacerbation (11.7%)	491.21 COPD exacerbation (8.8%)	038.9 Septicaemia (8.5%)	518.84 Acute & chronic respiratory failure (7.0%)
494.1 Bronchiectasis exacerbation (13.2%)	494.1 Bronchiectasis exacerbation (27.4%)	038.9 Septicaemia (5.0%)	038.9 Septicaemia (4.4%)	486 Pneumonia (6.1%)	038.9 Septicaemia (6.7%)
482.1 Pseudomonal pneumonia (9.7%)	482.1 Pseudomonal pneumonia (13.2%)	491.22 COPD w acute bronchitis (2.9%)	518.84 Acute & chronic respiratory failure (3.4%)	518.81 Acute respiratory failure (4.7%)	518.81 Acute respiratory failure (5.6%)
482.83 Pneumonia, gram-negative bacteria (3.0%)	482.83 Pneumonia, gram-negative bacteria (2.8%)	518.84 Acute & chronic respiratory failure (2.9%)	491.22 COPD w acute bronchitis (3.1%)	518.84 Acute & chronic respiratory failure (4.5%)	491.21 COPD exacerbation (4.1%)
482.42 MRSA pneumonia (2.5%)	482.9 Bacterial pneumonia (2.2%)	518.81 Acute respiratory failure (2.6%)	427.31 Atrial Fibrillation (2.6%)	491.21 COPD exacerbation (4.5%)	486 Pneumonia (3.7%)
482.41 MSSA pneumonia (1.9%)	482.42 MRSA pneumonia (1.9%)	493.22 Chronic obstructive asthma exacerbation (2.5%)	518.81 Acute respiratory failure (2.5%)	507.0 Food/vomit pneumonitis (3.1%)	507.0 Food/vomit pneumonitis (2.2%)
482.9 Bacterial pneumonia (1.9%)	482.41 MSSA pneumonia (1.6%)	507.0 Food/vomit pneumonitis (2.3%)	507.0 Food/vomit pneumonitis (2.3%)	515 Post-inflammatory pulmonary fibrosis (1.6%)	482.1 Pseudomonal pneumonia (1.9%)
481. Pneumococcal pneumonia (1.6%)	481. Pneumococcal pneumonia (0.9%)	427.31 Atrial Fibrillation (2.1%)	493.22 Chronic obstructive asthma exacerbation (1.8%)	428.0 Congestive heart failure (1.0%)	515 Post-inflammatory pulmonary fibrosis (1.9%)
485. Bronchopneumonia (1.0%)	485. Bronchopneumonia (0.9%)	428.0 Congestive heart failure (1.8%)	584.9 Acute kidney failure (1.4%)	410.71 Subendocardial infarction, initial (0.9%)	820.21 Intertrochanteric fracture (1.1%)
487.0 Influenza with pneumonia (0.8%)	482.0 Klebsiella pneumoniae pneumonia (0.6%)	599.0 Urinary tract infection (1.5%)	414.01 Coronary atherosclerosis (1.4%)	428.33 Acute on chronic diastolic heart failure (0.9%)	428.0 Congestive heart failure (1.1%)

Note: ns refer to the number of outcome events.
COPD=chronic obstructive pulmonary disease [obstructive chronic bronchitis], MRSA=methicillin-resistant *Staphylococcus aureus*, MSSA=methicillin-sensitive *Staphylococcus aureus*, w=with

*ICS: 1,135 (33.7%) & macrolide: 85 (31.5%) no cause of death available

Figure 1. Selection of bronchiectasis cohorts of clean new users of chronic inhaled corticosteroids and macrolide monotherapy

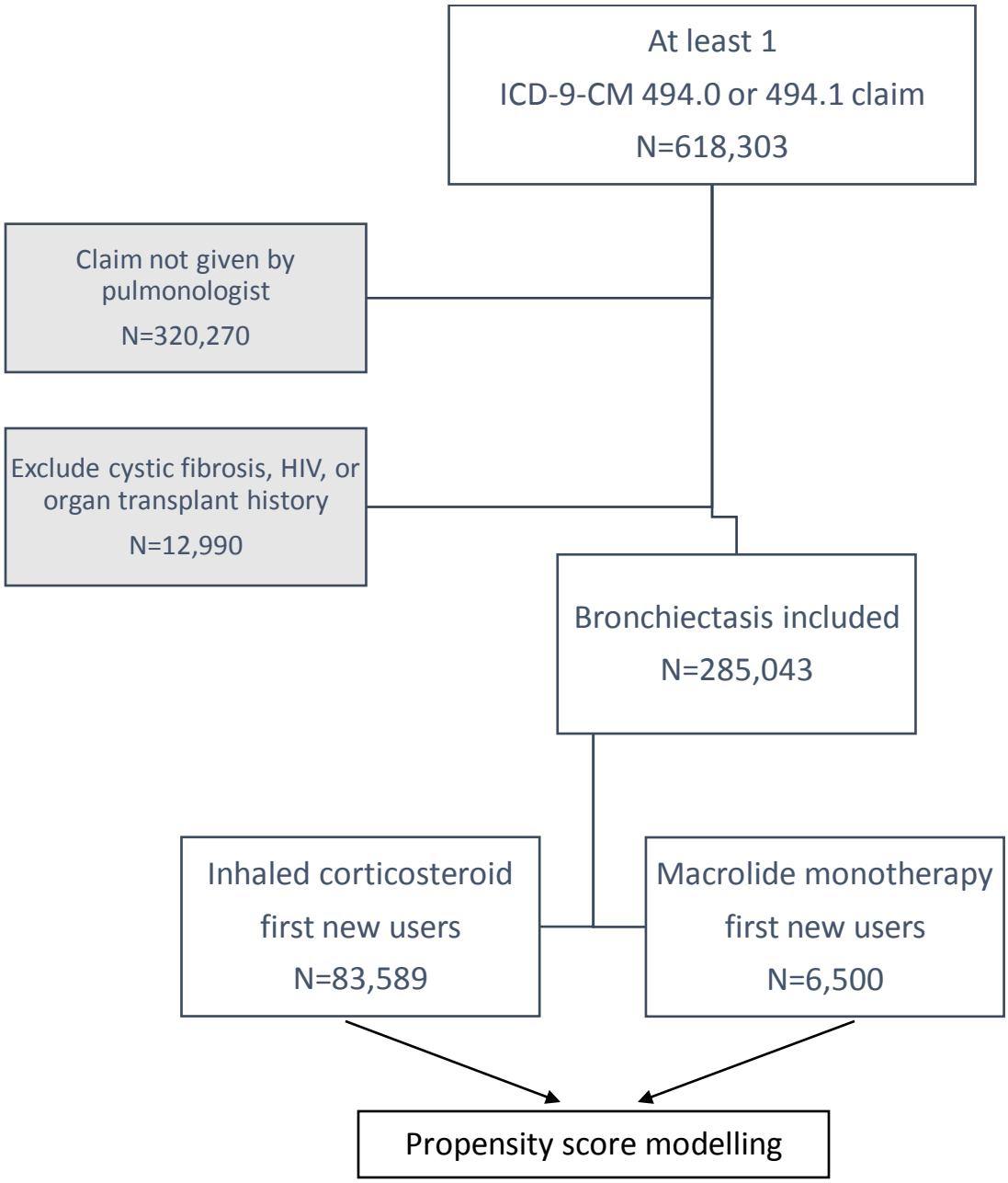
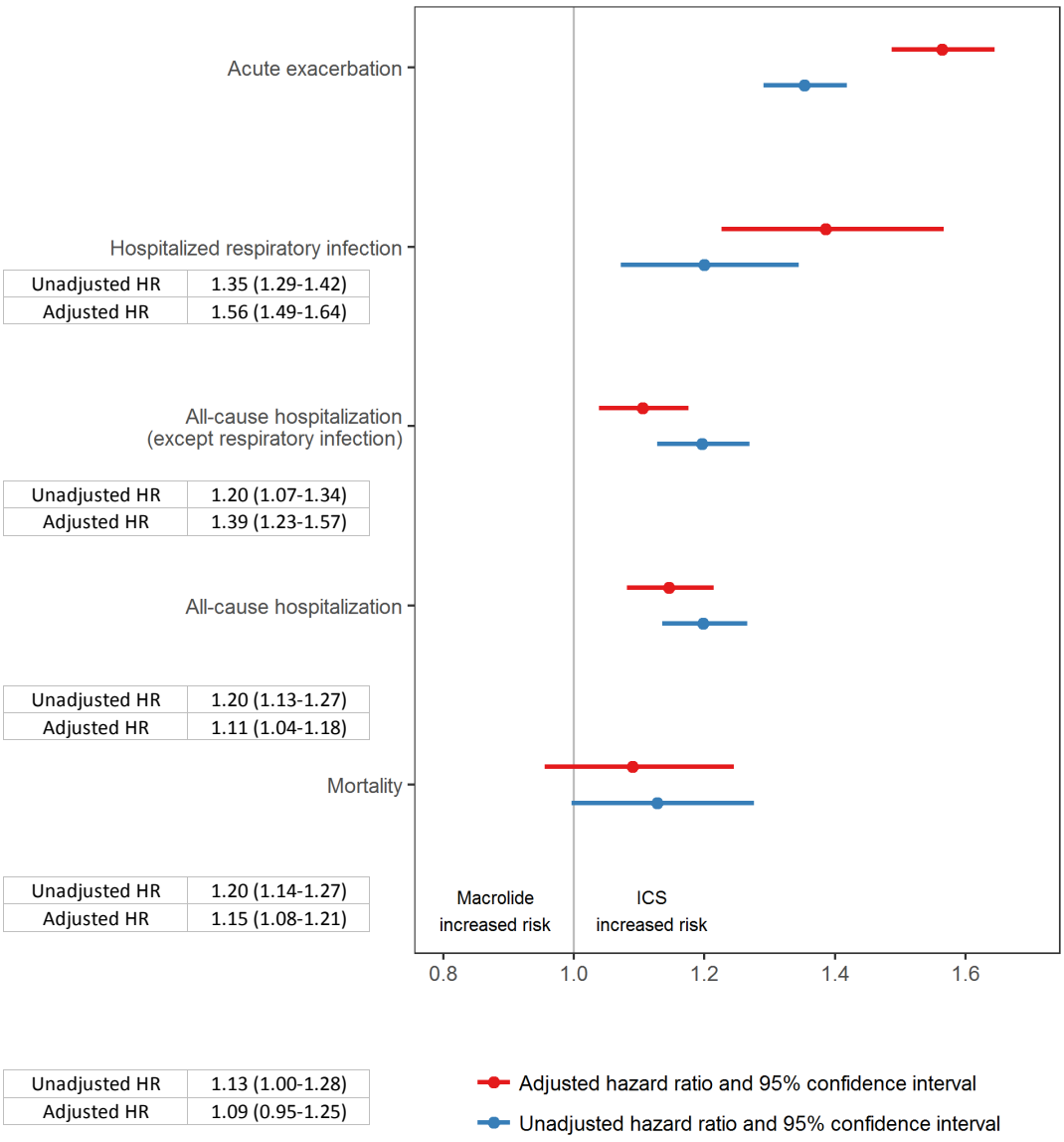
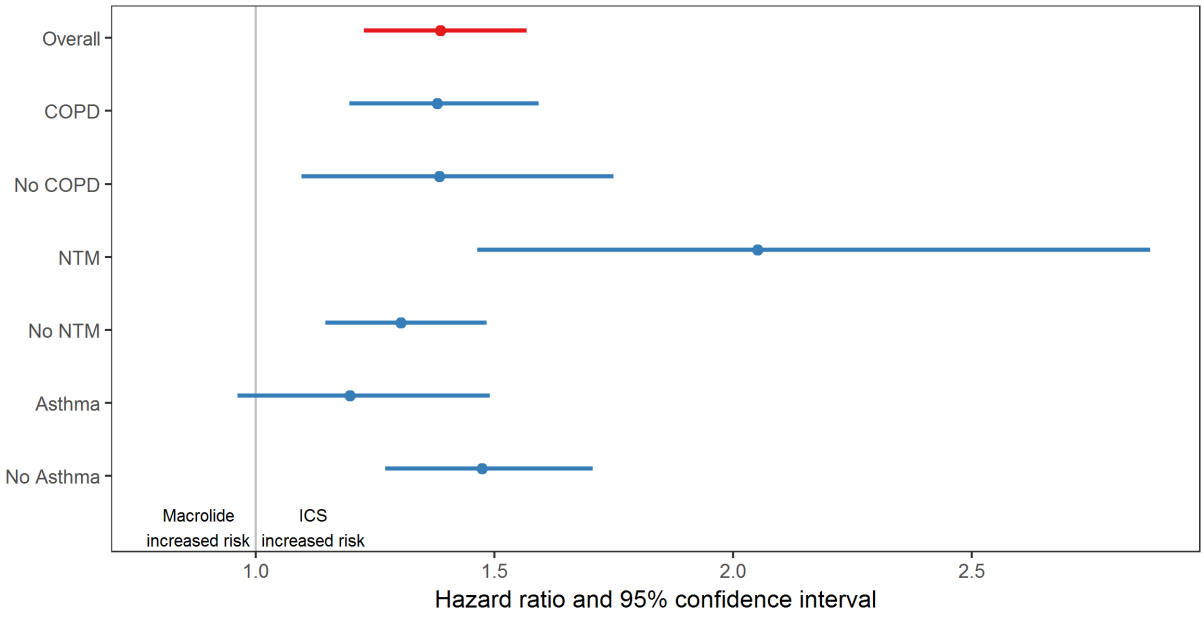


Figure 2. Forest plot of unadjusted and adjusted* hazard ratio and 95% confidence interval of key outcomes comparing new use of inhaled corticosteroids to macrolide monotherapy for bronchiectasis



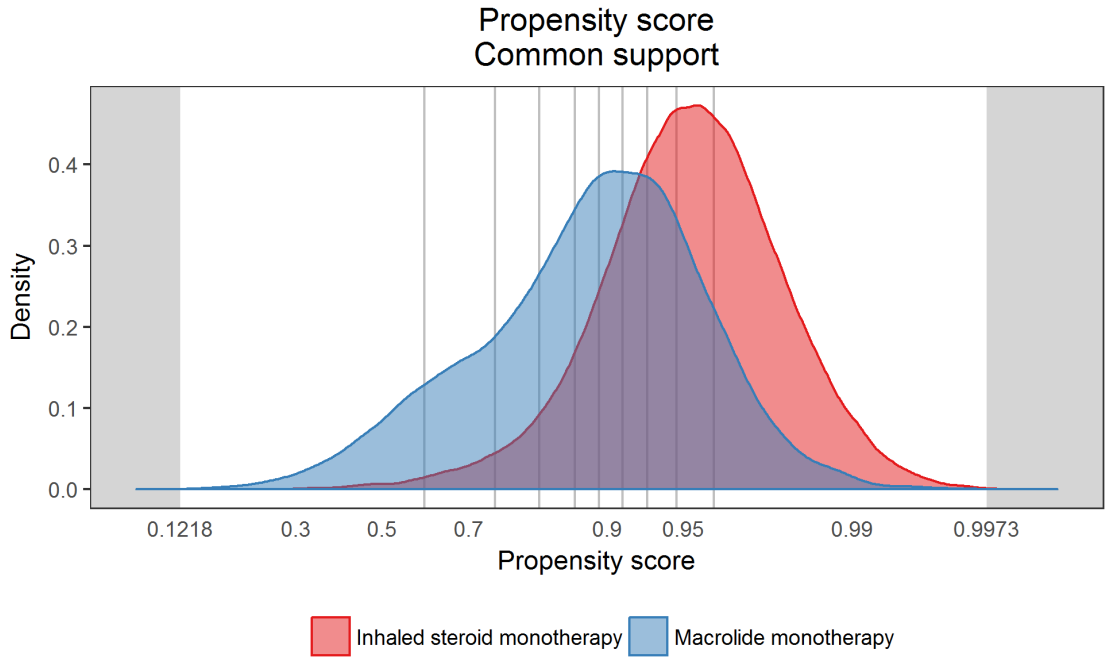
*Adjusted hazard ratio (HR) included propensity score decile, oral corticosteroid dose category, and NTM history.

Figure 3. Forest plot of adjusted* hazard ratio and 95% confidence interval of hospitalized respiratory infection comparing new use of inhaled corticosteroids to macrolide monotherapy for bronchiectasis, overall and stratified by underlying lung disease.



*Adjusted hazard ratio (HR) included propensity score decile, oral corticosteroid dose category, and NTM history.

Supplemental Figure 1. Propensity score (PS) overlap and cutoffs for decile of PS for the macrolide monotherapy group. Deciles were defined based on macrolide monotherapy PS to ensure balanced numbers in each decile.



Supplemental Figures 2A-F. Comparison of balancing of key variables by exposure group (inhaled corticosteroids and macrolide monotherapy) and propensity score decile. Balancing for a given variable is indicated by having a similar proportion in the two exposure groups within a propensity score decile.

Figure 2A. Proportion with NTM history

Figure 2B. Proportion with *Pseudomonas* history

Figure 2C. Proportion with COPD history

Figure 2D. Proportion with asthma history

Figure 2E. Proportion with 4+ acute infections in prior year

Figure 2F. Proportion with 0 acute infections in prior year

Figure 2A

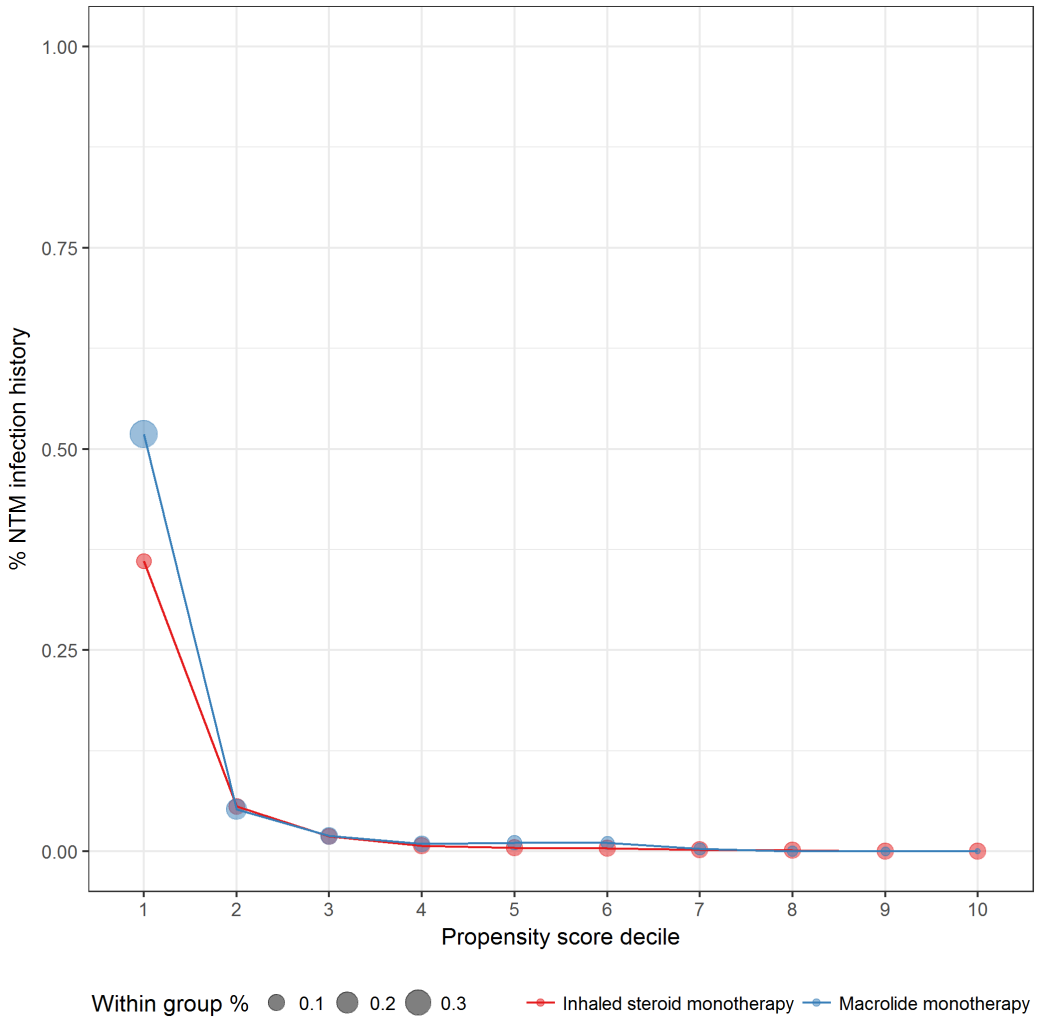

1.00
0.75
0.50
0.25
0.00
% NTM infection history
1
2
3
4
5
6
7
8
9
10
Propensity score decile
Within group %
0.1
0.2
0.3
Inhaled steroid monotherapy
Macrolide monotherapy

Figure 2B

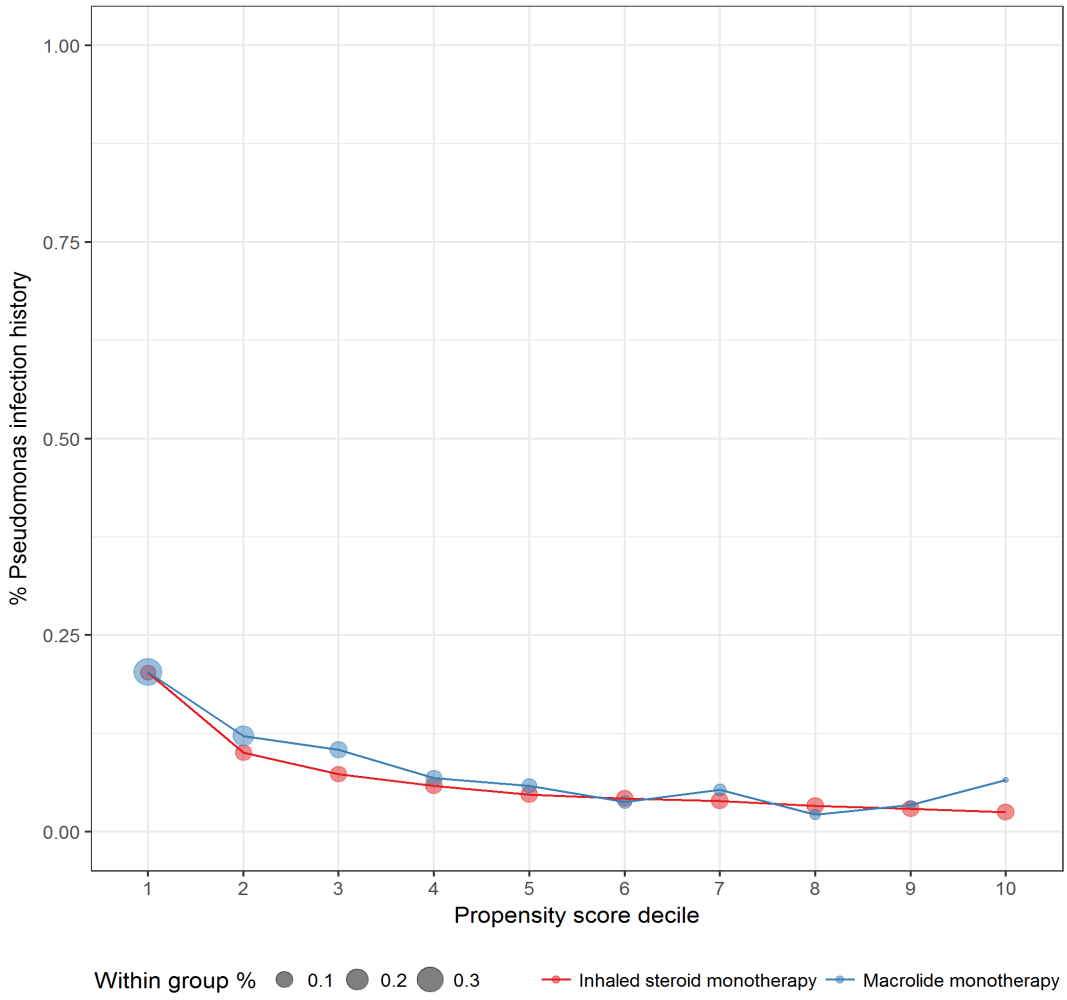

1.00
0.75
0.50
0.25
0.00
% Pseudomonas infection history
1
2
3
4
5
6
7
8
9
10
Propensity score decile
Within group %
0.1
0.2
0.3
Inhaled steroid monotherapy
Macrolide monotherapy

Figure 2C

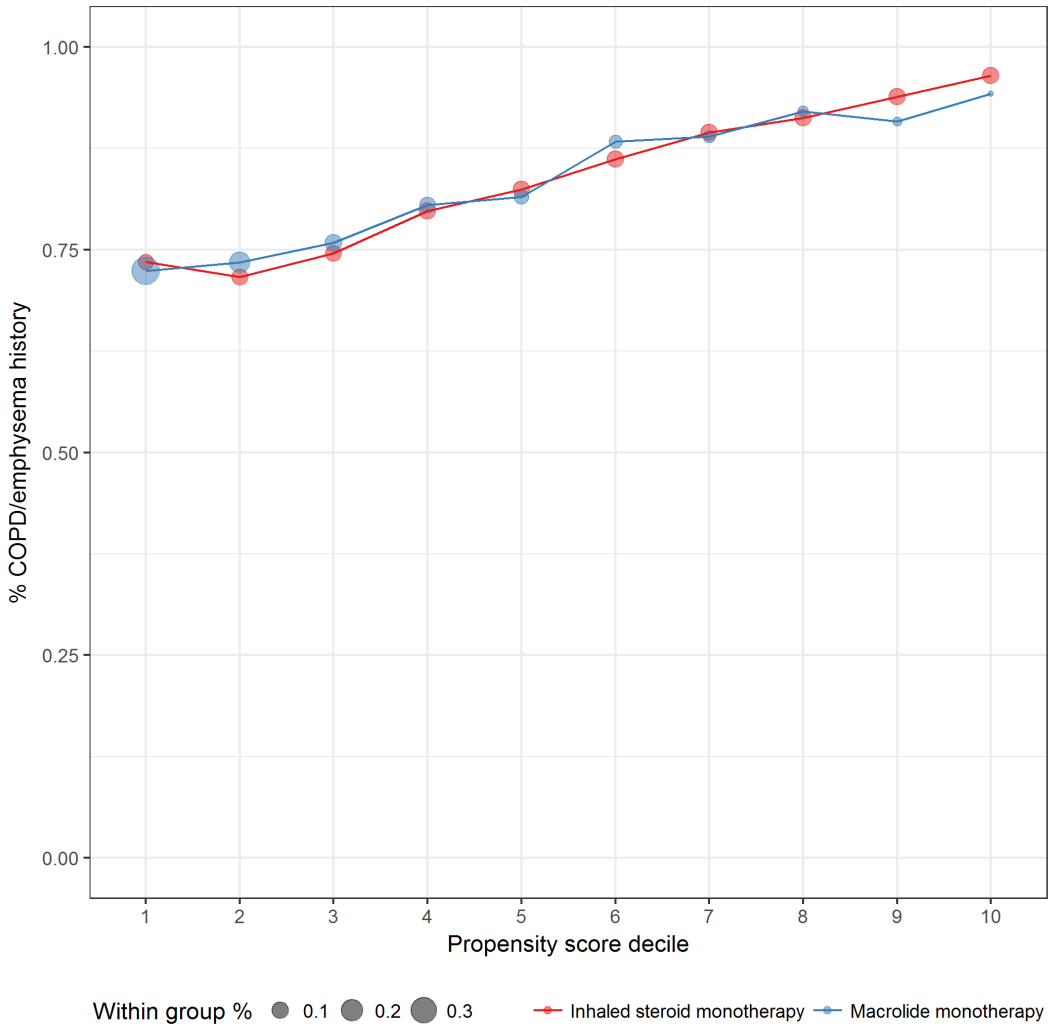

1.00
0.75
0.50
0.25
0.00
% COPD/emphysema history
1
2
3
4
5
6
7
8
9
10
Propensity score decile
Within group %
0.1
0.2
0.3
Inhaled steroid monotherapy
Macrolide monotherapy

Figure 2D

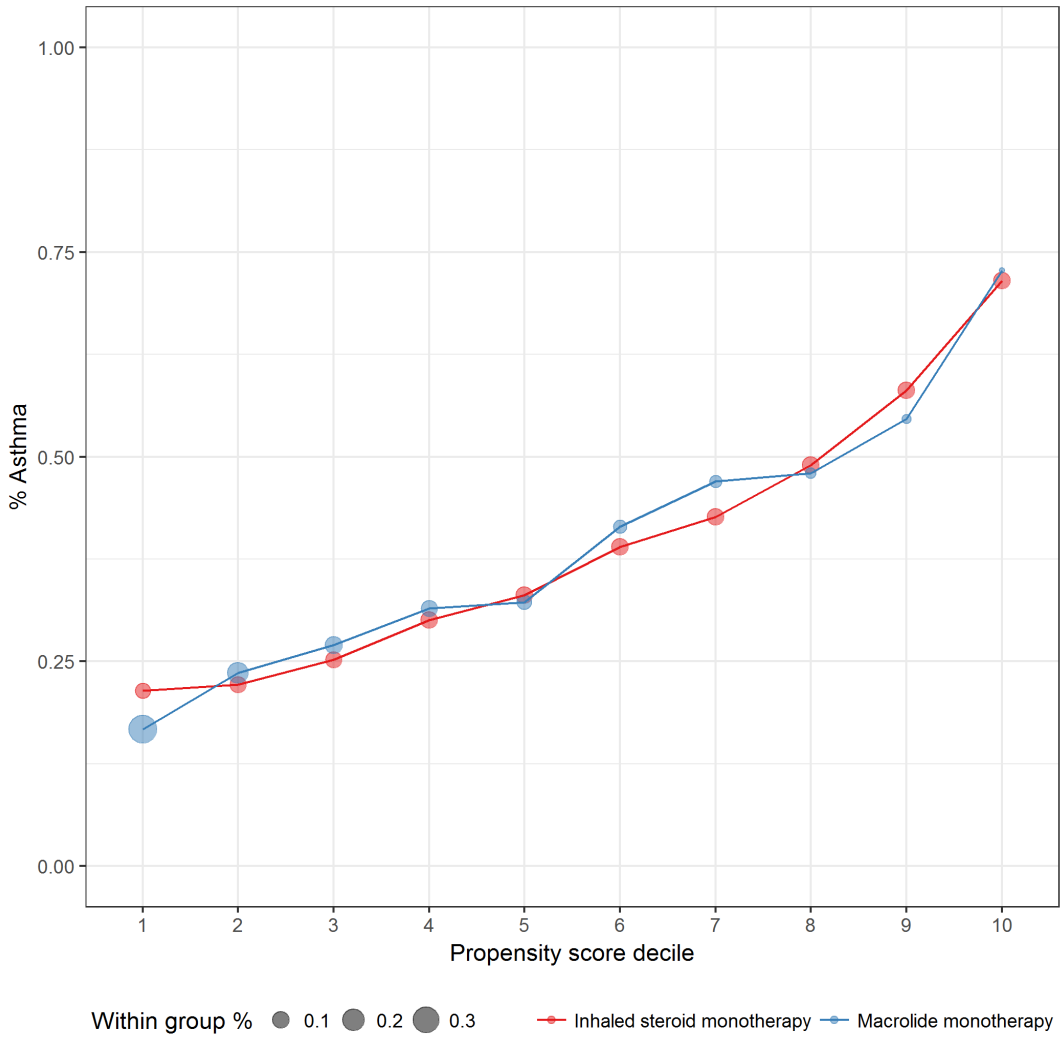

1.00
0.75
0.50
0.25
0.00
% Asthma
1
2
3
4
5
6
7
8
9
10
Propensity score decile
Within group %
0.1
0.2
0.3
Inhaled steroid monotherapy
Macrolide monotherapy

Figure 2E

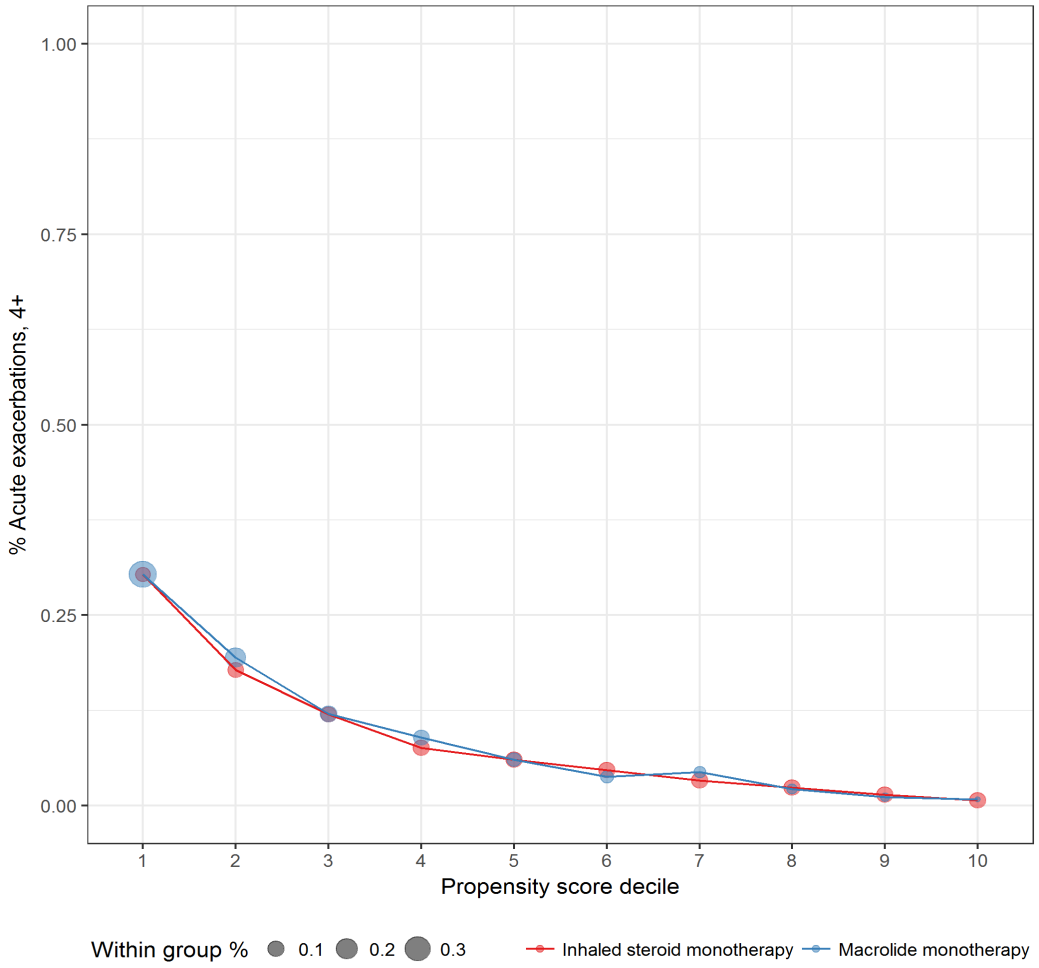
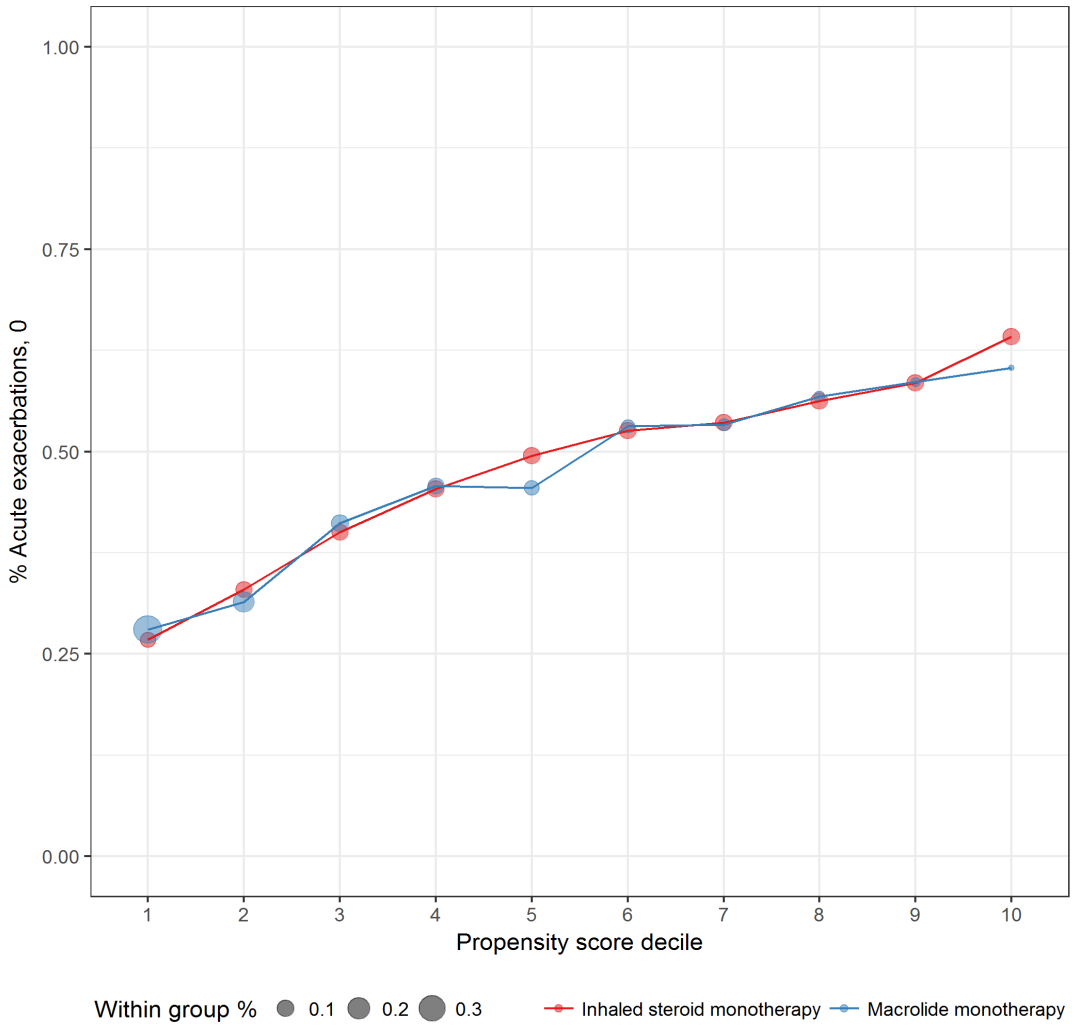

1.00
0.75
0.50
0.25
0.00
% Acute exacerbations, 4+
1
2
3
4
5
6
7
8
9
10
Propensity score decile
Within group %
0.1
0.2
0.3
Inhaled steroid monotherapy
Macrolide monotherapy

Figure 2F


1.00
0.75
0.50
0.25
0.00
% Acute exacerbations, 0
1
2
3
4
5
6
7
8
9
10
Propensity score decile
Within group %
0.1
0.2
0.3
Inhaled steroid monotherapy
Macrolide monotherapy