Supplementary material

Table S1. List of ICD-9 [1] and ICD-10 codes [2] used for the diagnosis of pneumonia.

Diagnostic code	Diagnosis
ICD-9	
481.x–486.x	Pneumococcal pneumonia (Streptococcus pneumoniae pneumonia); other bacterial pneumonia; pneumonia due to other specified organism; pneumonia in infectious diseases classified elsewhere; bronchopneumonia, organism unspecified; pneumonia, organism unspecified
487.0	Influenza
507.x	Pneumonitis due to solids and liquids
507.0	Pneumonitis due to inhalation of food or vomitus
507.1	Pneumonitis due to inhalation of oils and essences
507.8	Pneumonitis due to other solids and liquids
510.0	Empyema with fistula
510.9	Empyema without mention of fistula
511.0	Pleurisy without mention of effusion or current tuberculosis
513.0	Abscess of lung
514.x	Pulmonary congestion and hypostasis
517.1	Rheumatic pneumonia
519.8	Other diseases of respiratory system, not elsewhere classified
530.84	Tracheoesophageal fistula
ICD-10	
J10.0	Influenza due to other identified influenza virus with pneumonia
J11.0	Influenza due to unidentified influenza virus with pneumonia
J12–J18	Viral pneumonia, not elsewhere classified; pneumonia due to Streptococcus pneumoniae; pneumonia due to Hemophilus influenzae; bacterial pneumonia, not elsewhere classified; pneumonia due to other infectious organisms, not elsewhere classified; pneumonia in diseases classified elsewhere; pneumonia, unspecified organism
J22	Unspecified acute lower respiratory infection
J69	Pneumonitis due to solids and liquids
J85.0	Gangrene and necrosis of lung
J85.1	Abscess of lung with pneumonia
J86	Pyothorax

ICD, International Classification of Diseases.

Supplementary methods 1. Sensitivity analysis

- To assess the presence of potential biases from the as-treated analysis, such as reverse causality, a first treatment carry-on analysis (analogous to an intention-to-treat approach used in randomized controlled trials) was used to compare the use of tiotropium/olodaterol with LABA/ICS at cohort entry with respect to the outcome occurrence in the subsequent year, irrespective of the patterns of change in treatment during the 1-year follow-up.
- In addition to the intention-to-treat/first treatment carry-on analysis to compare the use of tiotropium/olodaterol or LABA/ICS at cohort entry, the following sensitivity analyses were conducted:
    - Limited to moderate or severe exacerbation events (rather than aggregated, as for the primary analysis)
    - Excluding events in the first 30 days of follow-up
    - Revising the grace period following a dispensation to 30 days
    - Revising the grace period following a dispensation to 60 days
    - Allowing either free or fixed combination LABA/ICS use
    - Patients with prior monotherapy
    - Patients with no prior monotherapy
    - Extending follow-up to include all available exposed time

Table S2. Sensitivity analysis for treatment with tiotropium/olodaterol versus LABA/ICS and COPD exacerbations

		Adjusted HR		
		HR	**LCL**	**UCL**
COPD exacerbations				
Full population				
	Intention-to-treat/first treatment carry-over	0.89	0.83	0.96
	Limited to moderate exacerbation events	0.69	0.61	0.79
	Limited to severe exacerbation events	0.90	0.77	1.06
	Excluding events in the first 30 days of follow-up	0.91	0.79	1.05
	Revising the grace period following a dispensation to 30 days	0.79	0.71	0.87
	Revising the grace period following a dispensation to 60 days	0.85	0.78	0.92
	Allowing either free or fixed combination LABA/ICS use	0.76	0.68	0.85
	Patients with prior monotherapy	0.73	0.60	0.89
	Patients with no prior monotherapy	0.74	0.65	0.84
	Extending follow-up to include all available exposed time	0.78	0.70	0.86
Subgroup of patients with low exacerbation history				
	Intention-to-treat/first treatment carry-over	0.94	0.86	1.03
	Limited to moderate exacerbation events	0.73	0.62	0.87
	Limited to severe exacerbation events	0.91	0.74	1.13
	Excluding events in the first 30 days of follow-up	0.87	0.72	1.04
	Revising the grace period following a dispensation to 30 days	0.81	0.72	0.92
	Revising the grace period following a dispensation to 60 days	0.86	0.77	0.96
	Allowing either free or fixed combination LABA/ICS use	0.79	0.69	0.90
	Patients with prior monotherapy	0.81	0.63	1.05
	Patients with no prior monotherapy	0.74	0.62	0.87
	Extending follow-up to include all available exposed time	0.80	0.70	0.92
Subgroup of patients with high exacerbation history				
	Intention-to-treat/first treatment carry-over	0.80	0.71	0.91
	Limited to moderate exacerbation events	0.64	0.51	0.79
	Limited to severe exacerbation events	0.84	0.66	1.08
	Excluding events in the first 30 days of follow-up	0.94	0.75	1.17
	Revising the grace period following a dispensation to 30 days	0.73	0.62	0.85
	Revising the grace period following a dispensation to 60 days	0.79	0.68	0.91
	Allowing either free or fixed combination LABA/ICS use	0.71	0.60	0.85
	Patients with prior monotherapy	0.61	0.44	0.83
	Patients with no prior monotherapy	0.76	0.62	0.94
	Extending follow-up to include all available exposed time	0.72	0.61	0.86
Subgroup of patients with baseline eosinophils ≥300 cells/µL				
	Intention-to-treat/first treatment carry-over	1.04	0.72	1.49
	Limited to moderate exacerbation events	0.97	0.52	1.82
	Limited to severe exacerbation events	0.72	0.29	1.80
	Excluding events in the first 30 days of follow-up	0.84	0.40	1.76
	Revising the grace period following a dispensation to 30 days	0.90	0.55	1.49
	Revising the grace period following a dispensation to 60 days	0.83	0.54	1.26
	Allowing either free or fixed combination LABA/ICS use	0.94	0.56	1.58
	Patients with prior monotherapy	0.82	0.48	1.39
	Patients with no prior monotherapy	0.93	0.55	1.57
	Extending follow-up to include all available exposed time	1.04	0.60	1.81

		Adjusted HR		
		HR	**LCL**	**UCL**
Subgroup of patients with baseline eosinophils <300 cells/µL				
	Intention-to-treat/first treatment carry-over	0.71	0.54	0.92
	Limited to moderate exacerbation events	0.57	0.35	0.92
	Limited to severe exacerbation events	0.66	0.35	1.25
	Excluding events in the first 30 days of follow-up	0.78	0.47	1.31
	Revising the grace period following a dispensation to 30 days	0.56	0.39	0.82
	Revising the grace period following a dispensation to 60 days	0.61	0.43	0.86
	Allowing either free or fixed combination LABA/ICS use	0.54	0.36	0.82
	Patients with prior monotherapy	0.55	0.37	0.83
	Patients with no prior monotherapy	0.53	0.35	0.81
	Extending follow-up to include all available exposed time	0.53	0.34	0.84

COPD, chronic obstructive pulmonary disease; HR, hazard ratio; LABA/ICS, long-acting β_2-agonist/inhaled corticosteroid therapy; LCL, lower confidence limit; UCL, upper confidence limit.

Supplementary methods 2. Quantitative bias analysis

- To explore the expected impact of exposure and outcome misclassification, simple bias corrections for sensitivity and specificity were applied based on sensitivity and specificity values drawn from the literature; single values were drawn and applied to both tiotropium/olodaterol and LABA/ICS users.
- To assess differential misclassification, specificity parameters were varied for tiotropium/olodaterol and LABA/ICS users based on observed differences across medications in other data sources.
- Estimates are presented correcting for assumed values of poorly measured confounders (tobacco use and obesity).
- A probabilistic analysis on summary level data was performed.
    - Rather than using single, fixed values, we specified distributions for the expected prevalence of each confounder in each group and the strength of the relation between the confounder and the outcome of interest.
    - Following this, 10,000 copies of the summary data set were created where each was deterministically corrected for a sensitivity and specificity combination drawn from the distributions as defined.
    - The median bias corrected estimate was reported along with a 95% simulation interval.
    - The median estimate was presented after adding in random error that is typically expressed in a traditional 95%CI as total study error.

Table S3. Bias analysis for treatment with tiotropium/olodaterol versus LABA/ICS and COPD exacerbations

		Adjusted HR		
		HR	**LCL**	**UCL**
COPD exacerbation				
Full population		0.76	0.68	0.85
	Correcting for assumed rates of obesity	0.77	0.69	0.85
	Correcting for assumed rates of smoking	0.74	0.67	0.85
	Correcting for assumed rates of alcohol use	0.76	0.68	0.85
	Correcting for outcome misclassification, non-differential	0.50		
	Correcting for outcome misclassification, differential	0.24		
	Correcting for exposure misclassification, non-differential	0.76		
	Correcting for exposure misclassification, differential	0.56		
Full population, low exacerbation history		0.79	0.69	0.90
	Correcting for assumed rates of obesity	0.80	0.70	0.91
	Correcting for assumed rates of smoking	0.78	0.68	0.90
	Correcting for assumed rates of alcohol use	0.79	0.69	0.90
	Correcting for outcome misclassification, non-differential	0.16		
	Correcting for outcome misclassification, differential	0.10		
	Correcting for exposure misclassification, non-differential	0.79		
	Correcting for exposure misclassification, differential	0.64		
Full population, high exacerbation history		0.71	0.60	0.85
	Correcting for assumed rates of obesity	0.71	0.60	0.85
	Correcting for assumed rates of smoking	0.70	0.61	0.82
	Correcting for assumed rates of alcohol use	0.71	0.60	0.85
	Correcting for outcome misclassification, non-differential	0.49		
	Correcting for outcome misclassification, differential	0.25		
	Correcting for exposure misclassification, non-differential	0.71		
	Correcting for exposure misclassification, differential	0.43		
Lab result population, eosinophils ≥300 cells/µL		0.94	0.56	1.58
	Correcting for assumed rates of obesity	0.95	0.58	1.56
	Correcting for assumed rates of smoking	0.93	0.56	1.51
	Correcting for assumed rates of alcohol use	0.94	0.56	1.58
	Correcting for outcome misclassification, non-differential	0.44		
	Correcting for outcome misclassification, differential	0.26		
	Correcting for exposure misclassification, non-differential	0.94		
	Correcting for exposure misclassification, differential	0.82		
Lab result population, eosinophils <300 cells/µL		0.54	0.36	0.82
	Correcting for assumed rates of obesity	0.54	0.36	0.82
	Correcting for assumed rates of smoking	0.53	0.35	0.80
	Correcting for assumed rates of alcohol use	0.54	0.36	0.82
	Correcting for outcome misclassification, non-differential	0.08		
	Correcting for outcome misclassification, differential	0.05		
	Correcting for exposure misclassification, non-differential	0.54		
	Correcting for exposure misclassification, differential	0.37		

COPD, chronic obstructive pulmonary disease; HR, hazard ratio; LABA/ICS, long-acting β_2-agonist/inhaled corticosteroid therapy; LCL, lower confidence limit; UCL, upper confidence limit.

For estimates corrected for assumed rates of obesity and smoking, confidence limits reflect the region where 95% of simulations fall within the probabalistic bias analysis. No confidence limits are present for outcome and exposure misclassification estimates as these were created based on a single parameter rather than a distribution.

References

1. Centers for Disease Control and Prevention. International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). 2015 [cited December 10 2019]; Available from: https://www.cdc.gov/nchs/icd/icd9cm.htm
2. ICD10Data.com. Diseases of the respiratory system J00-J99. 2020 [cited December 24 2020]; Available from: https://www.icd10data.com/ICD10CM/Codes/J00-J99