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REVIEW



Comparative safety and effectiveness of inhaled bronchodilators and corticosteroids for treating asthma–COPD overlap: a systematic review and meta-analysis

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ABSTRACT

Objective: To determine the safety and effectiveness of current pharmacotherapies consisting of long-acting beta₂-agonist (LABA) and/or inhaled corticosteroids (ICS) in patients with asthma–COPD overlap.

Data sources: A systematic search was conducted using the PubMed, EMBASE, and Web of Science databases up to June 2018.

Study selections: Only studies comparing the safety and effectiveness of LABA and/or ICS in patients with asthma–COPD overlap were included. A meta-analysis was performed to calculate risk ratio (RR) and 95% confidence interval (CI) using Inverse Variance Random-effects model.

Results: From a total of 3382 articles retrieved, three randomized controlled trials (RCTs), six cohort studies (CS), one nested case control study fulfilled the inclusion criteria for three independent meta-analyses representing 181,603 participants. Three CS results show LABA was associated with decreased risk of myocardial infarction (combined RR: 0.80, 95% CI 0.74–0.87) versus non-LABA use; ICS/LABA was associated with a lower risk of death or hospitalization (combined RR: 0.82, 95% CI 0.75–0.90) compared to no use. Results from RCTs, no clear difference in lung function decline in FEV₁ was found (combined mean difference: 0.08, 95% CI 0.15–0.32) in patients receiving ICS and/or LABA compared to placebo. However, due to lack of data, exacerbations, fractures and nontuberculous mycobacterial pulmonary disease outcomes were not meta-analyzed.

Conclusions: Among patients with asthma–COPD overlap, LABA is associated with decreased risk of myocardial infarction; and the combination therapy of ICS/LABA appears to reduce the risk of death or hospitalization. More studies of quality data and larger number of patients are needed.

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Introduction

The notion that asthma and COPD share a common etiology has been discussed and debated since 1961 when Orie and Sluiter proposed the “Dutch hypothesis” (1). The controversy continues today as clinicians assess and treat patients with symptoms of both asthma and COPD. This phenotype of obstructive airway diseases is known as asthma–COPD overlap (ACO). ACO was recently described in 2015 by both The Global Initiative for Asthma (GINA) and Global

Initiative for Chronic Obstructive Lung Disease (GOLD) as “persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD”. The GINA guideline also reported that ACO includes different clinical phenotypes with several underlying mechanisms (2,3).

Just as the classification of asthma and COPD as completely separate disease is still debatable (4,5), the primary definition of ACO is not yet clear. Various

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Table 1. Criteria used to describe and diagnose individuals with asthma–COPD overlap in publications.

GesEPOC/SEPAR Consensus Guideline 2012 (6)	COPD per GOLD and either 2 major criteria or 1 major and 2 minor criteria are met Major Criteria: 1. Very positive BDT (increase in FEV ₁ >15% and >400 ml) 2. Eosinophilia in sputum 3. Personal history of asthma	Minor criteria: 1. High total IgE 2. Personal history of atopy 3. Positive BDT (increase in FEV ₁ >12% and >200 ml) on two or more occasions
Louie et al. 2013 (7)	Major criteria: (2 major) 1. Physician diagnosis of asthma and COPD in the same patient 2. Post-bronchodilator FEV ₁ < 80% predicted and COPD per GOLD 3. >40 years old 4. Smoking >10 pack years	Minor criteria: (2 minor and 1 major) 1. ≥15% increase in post-bronchodilator FEV ₁ or 2. ≥12% and ≥200 ml in post-bronchodilator FEV ₁
Menezes et al. 2014 (8)	Post-bronchodilator FEV ₁ /FVC < 0.7 and asthma (wheezing in the last 12 months plus bronchodilator response of FEV ₁ /FVC 200 ml and 12% or medical diagnosis of asthma)	
Kiljander et al. 2015 (7)	Adults with a diagnosis of asthma and smoking (≥10 p-y) with PBD FEV ₁ /FVC ≤ 0.70	
Sin et al. 2016 (9)	Major Criteria: (2 major) COPD plus; 1. Persistent airflow limitation (post-bronchodilator FEV ₁ /FVC < 0.7 or LLN in patients ≥40 years of age) 2. 2 Methacholine challenge test positivity 3. FENO ≥ 45–50 ppb and/or sputum eosinophils >3% 4. History of asthma	Minor Criteria: (2 minor and 1 major) COPD plus: 1. Documented history of atopy or allergic rhinitis 2. Bronchodilator reversibility of FEV ₁ ≥200 ml and 12% from baseline on ≥2 visits 3. Peripheral blood eosinophil count of ≥300 cells/ml
Van Boven et al. 2016 (10)	Primary care diagnosis of both asthma and COPD	
GesEPOC/GEMA Consensus Clinical Practice Guideline 20174 (11)	≥35 years of age, smoker (ex-smoker) ≥10 p-y; FEV ₁ /FVC < 0.7 post PBD < 70% that persists after treatment with ICS/LABA; and Current diagnosis of asthma(GEMA criteria)	If a diagnosis of asthma cannot be established, PBD ≥ 15% and 400 ml, and/or Eosinophilia in blood ≥300 c/μl
Koblizek et al. 2017 (12)	Patients with COPD and asthma diagnosed before the age of 40 years; or with a positive bronchodilator response plus atopy	
GINA/GOLD Consensus Statement2018 (13)	Characterize by persistent airflow limitation with several features associated with asthma and several features associated with COPD	Asthma–COPD overlap is therefore identified in clinical practice by the features it shares with both asthma and COPD

Abbreviations: BDT, bronchodilator treatment; COPD, chronic obstructive pulmonary disease; FENO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; GEMA, Spanish Guideline on the Management of Asthma; GesEPOC, Spanish COPD guideline; GINA, global initiative for asthma; GOLD global initiative for chronic obstructive lung disease; IgE, Immunoglobulin E; SEPAR, Spanish Society of Pulmonology and Thoracic Surgery.

criteria which have been used over the years to describe and diagnose individuals with ACO in publications are detailed in Table 1. The updated 2018 GINA clinical guideline for ACO recommendations for initial treatment for clinical efficacy and safety proposes the use of corticosteroid at a low or moderate dose depending on level of symptoms; and add-on treatment with long-acting beta₂-agonist (LABA) and/or long-acting muscarinic antagonist (LAMA) if necessary, or continue these together with inhaled corticosteroid (ICS) if already prescribed (13). This consensus based treatment for patients with ACO is intended to provide interim advice to clinicians in managing the disease.

The safety and effectiveness of pharmacotherapy treatment for this overlap population is poorly recognized and given less attention in part because clinical trials have consistently ignored this condition, as evidenced by strict inclusion and exclusion criteria that

either exclude asthma patients from COPD studies or COPD patients from asthma studies plus uncertainty around disease definition precludes RCT evidence generation (14,15). Despite these shortcomings, the effect and impact of bronchodilators on the cardio-respiratory outcomes has been documented for patients with COPD (16–18). However, the incidence and severity of cardiorespiratory events associated with the use of inhaled bronchodilators have not been documented in the context of ACO. This is of particular concern because this population with features of both asthma and COPD experience frequent exacerbations, has poor quality of life, a more rapid decline in lung function and high mortality, and consumes a disproportionate amount of medications than asthma or COPD alone (19). The clinical practice guideline on ACO also reported that patients with ACO experience worst quality of life than patients with asthma or COPD alone, yet there is limited

evidence concerning the effectiveness and safety of inhaled bronchodilators and corticosteroids for patients with ACO (13).

This study aims to address the literature gap surrounding the safety and effectiveness of ICS, LABA, and LAMA medications in ACO patients. We performed a systematic review of the literature to provide a general overview of what the comparative effectiveness and safety of inhaled medications (corticosteroids and bronchodilators) is in combination or alone in patients with ACO. Furthermore, when possible, we meta-analyzed included studies to quantify the association between inhaled corticosteroid and long-acting bronchodilator medications and the risk of cardiorespiratory outcomes and other important clinical outcomes in patients with ACO.

Methods

Study design and protocol registration

This systematic review and meta-analysis was conducted following a pre-specified protocol and guidelines of the preferred reporting items for systematic reviews and meta-analysis (PRISMA) and meta-analysis of observational studies in epidemiology (20,21). The predefined protocol is registered in PROSPERO (CRD42018090863).

Eligibility criteria

In order to identify the totality of evidence for both the effectiveness and safety of inhaled corticosteroids and long-acting bronchodilators within the context of ACO, we included both RCTs and non-randomized designs. The latter may be particularly useful for quantifying the association between drug therapies and uncommon safety events as well as studying patient populations not represented in clinical trials (22). Therefore, we included the following type of study designs to evaluate the effectiveness or safety of inhaled corticosteroids and bronchodilators medications in the context of cardio-respiratory outcomes: RCTs, cohort studies or nested case control studies. We excluded study designs such as meta-analyses, systematic reviews, classic case-control studies, case series, case reports or cross-sectional. Studies that did not report at least one of the following were also excluded; (a) total number patients and number of patients with an event in treatment and control groups of interest and (b) measure of association (risk ratio, odds ratio or mean difference) along with either confidence intervals (CIs) or *p* values. Furthermore,

we meta-analyzed included studies to quantify the association between inhaled corticosteroid and long-acting bronchodilator medications and the risk of cardiorespiratory outcomes and other important clinical outcomes in patients with ACO.

Outcomes of interest

The primary outcome of interest was the incidence of cardiorespiratory disease, defined as outcomes relating to both heart and lungs (cardiopulmonary diseases affect either hearts or lungs or both). This included myocardial infarction, change in pulmonary function values or pulmonary function testing (FEV₁), exacerbation and nontuberculous mycobacterial pulmonary disease (NTM-PD). Secondary outcomes considered were fracture rates, death or ACO hospitalization.

Data sources and searches

A comprehensive literature search was conducted in EMBASE, MEDLINE, and Web of Science databases. Microsoft Excel (Microsoft Office Professional Plus 2013, Version 15.0.5007.1000) and EndNote (Version X7, Thomson Reuters) software were used to manage the study articles, references, and study data.

Records were screened and selected based on a search strategy that combined free-text, medical subject headings (MeSH), Emtree, and title/abstract (tiab or ab,ti) to identify all records examining the association between inhaled LABA or LAMA or ICS monotherapies or combination therapies of ICS/LABA, and ACO primarily based on our eligibility criteria. Emtree, title/abstract (ab,ti) and free-text terms were used to search EMBASE. This was done and led by an experienced librarian, AF, from the Health Science Library (HSL) of Memorial University together with MS, SMA and JEA. The MeSH, title/abstract and free-text terms were used to search MEDLINE. The initial search was performed on all available studies on March 6, 2018 and was subsequently updated weekly until June 1, 2018.

We also reviewed reference lists of all primary studies for additional references. We contacted authors of those identified articles with missing figures and values. Among three authors contacted, two responded and one author did not; however, this did not lead to exclusion of any of our articles identified. The search was restricted to English language. In order to identify the ACO description, we created a search strategy likely to contain studies on the combination of terms based on criteria expounded in

Table 1 used to describe and diagnose individuals with ACO in publications. The detailed search strategy is reported in [Supplementary material](#) Appendix 1.

Data items and data abstraction process

A data extraction form was developed and piloted on three of the included studies. An experienced respiratory specialist, JF, independently reviewed all selected studies to ascertain that each included study clearly described patients with ACO. Data extraction was performed by two independent reviewers, JEA and LA. This was to ensure accuracy in data encoding. Discrepancies in determining whether the study met our inclusion criteria during the full text review were resolved by consensus between reviewers. If consensus could not be reached, discrepancies were resolved through a third reviewer, JG. The following information was abstracted independently by JEA and LA from each included study: (1) Study characteristics (study design, sample size, source population, country, type of database used to ascertain information about exposure and outcome); (2) Patient characteristics (mean age and sex); (3) Exposure and control/comparator definitions (duration of use, dose, current/new versus never, use of time-dependent or time-window approach or time-dependent approach); (4) Incidence of cardiorespiratory outcomes; (5) Hazard ratios, risk ratios, rate ratios, odds ratio, mean difference with corresponding 95% CIs; and (6) Methods of adjustment for confounders (matching, newer design, risk-set sampling, regression-based adjustments, propensity scores, disease risk scores) and list of potential confounders.

Risk of bias assessment

The quality of each study was independently assessed by two authors (JG and LA) based on the cochrane risk-of-bias assessment tool for randomized controlled trials (23,24). In the case of any disagreement, a third author (JEA) also assessed the study. Studies score were rated as having a high, low or unclear level of bias across seven domains. The risk of bias for the observational studies was appraised through the Newcastle-Ottawa Quality Assessment Scale (NOS) (25) according to the procedures recommended in the Cochrane Handbook of Systematic Reviews. JEA and JG assessed the methodological quality of all the selected studies. Three parameters were evaluated: (1) population selection, (2) comparability of results, and (3) ascertainment of exposure (nested case-control) or

outcome (cohort studies). Studies score one star for each area addressed, with scores between 0 and 9 (the highest level of quality). We categorize study quality according to the study score into poor (score 0–3), moderate (score 4–6) and high quality (score 7–9). The procedure in the NOS was used in conjunction with key pharmacoepidemiological (PE) study biases including but not limited to time-related biases, confounding, residual confounding, channeling bias, depletion of susceptible, lack of statistical power and switchers bias. We believe that PE studies may differ with regard to database characteristics (e.g. claims or electronic health records, EHRs database), inclusion criteria, exposure, follow-up period, definition of outcome, and the confounders adjusted for in multivariate models as done elsewhere (26). This additional in-depth bias analysis was independently assessed by JEA and JG.

Statistical analysis

Review Manager (RevMan version 5.3.5, Cochrane Collaboration, Oxford, UK) was used to perform data analysis at the quantitative synthesis stage. We employed the inverse variance method to quantify the association between inhaled medications of interest (ICS and/or LABA) and the risk of cardiorespiratory outcomes. A quantitative statistical analysis for dichotomous variables was carried out using the risk ratio (RR) as the summary statistic. Mean difference (MD) was used as the summary statistic for quantitative analysis of continuous variables. Both the RR and MD values were reported as 95% CI. The level of heterogeneity between studies was evaluated by I^2 statistics. $I^2 < 30\%$ was considered to be low heterogeneity and $I^2 > 50\%$ represented high heterogeneity. A random effects model was applied for all comparisons. Statistical significance across the studies was defined as $p < 0.05$. Weights from each study were provided by the Inverse Variance method available in RevMan. There was an inadequate number of included studies (< 10) in each of the individual meta-analysis conducted for either outcome to adequately assess publication bias through a funnel plot.

Subgroup analysis

In the quantitative analysis of inhaled combination therapy with ICS/LABA versus an active comparator and risk for death or hospitalization of ACO, heterogeneity was explored through subgroup analysis

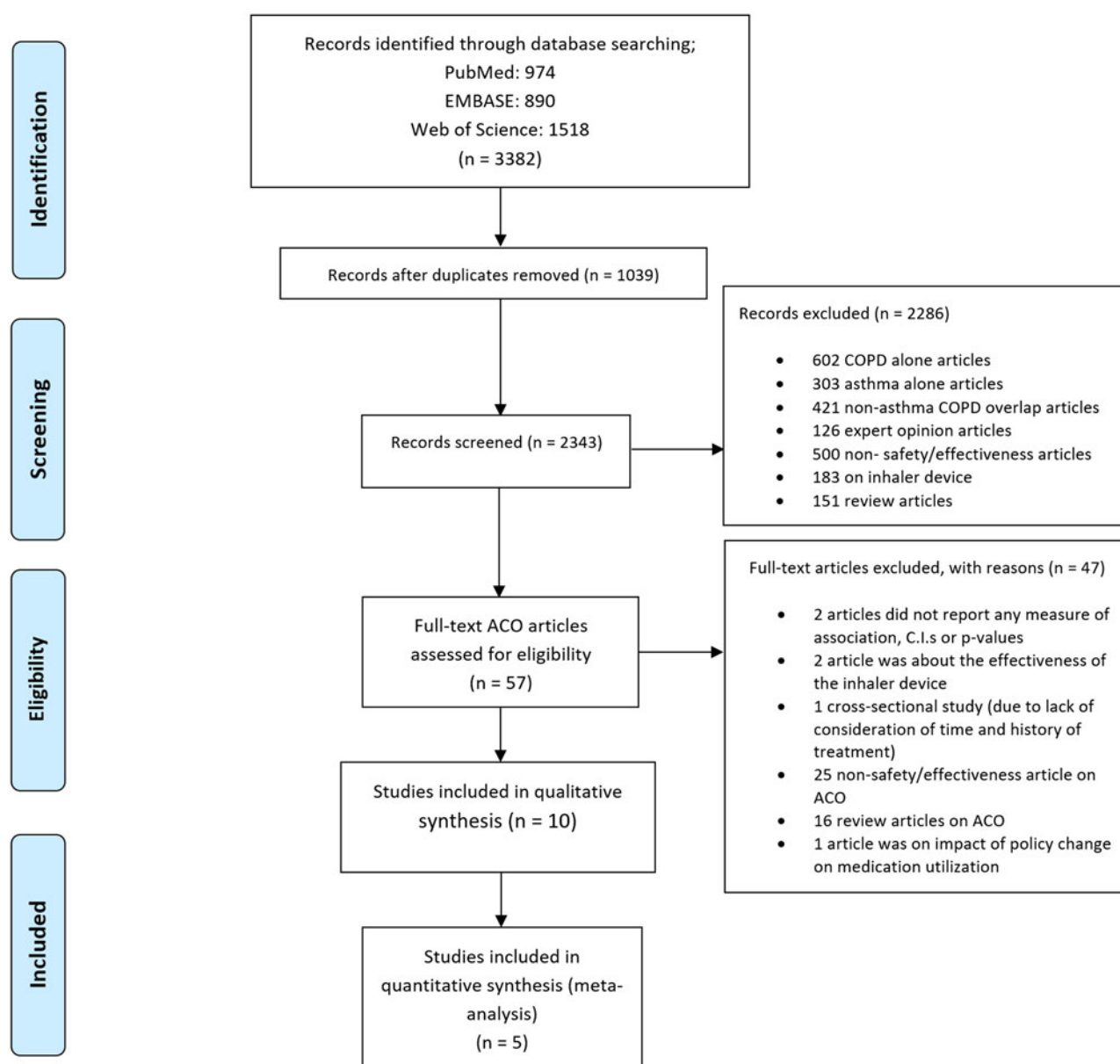


Figure 1. A PRISMA flow diagram details the flow of information through the different phases of the review; maps out the number of records identified, included, excluded and the reasons for their exclusion.

whereby results were stratified by use of LAMA or LABA monotherapy.

Results

Literature search and study selection

A detailed flow diagram of the review selection process is shown in Figure 1. During the search process, English language, human and full-text articles filters were applied to both PubMed and EMBASE database searches, whereas English language and full-text articles filters were applied to Web of Science reference search. A total number of 3382 references were identified via EMBASE, Medline and Web of Science

out of which 2343 original articles and abstracts were independently identified and evaluated by two reviewers JEA and LA after removing 1039 duplicates. After title and abstract review, 2286 studies were excluded due to specific reasons as outlined in Figure 1. Of 57 studies meeting our initial criteria, 10 publications were retained for data extraction. However, five were not included in the meta-analysis (one RCT, one nested case-control and three cohort studies) because there were less than two studies with either a common exposure or an outcome. This was done to ensure that we were analyzing the same class of medication based on their therapeutic activity and duration of action.

Table 2. Characteristics of included studies.

Author and publication year	Study design	Sample size (n)	Age (years)	ACO description and/or diagnosis method	Exposure/ intervention	Comparator/control	Follow-up period	Outcome assessed
Afonso et al. 2016 (27)	Cohort	51,308 4940	65.7 53.8	Patients with both features of "asthma AND COPD" as described by GINA/ GOLD guideline (based on Read codes and ICD-9-CM documented diagnosis of both asthma and COPD).	LABA monotherapy	SABA and/or LABA and/or SAMA monotherapies	90 days	AMI
Brode et al. 2017 (28)	Nested Case Control	Cases: 2966 Controls: 11851	76.6	Patients who meet criteria for ACO as defined by the clinical guideline and documented in the database.	ICS monotherapy	SABA, LABA, SAMA, or LABA monotherapies	≤30 days	NTM-PD
Fingleton et al. 2015 (29)	RCT	389	53.4	Physician diagnosis of patients with features of atopic asthma, with marked variability in airflow obstruction, emphysema, and chronic bronchitis in current smokers or ex-smokers	ICS monotherapy	SABA or SAMA monotherapies	12 weeks	FEV ₁
Gershon et al. 2014 (30)	Cohort	11,967	76.8	COPD patients with a codiagnosis of asthma (based on documented diagnosis of asthma and COPD); which the authors described as patients with asthma-COPD overlap syndrome	ICS/LABA combination	LABA monotherapy or LABA monotherapy	2.7 years	Composite outcome of death and hospitalization
Hubbard et al. 2006 (31)	Cohort	407	81.0	Patients with diagnosis of airflow obstruction of both asthma and COPD described as asthma-COPD overlap syndrome based on documented Read codes in the database.	ICS monotherapy	SABA or LABA monotherapies	4.7 years	Fracture
Ishiura et al. 2015 (32)	RCT	16		Subjects with episodic respiratory symptoms, increased airflow variability (asthma; i.e., AHR or BDR) as well as incompletely reversible airway obstruction (COPD; FEV ₁ / FVC < 70% and post-bronchodilator FEV ₁ < 80% of predicted). AHR was defined if a ≥20% FEV ₁ fall from baseline occurred after inhalation of methacholine. BDR was also defined as an increase in post-bronchodilator FEV ₁ ≥200 ml and 12% compared with pre-bronchodilator FEV ₁ .	ICS/LABA combination therapy	Placebo	12 weeks	FEV ₁
Lim et al. 2014 (33)	Cohort	125	65.2	ACO was defined based on physician diagnosis of a post-bronchodilator FEV ₁ /FVC < 0.70 and a positive BDR (increase in FEV ₁ by at least 200 ml and 12% after inhalation of 200 mg of salbutamol) or AHR (a provocation concentration that caused a decrease in FEV ₁ of 20% no higher than 16 mg/ml) decrease	ICS monotherapy or in combination with LABA (defined as ICS/ LABA combination)	SABA, LABA or SAMA monotherapies	5.7 years	Severe exacerbations

Magnussen et al. 2008 (34)	RCT	472	60.2	in FEV ₁ of 20% no higher than 16 mg/ml. A smoking history of at least 10 pack-years and had undergone at least 2 spirometry assessments with bronchodilator reversibility testing at an interval of at least one 0.25 year.	LAMA monotherapy	Placebo	12 weeks	FEV ₁
Su et al. 2018 (35)	Cohort	251,398	64.5	Physician diagnosis of asthma (before the age 30), a diagnosis of COPD, post-bronchodilator FEV ₁ < 80% predicted normal and a postbronchodilator ratio of FEV ₁ /FVC (forced vital capacity) < 70%. Other inclusion criteria were: smoking history > 10 pack-years, age ≥ 40 years, treatment with ICS for ≥ 1 year prior to study entry, and an acute bronchodilator response ≥ 200 ml and ≥ 12% of prebronchodilator FEV ₁ .	ICS/LABA combination; LAMA monotherapy	LABA monotherapy or ICS monotherapy; LABA monotherapy or ICS monotherapy	1 year	Acute exacerbations
Uddin et al. 2016 (36)	Cohort	64,607	66.0	Patients with both features of "asthma AND COPD" as described by GINA/ GOLD guideline (based on Read codes and ICD-9-CM documented diagnosis of both asthma and COPD).	LABA monotherapy	SABA, SAMA, or LAMA monotherapies	5.61 years	MI

Abbreviations: ACO, asthma-COPD overlap; AHR, airway hyperresponsiveness; AMI, acute myocardial infarction; BDR, bronchodilator response; COPD, chronic obstructive pulmonary disease; CPRD, clinical practice research datalink; FEV₁, forced expiratory volume in 1 s; GINA, global initiative for asthma; GOLD, global initiative for chronic obstructive lung disease; ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; MI, myocardial infarction; NTM-PD, nontuberculosis mycobacterial-pulmonary disease; RCT, randomized control trial; SABA, short-acting beta-agonist; SAMA, short-acting muscarinic antagonist.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Fingleton et al 2015	+	+	+	+	+	+	+
Ishiyama et al 2015	+	+	+	+	+	+	+
Magnussen et al 2008	+	+	+	+	+	+	+

Figure 2. Risk of bias summary for RCT studies.

Study characteristics

A detailed overview of the characteristics of all selected studies is reported in Table 2. Of the 10 included studies, three were RCTs, six were cohort studies and one was a nested case-control study. Study interventions included combination therapy of LABA/ICS, ICS alone, and LABA or LAMA alone. These interventions were either compared with a placebo (32, 34) or active comparators of ICS (35), SABA or LAMA or short-acting muscarinic antagonist (SAMA) (28,30,31). The average follow-up time ranges between 30 days and 5.7 years for the observational studies whilst all the included RCTs have the same follow-up time of approximately 12 weeks. All the observational studies either used administrative ($n = 4$) or electronic health record ($n = 3$) databases.

These studies were carried out in Japan, South Korea, New Zealand, United Kingdom, Canada, Netherlands, United States and a multi-center trial conducted in Belgium, Canada, Germany, Denmark, France and Italy.

Risk of bias

A summary of study quality of the RCT studies is presented in Figure 2. In brief, all three RCTs were at low risk of selection bias (random sequence

generation), attrition bias and reporting bias; two studies were at low risk of selection bias (allocation concealment) (29,32) and detection bias (29,34); two studies were at high risk of performance bias (32, 34), one study was at high risk of selection bias and another study was at high risk of detection bias (32,34). Expanding more on the risk of bias in each RCT study; in one of these studies reviewed, allocation concealment (selection bias) was not described in the article (34). In another RCT of 168 steroid naïve participants, subjects were selected based on their self-report of symptomatology (29). Thus, the method they used to identify subjects to be included in their dataset had a low specificity. They aimed to minimize this effect by using validated questionnaires. In another RCT study which was an open-label trial, the authors provided detailed information on the process of randomization by the opaque-sealed envelope method (32). However, performance bias (study participants were not blinded to the intervention) was detected in this study (32) and also in another study (34). All studies reported random sequence generation; two studies reported allocation concealment and also blinding of outcome (29,34).

The Newcastle-Ottawa Quality Assessment Scale, NOS, was used for the quality assessment of the observational studies. In Table 3, the quality score for each study is reported. However, no studies were excluded based on the quality score grading. A summary of the in-depth key PE study quality is presented in Supplementary material Table S1. All the observational studies were evaluated by using an active comparator against an active treatment or exposure group. One study was susceptible to channeling bias, and depletion of susceptibles (31). Three studies may have had time-related bias (i.e., immortal time bias) (28,31,33). Nevertheless, these three time-related biased studies were not in any of meta-analysis based on our study exclusion and inclusion criteria. In addition, residual confounding may have occurred in all observational studies.

Quantitative analysis

Eight results from five different studies that included a total of 181,603 patients with data for at least one common exposure and same outcome were included in the meta-analysis. Two studies with three different results used LABA as the primary exposure of interest and were compared to a non-LABA active ingredient of SABA, LAMA or SAMA (27,36). Two other studies used ICS and/or LABA as the intervention drug which

Table 3. Quality Assessment of cohort and nested case-control studies using Newcastle-Ottawa Quality Assessment Scale (NOS).

Nested case control studies									
Study	Selection			Comparability		Exposure			Quality level
	Is the case definition adequate?	Representativeness of the cases	Selection of Controls	Definition of Control	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non response rate	
Brode et al. (2017)(28)	*	*	*	*	*	*	*	*	High quality
Cohort studies									
Study	Selection			Comparability		Outcome			Quality level
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	
Su et al. 2018 (35)	*	*	*	*	**	*	*	*	High quality
Afonso et al. 2016 (27)	*	*	*	*	**	*	*	*	High quality
Gershon et al. 2014 (30)	*	*	*	*	**	*	*	*	High quality
Hubbard et al. 2006(31)	*		*	*		*	*	*	Moderate
Lim et al. 2014 (33)	*		*	*		*	*	*	Moderate
Uddin et al. 2016 (36)	*	*	*	*	**	*	*	*	High quality

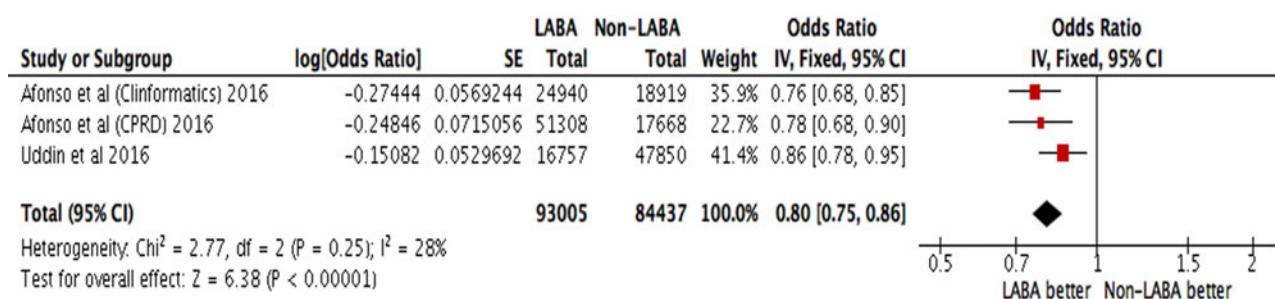


Figure 3. Risk for Myocardial Infarction (MI); Forest plot describing the association between long-acting beta2 agonist (LABA) monotherapy vs a non-LABA (SABA and/or LAMA and/or SAMA monotherapies) and risk for MI.

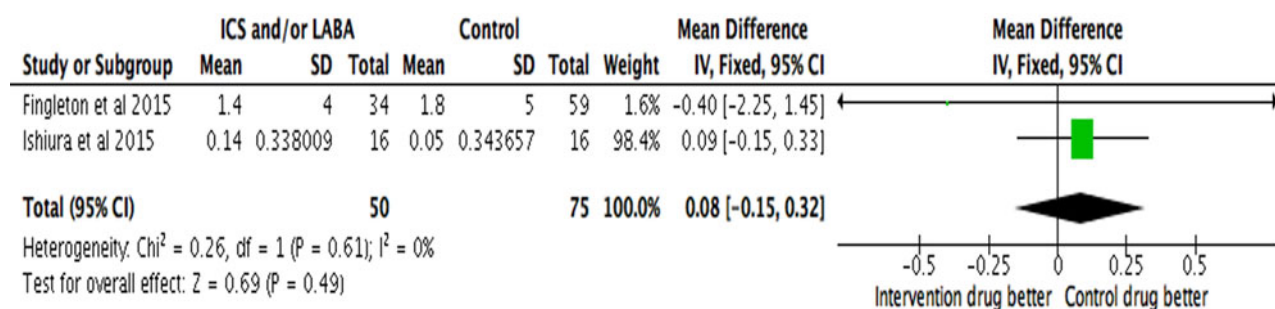


Figure 4. Risk for forced expiratory volume in 1 s; Forest plot describing the association between inhaled corticosteroid (ICS) alone or its combination with long-acting beta2 agonist (LABA) vs control and risk for decline in forced expiratory volume in 1 s (FEV1).

were compared to a placebo or any non-ICS treatment group (29,32). However, the study by Magnussen et al. (34) was excluded from the quantitative analysis because the intervention/exposure drug, a tiotropium (LAMA) was different from any group of intervention synthesized. Finally, one of the included study had three separate results for same exposure of ICS/LABA combination therapy but three different comparators/controls. This singular study assessed ICS/LABA combination therapy and the risk of death or hospitalization for ACO which was compared to either LABA monotherapy or long-acting anticholinergic (a LAMA) (30).

Myocardial infarction

Two studies, all cohort studies (27,36), reported on the incidence of myocardial infarctions among new users of LABA vs non-LABA group comprising of SABA, LAMA or SAMA in patients with ACO. Results from the study by Afonso et al. (27) were included as two separate estimators because risk ratios (RR) were provided for each database (Clinformatics and CPRD GOLD). The risk ratio was 0.80 (95% CI 0.74 to 0.87, $p < 0.0001$), calculated with Inverse Variance random-effects model with an I-squared of 28%, Figure 3.

Pulmonary function testing (FEV₁)

Post bronchodilator (BD) spirometry test of forced expiratory volume in 1 s (FEV₁) with pre- and post-bronchodilator results was provided in three RCT studies. In the meta-analysis performed, post-bronchodilator FEV₁ (in liter, L) was defined as the period during which the patient received the study drug of ICS and/or LABA spanning the 12-weeks' trial compared to placebo. However, in the forest plot shown, all RCTs and as depicted in Figure 4, we found no clear difference in lung function decline in FEV₁; mean difference (MD): 0.08 (95% CI: -0.15 to 0.32, $p = 0.49$, $I^2 = 0\%$).

In a different trial, Magnussen et al. (34) reported that improvements at 12 weeks with tiotropium (a LAMA) were observed for their primary endpoint of FEV₁ area under the curve, from 0 to 6 h (difference = 186 ± 24 ml, $p < 0.001$); and for morning pre-dose FEV₁ (difference = 98 ± 23 ml, $p > 0.00$). It was reported that patients with ACO achieved spirometry improvements along with symptomatic benefits resulting in reduced need for rescue inhaler medication.

Death or hospitalization for ACO

A composite endpoint of death or hospitalization occurring during the period at risk (defined as when the combination therapy of ICS/LABA versus non-LABA/ICS was prescribed during the study period up

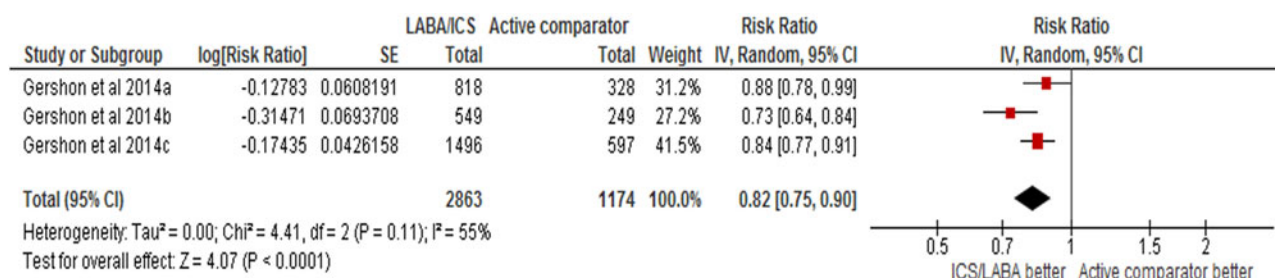


Figure 5. Risk for death or hospitalization; Forest plot describing the association between inhaled combination therapy of corticosteroid and long-acting beta2 agonist (ICS/LABA) vs an active comparator (LABA, LAMA, or non-LAMA) and risk for death or hospitalization of asthma–COPD overlap.

to 30 days was the study outcome by Gershon et al. (30). This singular study, a cohort study, had three separate results for same exposure of ICS/LABA combination therapy but three different comparators/controls. The primary exposure of interest was LABA/ICS combination therapy and the comparators were defined as the use of LAMA or LABA monotherapy. Thus, three separate results were reported by the authors. Our meta-analysis of pooled data showed that there was a lower risk of death or hospitalization due to ACO in the ICS/LABA group versus the comparator group of either LAMA or LABA monotherapy (RR = 0.82, 95% CI: 0.75–0.90, $p < 0.0001$, $I^2 = 55\%$; Figure 5).

ACO exacerbation

Su et al. (35) reported LAMA monotherapy or ICS/LABA combinations were associated with a lower risk of acute exacerbation (time-dependent model, 1 year: LAMA, HR = 0.51, 95% CI: 0.49–0.54; ICS/LABA combinations, HR = 0.61, 95% CI: 0.60–0.62; all $p < 0.0001$) than were those for LABAs or ICSs monotherapies in patients with ACO. Lim et al. (33) found that ICS did not show a decrease in the risk of severe exacerbation (RR = 1.24, 95% CI: 0.44–3.46) compared with non-ICS treatment group of LABA, SABA, or LAMA in patients with ACO.

Nontuberculous mycobacterial pulmonary disease

Nontuberculous mycobacterial pulmonary disease (NTM-PD) in patients with ACO was reported in one of the studies which compared current use of ICS with no use of ICS (28). The authors observed that current use of ICS was associated with increased risk of NTM-PD compared with no-use; (OR = 1.74, 95% CI 1.32–2.28; $p < 0.001$) (28).

Fracture rates

One study reported fracture finding of patients with ACO (31). Hubbard et al. reported that the use of ICS was associated with increased risk of fracture (RR =

2.24, 95% CI: 1.63–3.06) in subjects with both asthma and COPD diagnoses (31). This finding is based on subset of patients who have both asthma and COPD.

Subgroup analysis

A subgroup analysis was performed comparing data based on users of LAMA or LABA monotherapies. The meta-analysis of the first subgroup when ICS/LABA were compared to receipts of LAMA and LABA alone users gave a significant evidence of decreased risk of death or hospitalization due to ACO which had an adjusted RRs of 0.80 (95% CI of 0.67, 0.97, $p < 0.04$ and $I^2 = 76\%$) and 0.84 (95% CI 0.77, 0.91 and $p < 0.0001$), respectively. Results for death or hospitalization due to ACO when LABA/ICS were compared with LAMA or LABA monotherapies were found to be consistent when all studies were combined RR 0.82 (95% CI 0.75, 0.90; $p < 0.001$; Test for subgroup differences, $I^2 = 0\%$) (Figure 6).

Discussion

Results of this systematic review and meta-analysis comprise of 10 studies, including three randomized controlled studies, six cohort studies and one nested control study resulting in three independent meta-analyses. In our meta-analysis, we observed that LABA was associated with decreased risk of myocardial infarction compared with non-LABA (comprised of either SABA, LAMA or SAMA); and the combination therapy of ICS/LABA was associated with lower risk of death or hospitalization due to ACO compared with active comparator of either LABA or LAMA monotherapy. The result from the decline in FEV_1 meta-analysis remains inconclusive due to limited study power.

Myocardial infarction

Through the meta-analysis, we aimed to assess the association between new users of inhaled LABA and

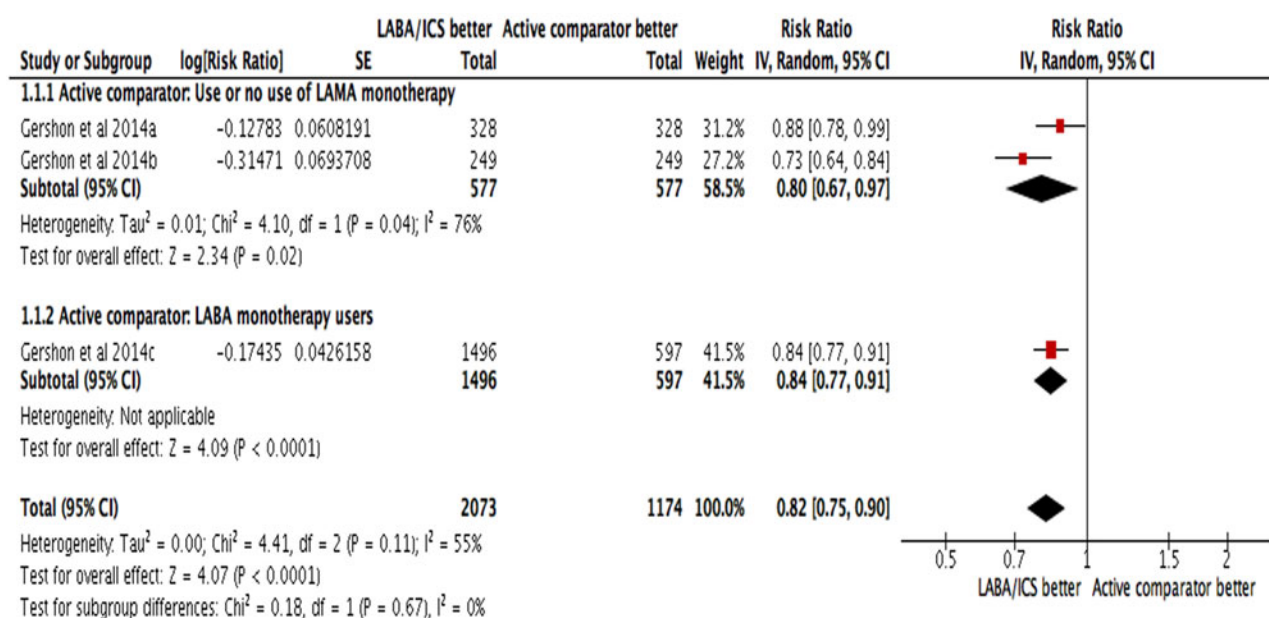


Figure 6. Risk for death or hospitalization; Forest plot subgroup analysis describing the association between inhaled combination therapy of corticosteroid and long-acting beta2 agonist (ICS/LABA) vs an active comparator (LABA, LAMA, or non-LAMA) and risk for death or hospitalization of asthma–COPD overlap.

the incidence of myocardial infarction (including acute MI) in patients with ACO. The summary result yielded a significant association (Figure 3) which showed that patients with ACO who were new users of LABA are associated with a reduced risk of a myocardial infarction compared with those patients with ACO never treated with LABA. All included studies in the meta-analysis referred to subjects with ACO as patients with both features of asthma and COPD as described by GINA/GOLD combination guideline (13). On the basis of result presented in the meta-analysis, physicians might consider LABA either in formulation depending on their preference. However, given the lack of randomized intervention studies of ACO patients and few high qualities observational data coupled with lack of true placebo groups, we believe that it is premature to recommend the designation of LABA as an effective agent in reducing the incidence of myocardial infarction in ACO patients. Furthermore, patients who are started on LABA may be more engaged with health care services and this could be reducing their risk of MI (was this association in LABA alone or ICS/LABA groups. Also, concerning the ongoing debate on the safety of LABAs in people with asthma (37), the use of LABAs in people with any suspicion of an asthmatic component should be of great concern to prescribing physicians. More research is therefore needed to predict treatment response in individual ACO patients prescribed with LABAs.

Pulmonary function testing (FEV₁)

BD spirometry test of forced expiratory volume in 1 s with pre- and post-bronchodilator results was provided in three of the included studies. However, only two studies, all RCTs, were included in the meta-analysis with a common exposure. In the meta-analysis conducted, patients with ACO, treated with ICS monotherapy or its combination therapy of ICS/LABA were compared with ACO patients not treated with ICS. We found no clear difference in decline in FEV₁ (Figure 4) between the intervention (ICS and/or LABA) assessed and placebo. Given the lack of trials evaluating the effectiveness of ICS alone or its combination with ICS and the small number of ACO patients involved in these published studies, no robust conclusions can be drawn due to lack of study power. Nevertheless, judging from the confidence interval from our meta-analysis, we cannot totally rule out a difference. There are recommendations that ACO patients should be started on ICS/LABA as first line therapy, however long-term use in COPD alone is however discouraged as it may cause various side effects (38,39).

One study that was not included in the meta-analysis (34), reported that improvements at 12 weeks with tiotropium, a LAMA, were observed for their primary endpoint of FEV₁. The authors found out that patient with ACO achieved spirometry improvements along with symptomatic benefits resulting in reduced need for rescue inhaler medication. Tiotropium, an antagonist of

M1 and M3 muscarinic receptor subtypes, which induce relaxation of airway smooth muscle, is extensively used in COPD because of its observed benefits. On the other hand, large and high quality RCTs evaluating the efficacy of tiotropium therapy in asthmatics have shown considerable improvements in FEV₁ when LAMA is used as add-on therapy to ICS or ICS/LABA combinations (40,41). Thus, the clinical benefits noticed in both asthma and COPD patients suggest that LAMA (tiotropium) therapy may be a therapeutic option for patients with ACO.

Death or hospitalization for ACO

This meta-analysis focused on death or hospitalization for ACO occurring during the exposure period of up to 30 days. Summary data from this study showed that there was a lower risk of death or hospitalization due to ACO in the ICS/LABA group versus the non-LABA/ICS group (Figure 6). Subjects in this study were referred to as COPD patients with co-diagnosis of asthma. COPD is characterized by a significant smoking history, airway obstruction that is persistent and progressive, lack of reversibility of airway obstruction, and neutrophil infiltration in the airways (42). As described above, it is however believed that reversibility, eosinophilia, and bronchial hyperresponsiveness may be present in COPD patients. Based on eosinophilic pathology, ICS and combinations with LABA have been recommended as treatment options for ACO patients because many clinicians have believed eosinophilia as a diagnostic criterion (43,44). Both GINA and GOLD have recommended well-defined treatment and management options for patients with asthma or COPD alone (13). Combination therapy of ICS/LABA is recommended in a subset of COPD patients or for those with asthma-type symptoms who continue to have symptoms and/or exacerbations despite LABA/LAMA use, thus making the use of ICS/LABA more appealing in ACO.

ACO exacerbation

Su et al. (35) found that LAMA or ICS/LABA combinations were associated with a lower risk of acute exacerbation than were those for LABAs or ICSs monotherapies in patients with ACO. On the contrary, Lim et al. (33) found that inhaled corticosteroids did not show a decrease in the risk of severe exacerbation compared with non-ICS treatment group of SABA, LABA or SAMA. The strength of evidence

for these recommendations is mixed, however. Different factors may contribute to exacerbation in asthma, COPD or ACO exacerbation. In the analysis of frequent exacerbations in 2138 patients in the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study, they observe that the single best predictor of exacerbations was an exacerbation in the preceding year (45). LABAs (salmeterol and formoterol) are first-line therapies in the treatment of COPD to manage symptoms and reduce exacerbations. While, LABA monotherapy use in asthma is not encouraged due to their associated risk of mortality, it is preferred as an add-on to ICS in asthma. ICSs also reduce the severity of COPD exacerbation, but their frequent use is discouraged as its continuous use is associated with incidence of pneumonia (46). Nevertheless, the likelihood that ICSs with or without LABA may provide benefit for eosinophilic ACO patients cannot be either dismissed or ignored due to lack of large RCT studies, lack of quality observational data and insufficient evidence. Thus, further investigation is warranted to be confident of the benefits of ICS and/or LABA in this patient group.

Nontuberculous mycobacterial pulmonary disease

One study compared incidence of nontuberculous mycobacterial pulmonary disease (NTM-PD) in patients with ACO with current use of ICS and those with no use of ICS (28). The authors observed that current use of ICS was associated with an increased risk of NTM-PD compared with no-use. Whilst, there have been studies on the associated risk of ICS use on the incidence of tuberculosis in asthmatic patients, little has been published on the potential risk of NTM-PD associated with ICS in asthma, COPD and especially in ACO patients. However, in this particular study, the population assessed is of prevalent users of medications which limit the generalizability of their result. Prevalent users are labeled as “survivors” of the early period of pharmacotherapy, a situation which can introduce substantial selection bias in comparative effectiveness research studies.

Fracture rates

Safety concerns of fractures and osteoporosis relating to long-term use of ICSs have been documented in the literature as clinical studies have shown that accelerated bone resorption occurs at all doses of ICS use (47). Only one study reported fracture finding of

patients with ACO (31). Hubbard et al. found out that the use of ICS was associated with increased risk of fracture in subjects with ACO (31). ACO patients who have any asthmatic features might benefit from inhaled glucocorticoids, thus long-term use of ICS and its associated risk of fracture cannot be discounted. Nevertheless, further studies are needed to assess whether and at what dose long term use of ICS increases the risk of fracture among ACO patients dispensed respiratory medications.

There are limitations that needed to be considered when interpreting the results. First and foremost is the small number of studies included in the final reviews and the meta-analyses. This is primarily due to the fact that ACO is a newly defined disease and its classification as a complete separate disease is still debatable. Another limitation is the variations in the intervention or the primary exposure drug used. Even though, the effective dosage and duration of action of these drugs may differ, we ensured that we were analyzing the same class of medication based on their therapeutic activity and duration of action. Also, there was considerable heterogeneity ($I^2 = 55\%$) between the data synthesized from one of the studies. Different active comparators used in the analysis may partly explained this heterogeneity, as there were not enough studies to conduct informative active subgroup analysis or meta-regression based on different active comparators. In this regard, there are currently four registered clinical trials that are either active or recruiting to evaluate the comparative safety and effectiveness of triple combinations of LABA/LAMA/ICS and double combinations of LABA/LAMA medications in ACO patients. These ongoing clinical trials, along with any data from yet-to-be published studies, may highlight distinctive findings on the safety and efficacy of inhaled medications in treating patients with ACO. Finally, we did not perform our search in the gray literature. Given the paucity of articles extracted in this review, we do not expect that this additional search would have contributed to our body of evidence.

Conclusion

This systematic review and meta-analysis primarily focused on the safety and effectiveness of inhaled corticosteroids and/or bronchodilators based therapies when compared with placebo or active comparators in patients with ACO and its associated risk of cardiorespiratory outcomes. In our meta-analysis, we observed that LABA was associated with decreased

risk of myocardial infarction; and the combination therapy of ICS/LABA was associated with lower risk of death or hospitalization due to ACO. The result from the decline in FEV₁ meta-analysis remains inconclusive due to limited study power. Future studies should include high quality data and larger number of patients which would help further characterizes the safety and efficacy of inhaled corticosteroids and bronchodilator based therapies in treating patients with a suspected overlap between asthma and COPD.

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Authors' contributions

JEA, JG, LA, J-MG, JF and ZG conceived the study and designed the study protocol. JEA was responsible for registering the study in PROSPERO. JEA developed the search strategy as well as conducted the search strategy with the help of two librarians. JEA, JG, LA, J-MG, JF and ZG conducted the screening and study selection. The inclusion and selection of ACO patients was prior verified by JF. Data analysis and interpretation was carried out by JEA, JG, LA, J-MG, JF and ZG. JEA, JG, LA, J-MG, JF and ZG drafted the manuscript, commented on and approved the final version of the manuscript. ZG is responsible for the study management and coordination and he is also the study guarantor.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

Disclaimer

The study funder was not involved in the study design or the writing of the protocol.

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APPENDIX 1

MEDLINE search strategy used to identify articles

1. Search ("Asthma"[Mesh]) AND "Pulmonary Disease, Chronic Obstructive"[Mesh]
2. Search asthma AND (COPD OR chronic obstructive pulmonary disease)
3. Search ((asthma AND (COPD OR chronic obstructive pulmonary disease))) OR (("Asthma"[Mesh]) AND "Pulmonary Disease, Chronic Obstructive"[Mesh])
4. Search "Adrenergic beta-2 Receptor Agonists"[Mesh]
5. Search "Adrenergic beta-2 Receptor Agonists"[Mesh] OR beta-2 adrenergic receptor agonists OR beta 2 agonists OR muscarinic antagonists OR inhaled corticosteroids OR ICS OR inhaledcorticosteroids OR cholinergic antagonists OR beclomethasone dipropionate OR budesonide OR flunisolide OR fluticasone propionate OR mometasone furoate OR triamcinolone acetonide OR ciclesonide OR Formoterol OR salmeterol OR formoterol OR vilanterol
6. Search (("Adrenergic beta-2 Receptor Agonists"[Mesh] OR beta-2 adrenergic receptor agonists OR beta 2 agonists OR muscarinic antagonists OR inhaled corticosteroids OR ICS OR inhaledcorticosteroids OR cholinergic antagonists OR beclomethasone dipropionate OR budesonide OR flunisolide OR fluticasone propionate OR mometasone furoate OR triamcinolone acetonide OR ciclesonide OR Formoterol OR salmeterol OR formoterol OR vilanterol)) AND (((asthma[tiab] AND (COPD[tiab] OR chronic obstructive pulmonary disease[tiab]))) OR (("Asthma"[Mesh]) AND "Pulmonary Disease, Chronic Obstructive"[Mesh]))

EMBASE search strategy used to identify articles

No.	Query	Results	Date
#7	((('asthma'/exp OR asthma) AND 'chronic obstructive pulmonary disease':jt) OR (asthma:ab,ti AND (copd:ab,ti OR chronic) AND obstructive AND pulmonary AND disease:ab,ti)) AND (('beta 2 adrenergic receptor stimulating agent' OR 'beta 2 agonists' OR 'inhaled corticosteroid' OR 'ics' OR 'muscarinic antagonists' OR	2046	1 Jun 2018

	'cholinergic antagonists' OR 'cholinergic receptor blocking agents') OR (budesonide OR fluticasone OR mometasone OR beclomethasone OR ciclesonide OR flunisolide OR ipratropium OR tiotropium OR salmeterol OR indacaterol OR olodaterol OR vilanterol OR formoterol OR salbutamol OR terbutaline OR fenoterol OR rimiterol OR pirbuterol OR reproterol OR orciprenaline))		
#6	('beta 2 adrenergic receptor stimulating agent' OR 'beta 2 agonists' OR 'inhaled corticosteroid' OR 'ics' OR 'muscarinic antagonists' OR 'cholinergic antagonists' OR 'cholinergic receptor blocking agents') OR (budesonide OR fluticasone OR mometasone OR beclomethasone OR ciclesonide OR flunisolide OR ipratropium OR tiotropium OR salmeterol OR indacaterol OR olodaterol OR vilanterol OR formoterol OR salbutamol OR terbutaline OR fenoterol OR rimiterol OR pirbuterol OR reproterol OR orciprenaline)	116522	1 Jun 2018
#5	budesonide OR fluticasone OR mometasone OR beclomethasone OR ciclesonide OR flunisolide OR ipratropium OR tiotropium OR salmeterol OR indacaterol OR olodaterol OR vilanterol OR formoterol OR salbutamol OR terbutaline OR fenoterol OR rimiterol OR pirbuterol OR reproterol OR orciprenaline	88013	1 Jun 2018
#4	'beta 2 adrenergic receptor stimulating agent' OR 'beta 2 agonists' OR 'inhaled corticosteroid' OR 'ics' OR 'muscarinic antagonists' OR 'cholinergic antagonists' OR 'cholinergic receptor blocking agents'	40278	1 Jun 2018
#3	((('asthma'/exp OR asthma) AND 'chronic obstructive pulmonary disease':jt) OR (asthma:ab,ti AND (copd:ab,ti OR chronic) AND obstructive AND pulmonary AND disease:ab,ti)	9765	1 Jun 2018
#2	asthma:ab,ti AND (copd:ab,ti OR chronic) AND obstructive AND pulmonary AND disease:ab,ti	9692	1 Jun 2018
#1	('asthma'/exp OR asthma) AND 'chronic obstructive pulmonary disease':jt		

Web of Science (WoS) summary search strategy used to identify articles

((('asthma OR asthma) AND 'chronic obstructive pulmonary disease') OR (((asthma AND (copd OR chronic)) AND obstructive) AND pulmonary) AND disease)) AND (((((((('beta 2 adrenergic receptor stimulating agent' OR 'beta 2 agonists') OR 'inhaled corticosteroid') OR 'ics') OR 'muscarinic antagonists') OR 'cholinergic antagonists') OR 'cholinergic receptor blocking agents') OR (((((((((((((((budesonide OR fluticasone) OR mometasone) OR beclomethasone) OR ciclesonide) OR flunisolide) OR ipratropium) OR tiotropium) OR salmeterol) OR indacaterol) OR olodaterol) OR vilanterol) OR formoterol) OR salbutamol) OR terbutaline) OR fenoterol) OR rimiterol) OR pirbuterol) OR reprotool) OR orciprenaline)))

Table A1: Risk of bias assessment in individual observational studies

Study	No active Comparator	Channeling bias	Depletion of Susceptible	Lack of Statistical Power	Residual confounding	Immortal time	Time-lag	Time-window
Afonso et al., 2016[29]					♦			
Brode et al., 2017[23]					♦	♦		
Gershon et al., 2014[24]					♦			
Hubbard et al., 2006[25]		♦	♦	♦	♦	♦		
Lim et al., 2014[27]				♦	♦	♦		
Su et al., 2018[22]					♦			
Uddin et al., 2016[28]					♦			

♦Indicates presence of bias or methodological issue in the study