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Long-acting muscarinic antagonist (LAMA) plus long-acting beta-agonist (LABA) versus LABA plus inhaled corticosteroid (ICS) for stable chronic obstructive pulmonary disease (COPD) (Review)

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TABLE OF CONTENTS

[Intervention Review]

Long-acting muscarinic antagonist (LAMA) plus long-acting beta-agonist (LABA) versus LABA plus inhaled corticosteroid (ICS) for stable chronic obstructive pulmonary disease (COPD)

Nobuyuki Horita[1], Atsushi Goto[2], Yuji Shibata[1], Erika Ota[3], Kentaro Nakashima[1], Kenjiro Nagai[1], Takeshi Kaneko[1]

[1]Department of Pulmonology, Yokohama City University Graduate School of Medicine, Yokohama, Japan. [2]Metabolic Epidemiology Section, Division of Epidemiology, Center for Public Health Sciences, National Cancer Center, Tokyo, Japan, Tokyo, Japan. [3]Global Health Nursing, St. Luke's International University, Graduate School of Nursing Sciences, Tokyo, Japan

Contact address: Nobuyuki Horita, Department of Pulmonology, Yokohama City University Graduate School of Medicine, Fukuura 3-9, Kanazawa, Yokohama, 236-0004, Japan. horitano@yokohama-cu.ac.jp, nobuyuki_horita@yahoo.co.jp.

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ABSTRACT

Background

Three classes of inhaler medications are used to manage chronic obstructive pulmonary disease (COPD): long-acting beta-agonists (LABA), long-acting muscarinic antagonists (LAMA), and inhaled corticosteroids (ICS). When two classes of medications are required, LAMA plus LABA (LAMA+LABA) and LABA plus ICS (LABA+ICS) are often selected because these combinations can be administered via a single medication device. The previous Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidance recommended LABA+ICS as the first-line treatment for managing stable COPD in high-risk people of categories C and D. However, the updated GOLD 2017 guidance recommends LAMA+LABA over LABA+ICS.

Objectives

To compare the benefits and harms of LAMA+LABA versus LABA+ICS for treatment of people with stable COPD.

Search methods

We performed an electronic search of the Cochrane Airways Group Specialised Register (2 February 2016), ClinicalTrials.gov (4 June 2016), and the World Health Organization Clinical Trials Search Portal (4 June 2016), followed by a handsearch (5 June 2016). Two review authors screened and scrutinised the selected articles.

Selection criteria

We included individual randomised controlled trials, parallel-group trials, and cross-over trials comparing LAMA+LABA and LABA+ICS for stable COPD. The minimum accepted trial duration was one month and trials should have been conducted in an outpatient setting.

Data collection and analysis

Two review authors independently extracted data and evaluated risk of bias. We resolved any discrepancies through discussion. We analysed dichotomous data as odds ratios (OR), and continuous data as mean differences (MD), with 95% confidence interval (CI) using Review Manager 5. Exacerbations were measured by counting the number of people experiencing one or more exacerbation.

Main results

We included 11 studies comprising 9839 participants in our quantitative analysis. Most studies included people with moderate to severe COPD, without recent exacerbations. One pharmaceutical sponsored trial that included only people with recent exacerbations was the largest study and accounted for 37% of participants. All but one study were sponsored by pharmaceutical companies, thus we rated them as having a high risk of 'other bias'. The unsponsored study was at high risk of performance and detection bias, and possible selective reporting.

Five studies recruited GOLD Category B participants, one study recruited Category D participants, two studies recruited Category A/B participants, and three studies recruited participants regardless of category. Follow-up ranged from 6 to 52 weeks.

Compared to the LABA+ICS arm, the results for the pooled primary outcomes for the LAMA+LABA arm were as follows: exacerbations, OR 0.82 (95% CI 0.70 to 0.96, P = 0.01, I^2 = 17%, low quality evidence); serious adverse events (SAE), OR 0.91 (95% CI 0.79 to 1.05, P = 0.18, I^2 = 0, moderate quality evidence); St. George's Respiratory Questionnaire (SGRQ) total score change from the baseline, MD -1.22 (95% CI -2.52 to 0.07, P = 0.06, I^2 = 71%, low quality evidence); and trough forced expiratory volume in one second (FEV_1) change from the baseline, MD 0.08 L (95% CI 0.06 to 0.09, P < 0.0001, I^2 = 50%, moderate quality evidence). Compared to the LABA+ICS arm, the results for the pooled secondary outcomes for the LAMA+LABA arm were as follows: pneumonia, OR 0.57 (95% CI 0.42 to 0.79, P = 0.0006, I^2 = 0%, low quality evidence); all-cause death, OR 1.01 (95% CI 0.61 to 1.67, P = 0.88, I^2 = 0%, low quality evidence); and SGRQ total score change from the baseline of 4 points or greater (the minimal clinically important difference for the SGRQ is 4 points), OR 1.25 (95% CI 1.09 to 1.44, P = 0.002, I^2 = 0%, moderate quality evidence).

Authors' conclusions

For the treatment of COPD, LAMA+LABA has fewer exacerbations, a larger improvement of FEV_1, a lower risk of pneumonia, and more frequent improvement in quality of life as measured by an increase over 4 units or more of the SGRQ. These data were supported by low or moderate quality evidence generated from mainly participants with moderate to severe COPD in heterogeneous trials with an observation period of less than one year. Our findings support the recently updated GOLD guidance.

PLAIN LANGUAGE SUMMARY

Which combination of inhaled medications are safe and effective for chronic obstructive pulmonary disease (COPD)

Background

Chronic obstructive pulmonary disease (COPD) is a long-term lung condition characterised by cough, sputum production (fluids from the lungs, i.e. phlegm), and difficulty breathing. It is now possible to give two types of medicine using one inhaler device: the medicines are long-acting muscarinic antagonist (LAMA) plus a long-acting beta-agonist (LABA) (LAMA+LABA) and a LABA plus an inhaled corticosteroid (ICS) (LABA+ICS). The recent guidelines recommend LAMA+LABA are preferable over LABA+ICS.

Study characteristics

We included 11 studies involving 9839 participants comparing the benefits and harms of LAMA+LABA and LABA+ICS for the treatment of people with COPD.

Key results

Although risk of serious side effects and death were not affected by the choice of treatment, compared to LABA+ICS, LAMA+LABA was associated with a lower risk of flare-ups, fewer episodes of pneumonia, larger improvement in how well the lungs work, and improved quality of life.

Quality of evidence

Since most of the analysed studies were sponsored by pharmaceutical companies, we had to interpret the results carefully. However, we judged the included studies to be generally conducted in an acceptable manner. These data were supported by low or moderate quality evidence from trials in people with mainly moderate to severe COPD who were studied for less than one year.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Long-acting muscarinic antagonist (LAMA) plus long-acting beta-agonist (LABA) versus LABA plus inhaled corticosteroid (ICS) for stable chronic obstructive pulmonary disease (COPD)

LAMA + LABA versus LABA + ICS for stable COPD

Population: stable COPD
Setting: outpatient. Studies were conducted in > 50 countries including low-, medium- and high-income countries from all continents.
Intervention: LAMA+LABA
Comparison: LABA+ICS

Outcomes	Anticipated absolute effects* (95% CI)		Relative effects	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	LABA+ICS	LAMA+LABA				
Exacerbations (number of people experiencing ≥ 1 exacerbations) Follow-up: 12 to 52 weeks	377 per 1000	332 per 1000 (298 to 368)	OR 0.82 (0.70 to 0.96)	8922 (9 RCTs)	⊕⊕⊖⊖ Low [1,2]	Low OR means favourable outcome
Serious adverse effects Follow-up: 12 to 52 weeks	96 per 1000	87 per 1000 (77 to 100)	OR 0.91 (0.79 to 1.05)	9793 (10 RCTs)	⊕⊕⊕⊖ Moderate [1]	Low OR means favourable outcome
SGRQ total score change from the baseline (MD) Follow-up: 12 to 52 weeks	-	-	MD -1.22 (-2.52 to 0.07)	6055 (6 RCTs)	⊕⊕⊖⊖ Low [1,3]	Low MD means favourable outcome
Trough FEV_1 change from the baseline Follow-up: 12 to 52 weeks	-	-	MD 0.08 L (0.06 to 0.09)	6238 (6 RCTs)	⊕⊕⊕⊖ Moderate [1]	High MD means favourable outcome
Pneumonia Follow-up: 12 to 52 weeks	26 per 1000	15 per 1000 (11 to 20)	OR 0.57 (0.42 to 0.79)	8540 (8 RCTs)	⊕⊕⊖⊖ Low [1,4]	Low OR means favourable outcome
All-cause death Follow-up: 12 to 52 weeks	7 per 1000	7 per 1000 (4 to 11)	OR 1.01 (0.61 to 1.67)	8200 (8 RCTs)	⊕⊕⊖⊖ Low [1,4]	Low OR means favourable outcome
SGRQ total score change from the baseline	445 per 1000	500 per 1000	OR 1.25	3192	⊕⊕⊕⊖	High OR means favourable outcome

(≥ 4 points, MCID) Follow-up: 24 to 52 weeks		(466 to 535)	(1.09 to 1.44)	(2 RCTs)	Moderate [1]

*The **absolute risk** (and its 95% CI) of LAMA+LABA group is based on the assumed risk in the LABA+ICS group and the **OR** of the intervention (and its 95% CI).
CI: confidence interval; **COPD:** chronic obstructive pulmonary disease; **FEV_1:** forced expiratory volume in one second; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta-agonist; **LAMA:** long-acting muscarinic antagonist; **MCID:** minimal clinically important difference; **MD:** mean difference; **OR:** odds ratio; **RCT:** randomised controlled trial; **SGRQ:** St. George's Respiratory Questionnaire.

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of effect but may be substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Every study had at least one domain of high risk of bias mostly due to conflicts of interest.
[2] Indirectness due to definition of exacerbation.
[3] There was a considerable heterogeneity, $I^2 = 71\%$.
[4] Downgraded due to imprecision.

BACKGROUND

Description of the condition

Chronic obstructive pulmonary disease (COPD) is characterised mainly by bronchial obstruction, systemic inflammation, and comorbidities. It is the third leading cause of death in the world, with more than three million people dying as a result of COPD every year (WHO 2015). The condition is a concern not only for pulmonologists, but also for physicians and general practitioners. In addition to active tobacco smoking, air pollution, and occupational exposures play a central role in the development of COPD. The most common symptoms of COPD - shortness of breath on exertion and cough - are present for a prolonged period and typically worsen over time (GOLD 2016).

Since the late 1960s, the definition of COPD has been modified repeatedly. Early definitions of COPD included chronic bronchitis, which is clinically characterised by chronic cough, and emphysema, which is pathologically defined by damaged sacs or alveoli in the lungs (Burrows 1966). Following the 1995 American Thoracic Society Statement, in 2001, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) released its first report, *Global Strategy for the Diagnosis, Management, and Prevention of COPD* (Pauwels 2001), which supported the definition of COPD that indicates the disorder is recognised primarily by chronic obstruction of lung airflow (Pauwels 2001).

If COPD is properly diagnosed and managed, some symptoms can be ameliorated. Smoking cessation and vaccination are the first steps in COPD management, and daily pharmacological treatment is required for most people with COPD (GOLD 2016).

Description of the intervention

Whilst asymptomatic people with mild airflow limitation can be treated with on-demand short-acting bronchodilators, key medications for symptomatic COPD management consist of three classes of inhaler device medications: long-acting beta-agonists (LABA), long-acting muscarinic antagonists (LAMA), and inhaled corticosteroids (ICS) (GOLD 2016). If the disease cannot be controlled adequately with LAMA or LABA monotherapy, administration of two or more medications from different classes may prove beneficial. When two classes of medications are required, LAMA plus LABA (LAMA+LABA) and LABA plus ICS (LABA +ICS) are often selected because these combinations can be administered via one medication device (Frampton 2014; Malerba 2014; Nannini 2013; Schachter 2013), which is most beneficial for improving patient adherence (Horita 2015a).

How the intervention might work

Currently, there is no medication that cures COPD. Thus, the practical goal of COPD treatment is to control symptoms, reduce frequency of exacerbations, and improve exercise tolerance. The treatment of COPD usually consists of smoking cessation, vaccination, inhaled bronchodilators, ICS, oral medication, long-term oxygen therapy, and pulmonary rehabilitation (GOLD 2017). According to the GOLD approach, people are classified into Categories A to D depending on the degree of symptoms and the risk of exacerbations (GOLD 2017). Medications belonging to specific class are recommended based on the following:

- category A: bronchodilator (short or long acting); consider switching to another depending on response;
- category B: long-acting bronchodilator (LAMA or LABA), or both LAMA and LABA if symptoms not controlled on one drug;
- category C: LAMA; consider switching to LAMA+LABA or to LABA +ICS if further exacerbations occur (LAMA+LABA now preferred over LABA+ICS);
- category D: LAMA+LABA initially (unless high blood eosinophil counts or people with asthma-COPD overlap syndrome (ACOS), in which case LABA+ICS may be preferred); consider triple therapy if symptoms persist. Roflumilast or a macrolide (e.g. azithromycin) (or both) may also be considered.

LAMA: LAMAs dilate the airway by selectively blocking acetylcholine M_3 receptors (Alagha 2014), and by inhibiting bronchoconstriction. Since the early 2000s, LAMAs, especially tiotropium, have been regarded as the first-choice medication for treating people with COPD. LAMAs confer anti-inflammatory, and even more importantly, anti-airway remodelling effects (Tashkin 2004).

LABA: beta-agonists widen the airways by relaxing airway muscles. Studies suggest that LABAs might also provide anti-inflammatory and protective effects against bronchoconstrictive substances. Regular use of a short-acting beta-agonist that works quickly and lasts for four to six hours is not currently recommended for people with asthma or COPD. A LABA that lasts for about 12 to 24 hours is considered to be a maintenance medication (Anderson 2014; Tashkin 2004).

ICS: ICSs reduce inflammation in the airways. Although ICSs are indicated for bronchial asthma in which eosinophils play a key role, they are not so effective when neutrophils are observed in the airways of people with COPD (Barnes 2010; Hanania 2008; Suissa 2009). The previous GOLD guideline recommended that ICS is prescribed combined with LABA for people with COPD with severe airflow limitation or with high risk of exacerbation (GOLD 2016). Studies suggest that LABA+ICSs may be highly effective for people with a high sputum/blood eosinophil count (Pascoe 2015).

Why it is important to do this review

The previous GOLD guidelines recommend first-line use of ICS only for people with category C and D COPD, that is, people with severe to very severe airflow limitation and two or more exacerbations per year, with one or more hospitalisations for exacerbations (GOLD 2016). The previous guidelines suggested that ICSs reduced the risk of exacerbations (GOLD 2016). Nonetheless, prescription rates for ICSs and combined LABA+ICS agents are high (Drivenes 2014; Price 2014; White 2013). This is probably because many randomised controlled trials (RCTs) have supported the hypothesis that salmeterol (LABA)/fluticasone propionate (ICS) combination, which is the oldest combination treatment, can improve quality of life, especially for people with dyspnoea, and can also decrease acute exacerbations of COPD, and reduce yearly declines in pulmonary function (GOLD 2016).

Although controversial (Wedzicha 2016), blood/sputum eosinophil counts can serve as predictive biomarkers for differentiating people with COPD who will derive the greatest benefit from ICS administration from people who will not benefit from an ICS (Pascoe 2015).

The GOLD 2017 guidance recommends LAMA+LABA over LABA+ICS for people belonging to categories B, C, and D (GOLD 2017).

It should be re-evaluated which type of combination treatment (LAMA+LABA or LABA+ICS) is most beneficial for people with COPD. Researchers must continue to evaluate the effectiveness of these treatments.

OBJECTIVES

To compare the benefits and harms of LAMA+LABA versus LABA+ICS for treatment of people with stable COPD.

METHODS

Criteria for considering studies for this review

Types of studies

We planned to include individual and cluster RCTs and cross-over trials, but not quasi-RCTs. However, we found no cluster RCTs. We included studies reported as full text, those published as abstract only, and unpublished data. When we could not obtain sufficient data from published articles, we contacted authors and sponsors, and accessed trial registration websites. We included open-label studies, single-blinded studies and double-blinded studies. The minimum accepted trial duration was one month.

Types of participants

We included adults with a diagnosis of COPD according to GOLD guidelines (GOLD 2016). We did not set specific exclusion criteria involving comorbidities. We planned to exclude original studies focusing on ACOS.

Types of interventions

We included trials comparing LAMA+LABA versus LABA+ICS. We permitted treatments administered via a single combined device or via two separate devices. We excluded trials of short-acting bronchodilators (e.g. ipratropium). We included cointerventions when they were not part of the randomly assigned treatment.

Types of outcome measures

Primary outcomes

- Exacerbations (participants with one or more).
- Serious adverse events (SAE) (participants with one or more).
- St. George's Respiratory Questionnaire (SGRQ) total score change from baseline (mean difference (MD)).
- Trough forced expiratory volume in one second (FEV_1) change from baseline.

Secondary outcomes

- Pneumonia* (participants with one or more occurrences).
- All-cause death.
- SGRQ total score change from baseline (4 points or greater).
- Hospitalisations for COPD exacerbations (participants with one or more occurrences).

*Pneumonia was assessed based on X-ray.

Search methods for identification of studies

Electronic searches

We identified trials from the Cochrane Airways Group Specialised Register (CAGR), which was maintained by the Information Specialist for the Group. The Register contains trial reports identified through systematic searches of bibliographic databases, including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), the Allied and Complementary Medicine Database (AMED), and PsycINFO, and by handsearching of respiratory journals and conference abstracts (see Appendix 1 for details). We searched all records in the CAGR on 2 February 2016 using the search strategy provided in Appendix 2.

We conducted a search of ClinicalTrials.gov (www.ClinicalTrials.gov) and the World Health Organization (WHO) Clinical Trials Search Portal (www.who.int/ictrp/en/) on 4 June 2016. We searched all databases from their inception, and we imposed no restrictions on language of publication.

Searching other resources

We checked reference lists of all primary studies and review articles for additional references, and we searched relevant manufacturers' websites for trial information. We searched for errata or retractions from included studies published as full text on PubMed (www.ncbi.nlm.nih.gov/pubmed), and reported within the review the date when this was done. These handsearches were done up to 5 June 2016.

Data collection and analysis

Selection of studies

Two review authors (NH and YS) independently screened the titles and abstracts of all studies identified by the search for possible inclusion, and coded studies as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We retrieved the full-text publications. Two review authors (NH and YS) independently screened the full texts to identify studies for inclusion and recorded reasons for exclusion of ineligible studies. We resolved disagreements through discussion, or, when required, we consulted a third review author (TK). We identified and excluded duplicates and collated multiple reports of the same study, so that each study, rather than each report, was the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram and 'Characteristics of excluded studies' table (Moher 2009).

Data extraction and management

We used a data collection form that had been piloted on at least one study in the review to document study characteristics and outcome data. Two review authors (NH and YS) extracted the following study characteristics from the included studies.

- Methods: study design, duration of study follow-up and 'run-in' period, number of study centres and countries, and study start date.
- Participants: number, mean and standard deviation (SD) age, gender, mean and SD of baseline FEV_1 key inclusion criteria,

number of participants randomised and completed, and follow-up duration.
- Interventions: intervention, comparison, and dosage of the intervention.
- Outcomes: primary outcomes specified and collected and time points reported.
- Notes: funding for trial and notable conflicts of interest (COI) of trial authors, trial registration, and other information if necessary.

Two review authors (NH and YS) independently extracted outcome data from the included studies. We noted in the Characteristics of included studies table if outcome data were not reported in a useable way. We resolved disagreements by consensus or by consultation with a third review author (TK). One review author (NH) transferred data into the Review Manager 5 (RevMan 2014). We double-checked that data were entered correctly by comparing data presented in the systematic review versus data provided in study reports. A second review author (YS) spot-checked study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Two review authors (NH and YS) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved disagreements by discussion or by consultation with another review author (EO). We assessed risk of bias according to the following domains.

- Random sequence generation.
- Allocation concealment.
- Blinding of participants and personnel.
- Blinding of outcome assessment.
- Incomplete outcome data.
- Selective outcome reporting.
- Other bias.

We graded each potential source of bias as high, low, or unclear and provided an explanation from the study report together with a justification for our judgement in the 'Risk of bias' table. We summarised risk of bias judgements across studies for each of the domains listed. We considered blinding separately for different key outcomes when necessary (e.g. for unblinded outcome assessment, risk of bias for all-cause mortality and risk of bias for a participant-reported outcome might be very different). When we requested information on risk of bias related to unpublished data or correspondence with a trialist, we noted this in the 'Risk of bias' table.

When considering treatment effects, we took into account risk of bias for studies that contributed to that outcome.

Assessment of bias in conducting the systematic review

We conducted the review according to the previously published protocol (Horita 2016).

Measures of treatment effect

We analysed dichotomous data as odds ratios (OR), and continuous data as MD with 95% confidence intervals (CI). We entered data presented as a scale with a consistent direction of effect (i.e. data in the LAMA+LABA arm minus data in the LABA+ICS arm). Although there is no universal rule to interpret the magnitude of the therapeutic effect from ORs, we believe that an OR greater than 1.5 and an OR of less than 0.7 mean that there is a considerable chance that the outcome is clinically important.

We undertook meta-analyses only when this was meaningful (i.e. if treatments, participants, and the underlying clinical question were similar enough for pooling to make sense).

We had planned to describe skewed data using medians and interquartile ranges; however, we found no report describing skewed data.

According to the original protocol, when multiple trial arms were reported in a single trial, we planned to include only the relevant arms. However, we did not find such studies.

Unit of analysis issues

We analysed the number of participants, not the number of events, as the unit of analysis for dichotomous data (i.e. participants with one or more events). For continuous data, we used MDs.

Dealing with missing data

We tried to contact investigators, study sponsors, and registration websites to verify key study characteristics and to obtain missing numerical outcome data when possible (e.g. when a study was only reported in an abstract format). When this was not possible, and when missing data were thought to introduce serious bias, we explored the impact of including such studies in the overall assessment of results by conducting a sensitivity analysis**.**

Assessment of heterogeneity

We used the I^2 statistic to measure heterogeneity among the trials in each analysis: 0% to 40%: might not be important; 30% to 60%: might represent moderate heterogeneity; 50% to 90%: might represent substantial heterogeneity; 75% to 100%: might show considerable heterogeneity (Higgins 2011). When we identified considerable heterogeneity, we reported this and explored possible causes by performing a prespecified subgroup analysis.

Assessment of reporting biases

We created and examined a funnel plot to explore possible small-study and publication biases when more than 10 trials could be pooled for an outcome.

Data synthesis

We used a random-effects model and performed a sensitivity analysis by using a fixed-effect model (Sensitivity analysis).

'Summary of findings' table

We created a 'Summary of findings' table that includes the following outcomes.

- Exacerbations (participants with one or more).
- SAEs (participants with one or more).
- SGRQ total score change from the baseline (MD).
- Trough FEV_1 change from the baseline.
- Pneumonia (participants with one or more occurrences).
- All-cause death.

- SGRQ total score change from the baseline (4 points or greater).

We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence (very low, low, moderate, and high quality of evidence) as it related to studies that contributed data to meta-analyses for prespecified outcomes (Guyatt 2008). We used the methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) with GRADEpro software (GRADEpro). We justified all decisions to downgrade or upgrade the quality of studies by using footnotes, and we provided comments to aid readers' understanding of the review when necessary.

Subgroup analysis and investigation of heterogeneity

We planned the following subgroup analyses for all primary and secondary outcomes. We believe these subgroup data are especially useful for identifying the cause of heterogeneity, however we were unable to perform the severity subgroup analysis because separate data for participants with different severities were not reported. We used the I^2 test to detect heterogeneity as discussed in (Higgins 2003).

- LAMA+LABA: "combined indacaterol + glycopyrronium bromide (QVA149, IND/GLY)" versus "combined umeclidinium + vilanterol (UMEC/VI)" versus "other LAMA/LABA inhalers".
- COPD severity: 'including only mild or moderate (or both) (% predicted FEV_1 50% or greater)' versus 'including severe and/or very severe (% predicted FEV_1 less than 50%)' versus 'including both categories.'

We used the formal test for subgroup interactions provided in Review Manager 5 (RevMan 2014).

Sensitivity analysis

We planned to carry out the following sensitivity analyses. We were only able to carry out the first two analyses.

- Excluding unblinded studies from the analysis.
- Analysing the data using a fixed-effect model.
- When a study was at high risk of bias for allocation concealment and attrition (greater than 20%), we planned to perform sensitivity analyses for primary outcomes by removing this study.

RESULTS

Description of studies

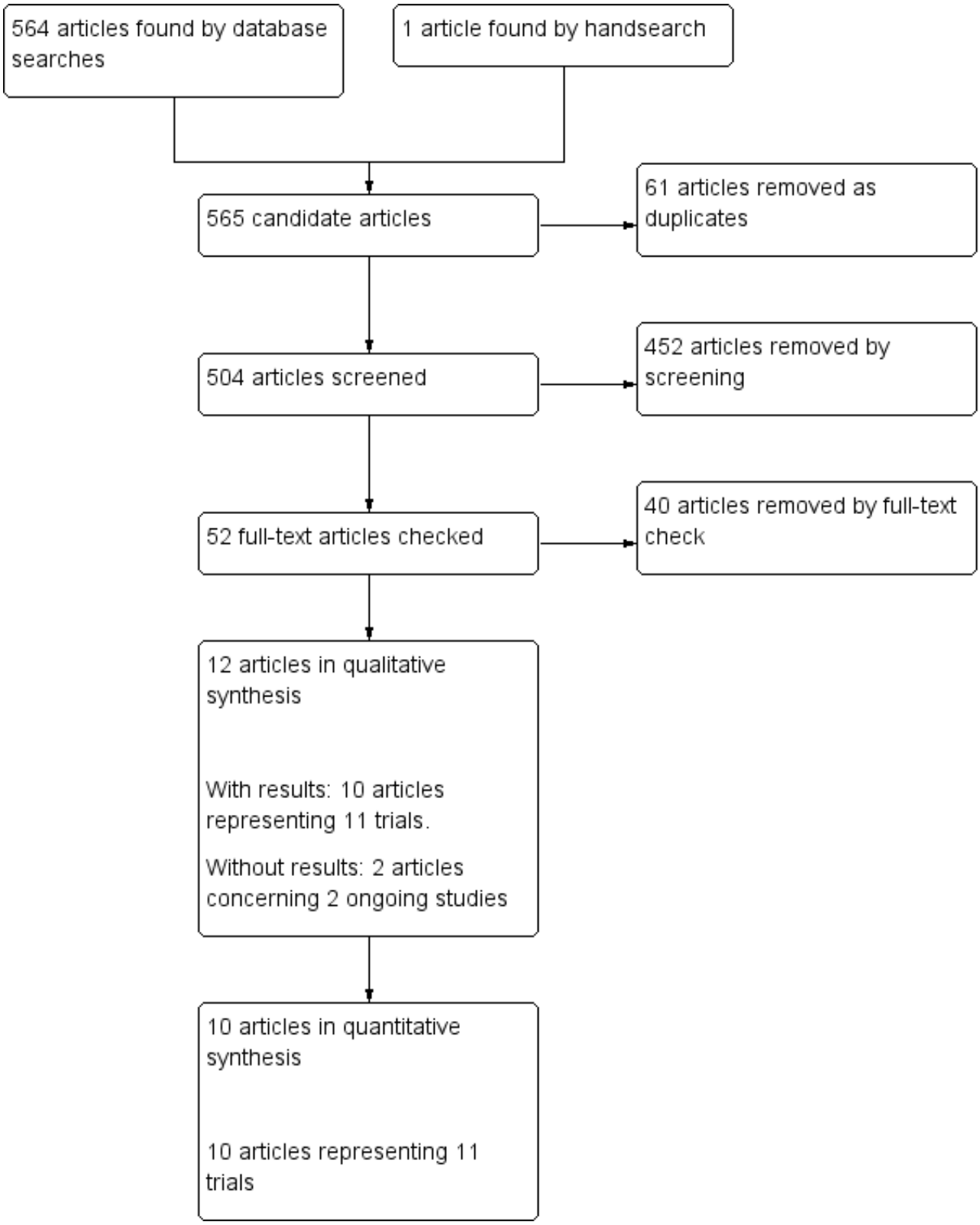
See Characteristics of included studies, (and Table 1), Characteristics of excluded studies, Characteristics of ongoing studies tables.

Results of the search

An electronic search of the CAGR (via the Cochrane Register of Studies) conducted by a trained librarian (ES) on 2 February 2016 identified 393 candidate reports, excluding duplicates. Additional search by ClinicalTrial.gov found 56 reports. Additional search by WHO search portal found 70 reports. Hand search found a report. Update search on 7th September 2016 found 45 reports. Therefore, the total number of candidates were 565. Among the 565, 61 were removed due to duplicate, 452 were removed by screening, 40 were removed by full-text check. The remaining 12 were used for quantitative synthesis. Among the 12, two ongoing studies without results were not used for quantitative synthesis. One paper reported two independent RCTs (Donohue 2015a; Donohue 2015b).

Eventually, the quantitative synthesis included 10 articles representing 11 trials (Figure 1).

Figure 1. Study flow diagram.



Included studies

We included 11 studies comprising 9839 participants. All reports used individual randomisation, 10 used parallel-group design, and one used a cross-over design. The number of participants included in each study ranged from 46 to 3362, with a median of 700 participants per study. Most studies included people with

moderate to severe COPD without recent exacerbations. One trial that included only people with a recent exacerbation was the largest study and accounted for 37% of total participants. In each study, 65% to 91% (median 72%) were men. Mean age in each study ranged 61 years to 71 years with a median mean of 63 years. Every study included participants with both per cent predicted (%pred) FEV_1 less than 50% and %pred FEV_1 greater than 50%. One study only included participants with recent exacerbations (Wedzicha 2016), while the other studies only included participants without recent exacerbations. Five studies recruited people with category B COPD, one study recruited people with category D COPD, two studies recruited people with category A/B COPD, and three studies recruited people regardless of category.

Treatment

Treatment duration ranged from 6 to 52 weeks. Of the LABA+ICS treatments used in these studies, one study used uncombined salmeterol/fluticasone propionate (Rabe 2008) and the other studies used combined salmeterol/fluticasone propionate. Of the administered LAMA+LABA treatments, three studies used indacaterol/glycopyrronium (Vogelmeier 2013; Wedzicha 2016; Zhong 2015), three studies used umeclidinium/vilanterol (Donohue 2015a; Donohue 2015b; Singh 2015), one study used tiotropium/olodaterol (Beeh 2016), one study used tiotropium/indacaterol (Hoshino 2015), one study used tiotropium/salmeterol (Magnussen 2012), one study used tiotropium/formoterol (Rabe 2008), and one study used aclidinium/formoterol (Vogelmeier 2016).

Outcomes

With regards to the primary outcomes, eight studies reported FEV_1-related outcomes (Beeh 2016; Donohue 2015a; Donohue 2015b; Rabe 2008; Singh 2015; Vogelmeier 2013; Vogelmeier 2016; Zhong 2015), one study reported airway dimensions (Hoshino 2015), one study reported rate of exacerbations (Wedzicha 2016), and one study reported both forced residual capacity and endurance time as coprimary endpoints (Magnussen 2012) (see Characteristics of included studies table).

Excluded studies

We excluded seven studies with reasons; six due to a no comparison between LAMA+LABA and LABA+ICS (Bruhn 2003; Calverley 2007; Knobil 2004a; Knobil 2004b; NCT00120978; Sciurba 2004), and one because the cost-effectiveness analysis design used previously published data (Price 2014) (see Characteristics of excluded studies table).

Ongoing studies

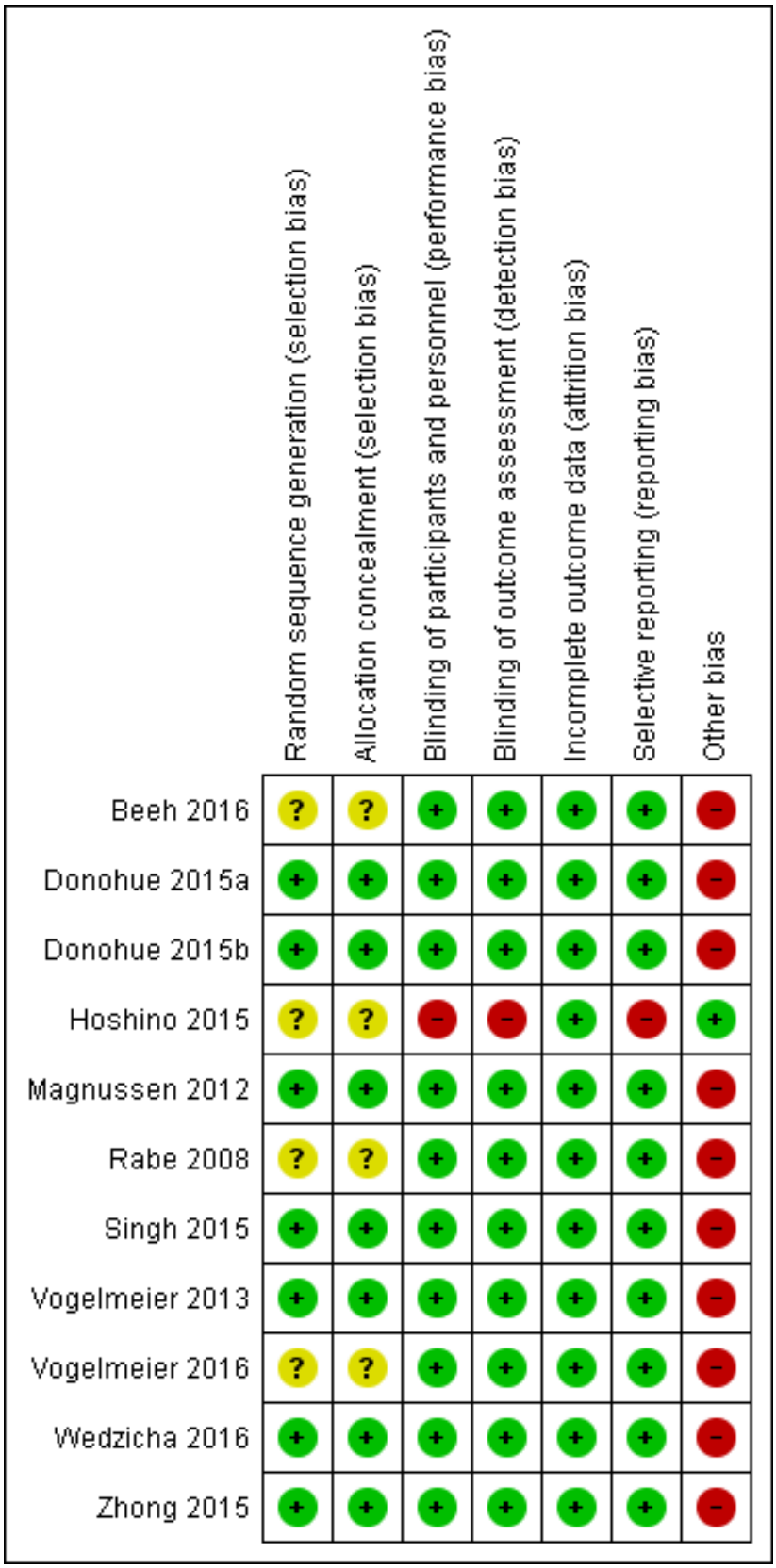
We found two ongoing studies awaiting results (NCT02497001; NCT02516592).

One study is a moderate-sized trial comparing indacaterol/glycopyrronium with salmeterol/fluticasone sponsored by Novartis. The study comparison and inclusion criteria are similar to those of included studies sponsored by Novartis. The second study is a large-sized four-arm trial comparing glycopyrronium/formoterol/budesonide (aerosol), glycopyrronium/formoterol (aerosol), formoterol/budesonide (aerosol), and formoterol/budesonide (powder). The primary outcomes of these studies are trough FEV_1 change from the baseline at the end of follow-up. Both studies started in 2015.

Risk of bias in included studies

Included studies had generally low risk of bias for random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting. However, all but one studies were sponsored by pharmaceutical companies, thus we marked them as high risk of other bias (Figure 2).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

While seven studies reported centralised randomisation using acceptable methods, the remaining four did not provide information on randomisation (Beeh 2016; Hoshino 2015; Rabe 2008; Vogelmeier 2016). These four studies had unclear risk of bias.

Blinding

While 10 studies were conducted in a double-blinded manner, one adopted neither double- nor single-blinding methods (Hoshino 2015).

Incomplete outcome data

Our prespecified criteria for high attrition bias was a dropout rate of more than 20% of randomised participants. However, no trial had a dropout rate of more than 20%. One study did not report the completion rate (Rabe 2008).

Selective reporting

Our criteria for rating a study as having a risk of selective reporting bias was if it was a non-registered trial or considerably deviated from the registered protocol concerning outcome reporting. One trial had a high risk of selective reporting bias due to non-registration (Hoshino 2015).

Other potential sources of bias

Ten out of 11 trials were sponsored by pharmaceutical companies, thus we marked them as high risk of other bias (Beeh 2016; Donohue 2015a; Donohue 2015b; Magnussen 2012; Rabe 2008; Singh 2015; Vogelmeier 2013; Vogelmeier 2016; Wedzicha 2016; Zhong 2015). We found no other source of bias apart from COIs.

Effects of interventions

See: **Summary of findings for the main comparison** Long-acting muscarinic antagonist (LAMA) plus long-acting beta-agonist (LABA) versus LABA plus inhaled corticosteroid (ICS) for stable chronic obstructive pulmonary disease (COPD)

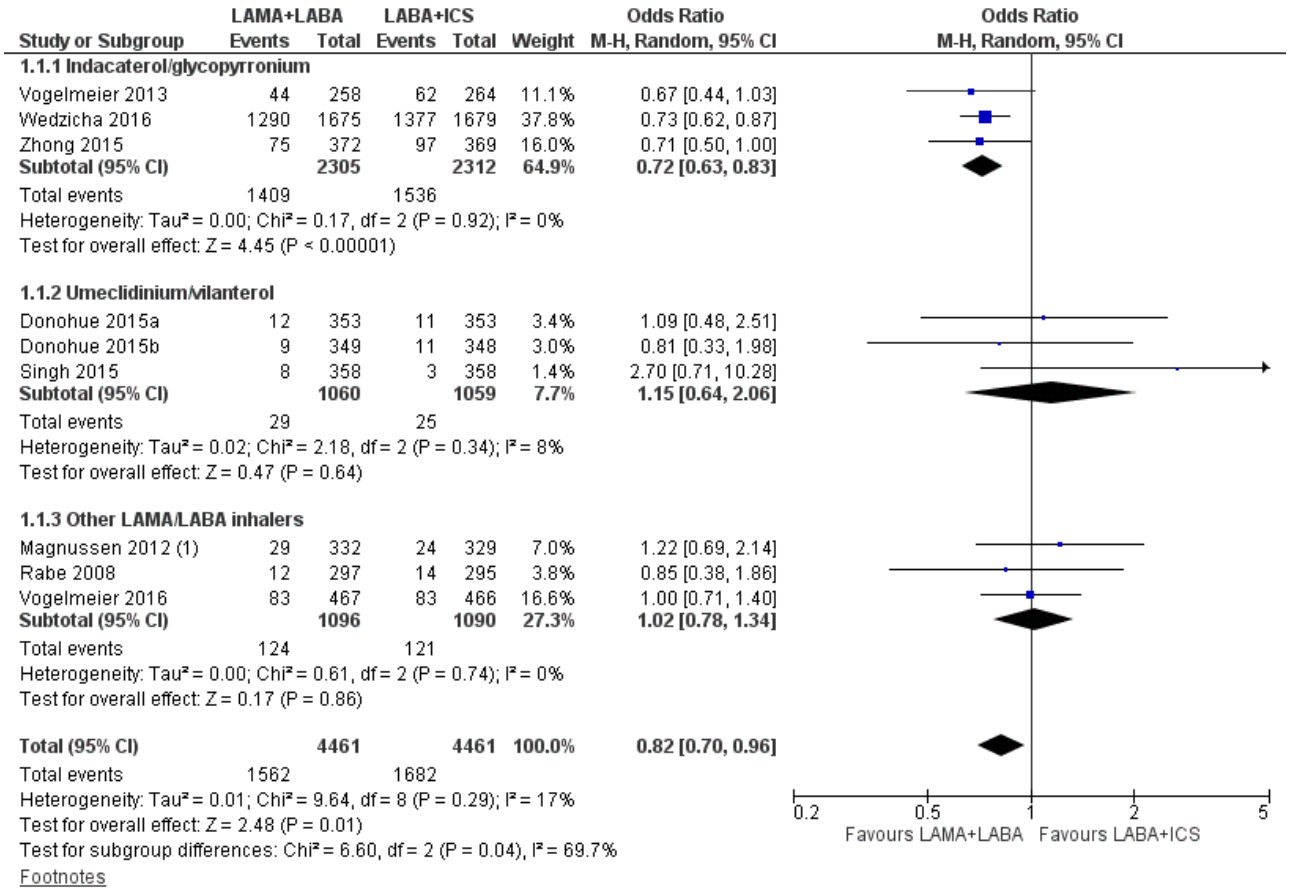
See Summary of findings for the main comparison for the main comparisons.

Primary outcomes

Exacerbations (participants with one or more)

Nine studies with 8932 participants evaluated exacerbations. Based on these nine studies with 12 to 52 weeks of observation, compared to LABA+ICS, there was a significant decrease in the number of people experiencing one or more exacerbations with LAMA+LABA (OR 0.82, 95% CI 0.70 to 0.96; P = 0.01; I^2 = 17%; Figure 3; Analysis 1.1; low quality evidence). In the LAMA+LABA subgroup analysis, participants who were treated with indacaterol/glycopyrronium had fewer exacerbations (OR 0.72, 95% CI 0.63 to 0.83; P < 0.001; I^2 = 0%) compared to participants treated with LABA+ICS. In contrast, LAMA+LABA was not related to reduced risk of exacerbation in umeclidinium/vilanterol and the other LAMA+LABA subgroups.

Figure 3. Forest plot of comparison: 1 Long-acting muscarinic antagonist (LAMA) plus long-acting beta-agonist (LABA) versus LABA plus ICS (inhaled corticosteroid), outcome: 1.1 Exacerbation.

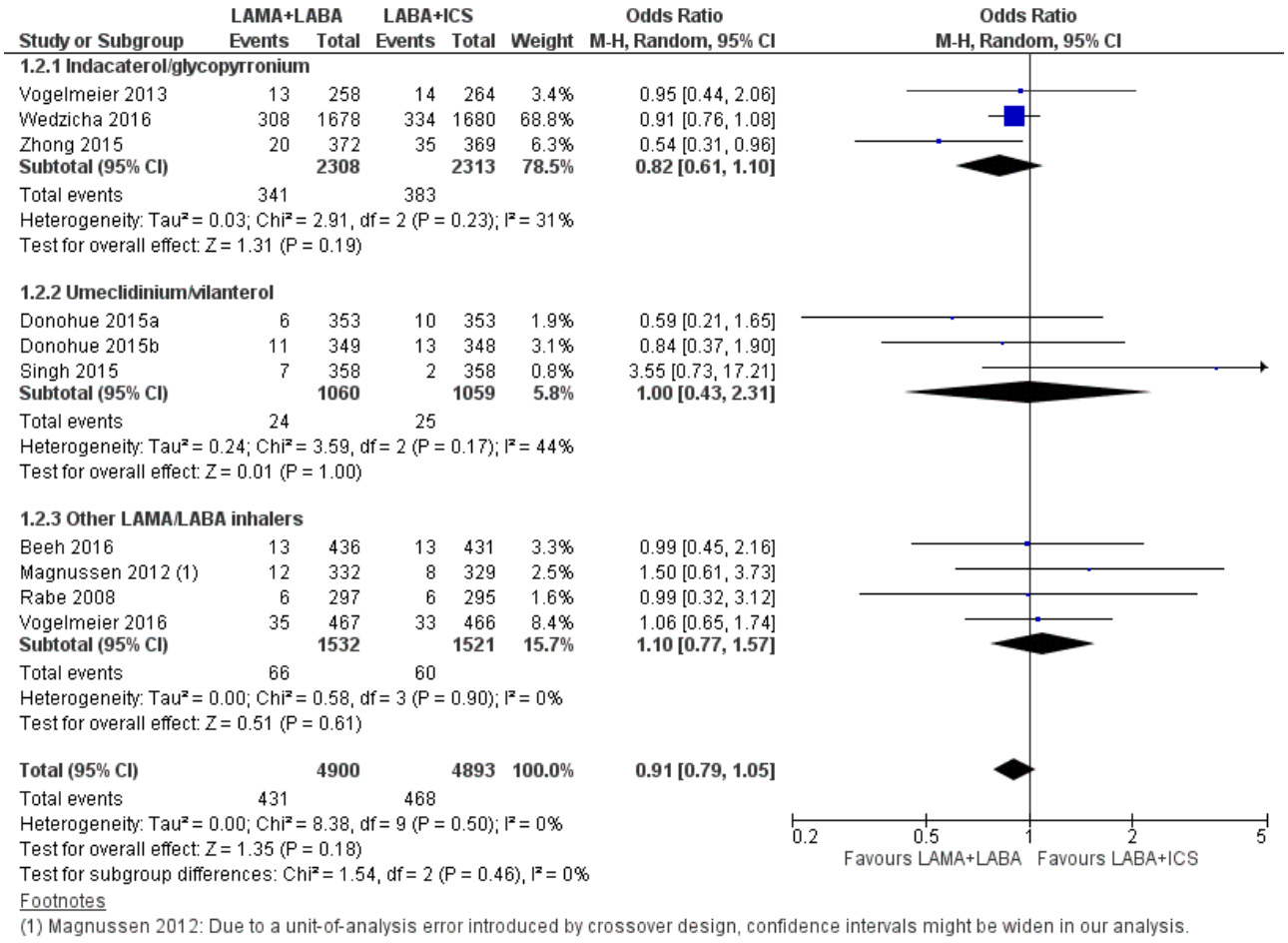


Although we did not plan to evaluate the time to first exacerbation in the protocol, one trial reported some useful data. The largest study evaluated the time to the first exacerbation (Wedzicha 2016). The hazard ratio for time to the first exacerbation was 0.84 (95% CI 0.78 to 0.91; P < 0.001) in favour of LAMA+LABA arm. The annual exacerbation rate was lower in the LAMA+LABA arm than in the LABA+ICS arm (3.59 per year versus 4.03 per year; rate ratio, 0.89, 95% CI 0.83 to 0.96; P = 0.003).

Serious adverse events (participants with one or more)

Eleven studies with 9793 participants evaluated SAEs with 12 to 52 weeks of observation. However, we discarded data from one study from the analysis because there were no SAEs in either arm (Hoshino 2015). Based on the remaining 10 studies, compared to LABA+ICS, LAMA+LABA was associated with a non-significant decrease in SAE (OR 0.91, 95% CI 0.79 to 1.05; P = 0.18; I^2 = 0; Figure 4; Analysis 1.2; moderate quality of evidence). In the LAMA+LABA subgroup analysis, we observed no heterogeneity (I^2 = 0%). Funnel plot did not indicate publication bias (Figure 5).

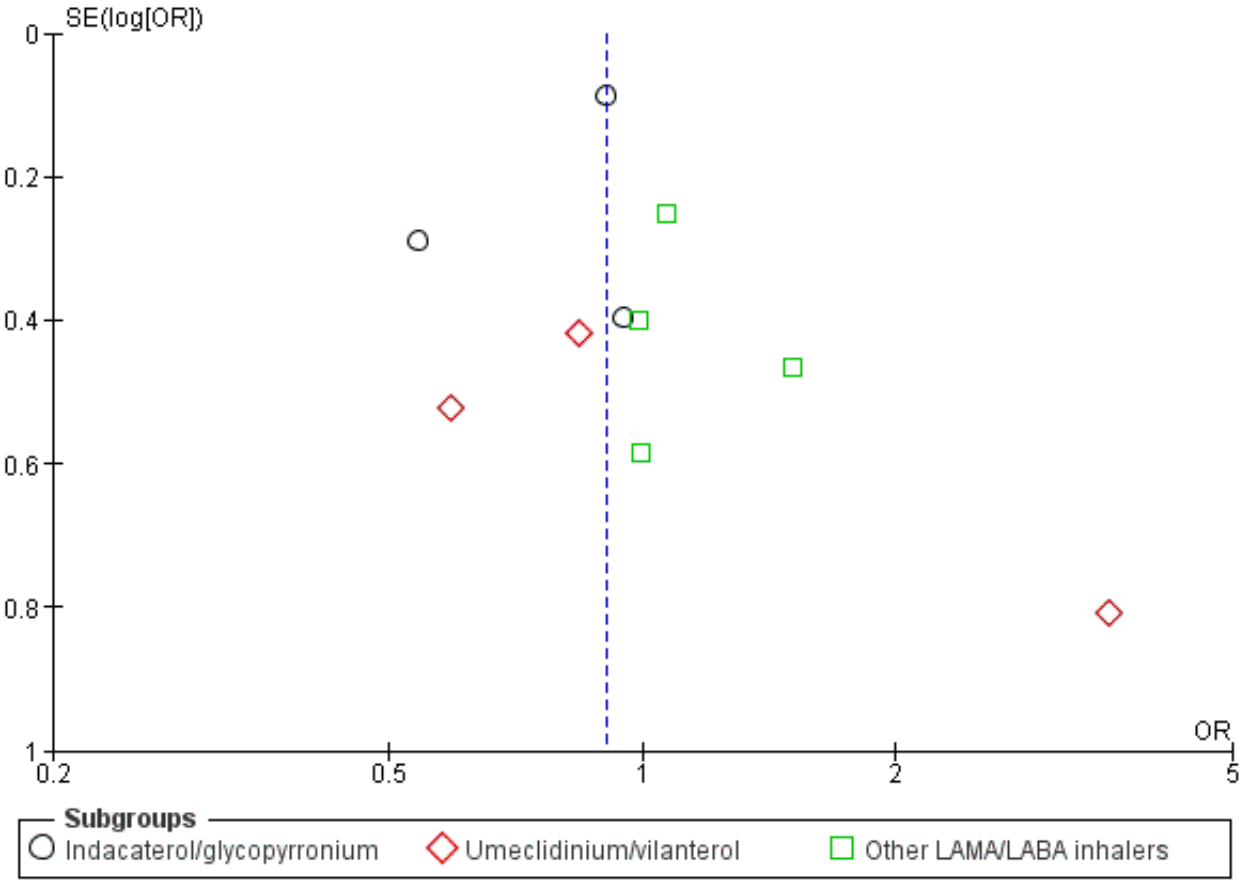
Figure 4. Forest plot of comparison: 1 Long-acting muscarinic antagonist (LAMA) plus long-acting beta-agonist (LABA) versus LABA plus ICS (inhaled corticosteroid), outcome: 1.2 Serious adverse events.



Footnotes

(1) Magnussen 2012: Due to a unit-of-analysis error introduced by crossover design, confidence intervals might be widen in our analysis.

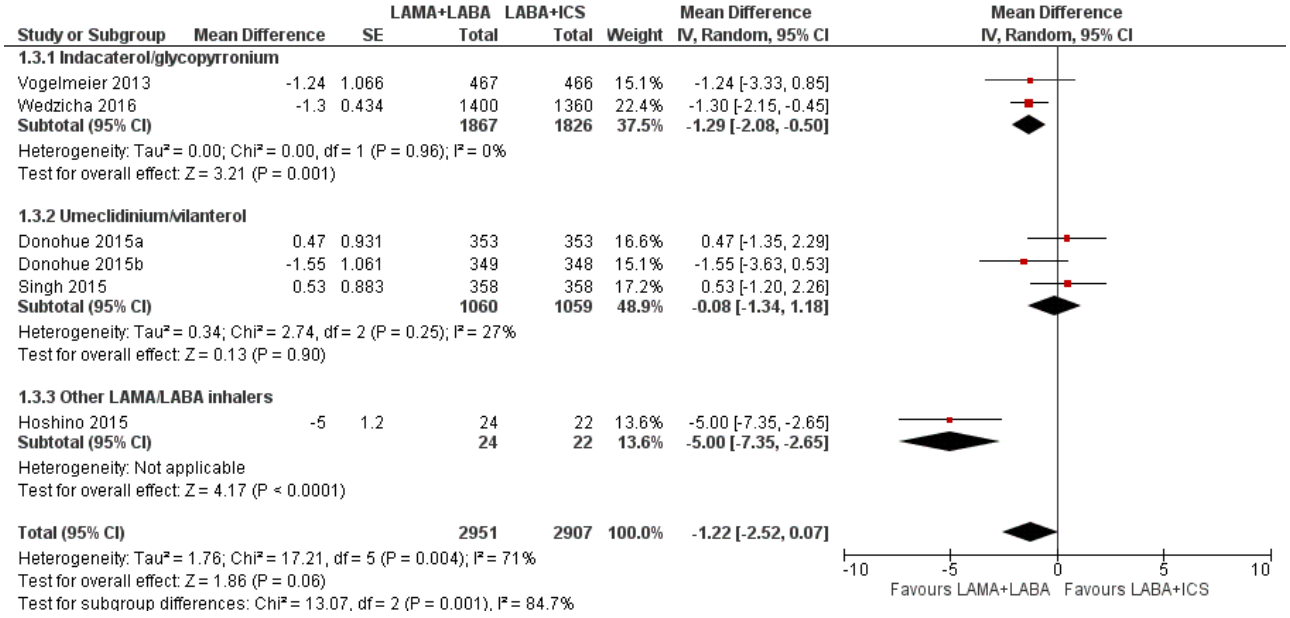
Figure 5. Funnel plot of comparison: 1 Long-acting muscarinic antagonist (LAMA) plus long-acting beta-agonist (LABA) versus LABA plus ICS (inhaled corticosteroid), outcome: 1.2 Serious adverse events.



SGRQ total score change from the baseline (mean difference)

Six studies with 5858 participants assessed SGRQ total score change from the baseline with 12 to 52 weeks of observation. In these six studies, compared to LABA+ICS, there was a non-significant decrease in SGRQ total score change from the baseline with LAMA+LABA, with an MD of -1.22 (95% CI -2.52 to 0.07; P = 0.06; I^2 = 71%; Figure 6; Analysis 1.3, low quality evidence). In the LAMA +LABA subgroup analysis, there was a significant decrease in scores in participants treated with indacaterol/glycopyrronium and 'other LAMA/LABA inhalers' compared to participants treated with LABA +ICS (indacaterol/glycopyrronium: MD -1.29, 95% CI -2.08 to -0.50; P = 0.001; I^2 = 0%; other LAMA/LABA inhalers: MD -5.00, 95% CI -7.35 to -2.65, P < 0.0001).

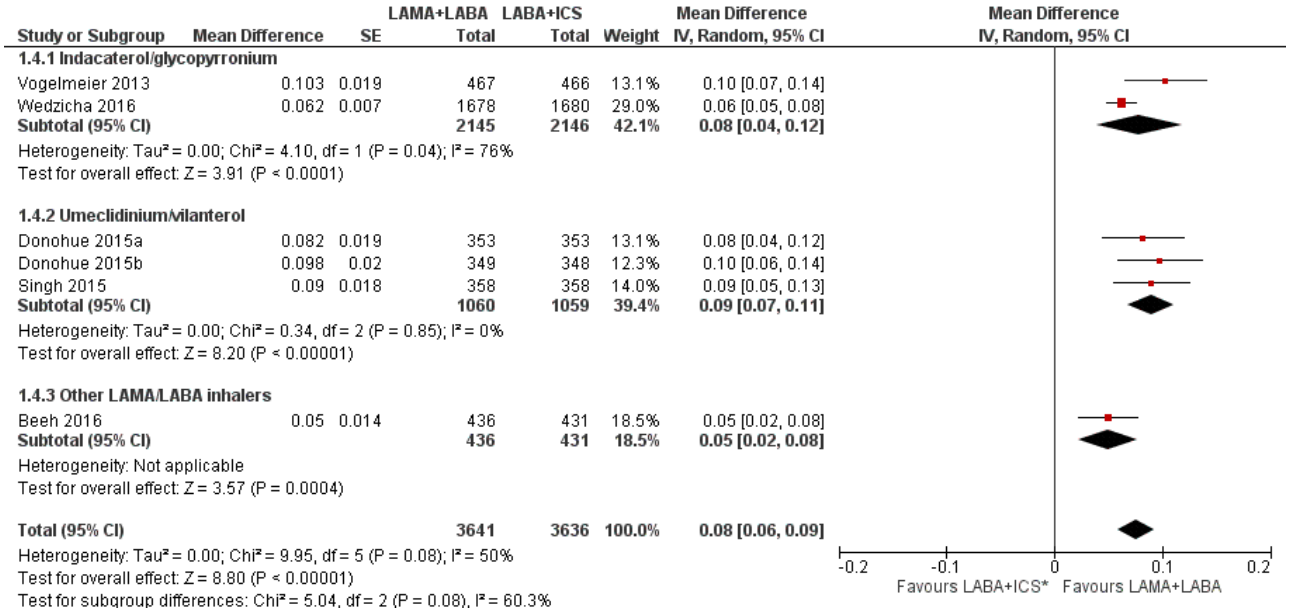
Figure 6. Forest plot of comparison: 1 Long-acting muscarinic antagonist (LAMA) plus long-acting beta-agonist (LABA) versus LABA plus inhaled corticosteroid (ICS), outcome: 1.3 St. George's Respiratory Questionnaire (SGRQ) total score change from the baseline (mean difference).



Trough forced expiratory volume in one second change from the baseline

In total, six studies with 7277 participants reported 12 to 52 weeks of observation for trough FEV_1 change from the baseline. Compared to LABA+ICS, there was a significant increase in trough FEV_1 change from the baseline with LAMA+LABA (MD 0.08 L, 95% CI 0.06 to 0.09; P < 0.0001; I^2 = 50%; Figure 7; Analysis 1.4, moderate quality evidence). This was larger than the minimal clinically important difference of 0.05 L. In the LAMA+LABA subgroup analysis, each LAMA+LABA subgroup was consistently associated with an increase in trough FEV_1 change from the baseline.

Figure 7. Forest plot of comparison: 1 Long-acting muscarinic antagonist (LAMA) plus long-acting beta-agonist (LABA) versus LABA plus ICS (inhaled corticosteroid), outcome: 1.4 Trough forced expiratory volume in one second (FEV_1) change from the baseline.



Secondary outcomes

Pneumonia (participants with one or more occurrences)

Eight studies with 8540 participants evaluated pneumonia with 12 to 52 week of observation. Compared to LABA+ICS, there was a significant reduction in the number of participants experiencing one or more episodes of pneumonia with LAMA+LABA (OR 0.57, 95% CI 0.42 to 0.79; P = 0.0006; I^2 = 0%; Analysis 1.5; low quality evidence). In the LAMA+LABA subgroup analysis, the estimated decrease of pneumonia expressed as pooled OR was within the range of 0.37 to 0.50. An OR of 0.57 almost halved the odds and was considered to be a large decrease in risk. Although it would be possible to calculate an absolute risk reduction, we decided not to, as the absolute effect size is highly dependent on study duration.

All-cause death

Eight studies with 8200 participants evaluated all-cause death with 12 to 52 weeks of observation. There was a similar risk of all-cause death with both treatment regimens (OR 1.01, 95% CI 0.61 to 1.67; P = 0.88; I^2 = 0%; Analysis 1.6; low quality evidence). Results were constant across all LAMA+LABA subgroups.

St. George's Respiratory Questionnaire total score change from the baseline (4 points or greater)

Two studies with 3192 participants evaluated SGRQ total score change from baseline (4 points or greater) with 24 to 52 weeks of observation. Compared to LABA+ICS, there was a more frequent change in SGRQ total score (4 points or greater) with LAMA+LABA (OR 1.25, 95% CI 1.09 to 1.44; P = 0.002; I^2 = 0%; Analysis 1.7; moderate quality evidence).

Hopsitalisations for COPD exacerbations

Outcome not reported.

Sensitivity analysis using a fixed-effect model

The sensitivity analysis using a fixed-effect model suggested a similar pooled OR and a similar pooled MD for all outcomes.

Sensitivity analysis excluding unblinded studies

We found one unblinded study that provided data for SGRQ total score change from the baseline (Hoshino 2015). After excluding this study, five studies evaluated SGRQ total score change from the baseline. Compared to LABA+ICS, there as a non-significant decreasing SGRQ total score change from the baseline with LAMA +LABA (MD -0.70, 95% CI -1.58 to 0.18; P = 0.12; I^2 = 34%) (Analysis 1.8).

DISCUSSION

Summary of main results

We conducted a systematic review and meta-analysis to compare the efficacy and safety of LAMA+LABA and LABA+ICS for people with stable COPD. We found 11 studies consisting of 9839 participants. Most studies were well designed, but may have been at high risk of bias due to commercial sponsorship. Compared to LABA+ICS, LAMA+LABA led to significantly fewer exacerbations, larger trough FEV_1 change from the baseline, a reduced risk of pneumonia, and more frequent SGRQ total score improvement more than minimal clinically important difference. In contrast, we did not detect any significant differences in SAEs, SGRQ total score change from the baseline, and all-cause death (Summary of findings for the main comparison).

Overall completeness and applicability of evidence

Most of the studies included in this analysis recruited people with moderate to severe COPD as categorised according to GOLD guidelines. Therefore, we should be careful when applying the results from our analysis to people with mild and very severe COPD.

Furthermore, many new medications have been developed in the LAMA and LABA classes, for example: glycopyrronium, umeclidinium and aclidinium (LAMA); and indacaterol, vilanterol, and olodaterol (LABA). These medications generally lead to larger improvements of FEV_1 than previous medications, such as tiotropium and salmeterol. Further investigations into the effects of combining these new medications are needed, namely glycopyrronium/indacaterol (QVA149, Ultibro, Novartis), glycopyrrolate/formoterol (PT003, Pearl Therapeutics), aclidinium/formoterol (AstraZeneca), tiotropium/olodaterol (Spiolt, Boehringer Ingelheim), and umeclidinium/vilanterol (Anoro, GSK). Our subgroup analysis suggested that more recent LAMA+LABA combinations, especially indacaterol/glycopyrronium and umeclidinium/vilanterol, may have better therapeutic potency over previously approved LAMA and LABA (Celli 2014; Horita 2015a). This should be evaluated further. In this review, we evaluated combined medications in the same class collectively; however, a meta-analysis assessing each combined medication separately would also be interesting.

Once-daily glycopyrronium 50 µg/indacaterol 110 µg (Ultibro) has been approved for use in many countries including within the EU, Canada, and Japan. Once-daily glycopyrronium 50 µg/indacaterol 110 µg was evaluated in many RCTs along with studies included in the current systematic review. However, twice-daily glycopyrronium 15.6 µg/indacaterol 27.5 µg (Utibron) has been approved in the USA. Therefore, the result from glycopyrronium/indacaterol subgroup analysis should be applied with care to people in the USA.

When all LAMA+LABA were evaluated collectively, LAMA+LABA was related with a reduction in the risk of exacerbation. This analysis was based on our original protocol. However, we observed substantial heterogeneity (I^2 = 69.7%) and there was a reduced risk only in the glycopyrronium/indacaterol subgroup (Figure 3). Thus, it is still not clear whether only glycopyrronium/indacaterol prevented the exacerbation or LAMA+LABA generally prevented the exacerbation.

Long-acting beta-agonist plus inhaled corticosteroid

It is well known that first-line LABA+ICS is frequently prescribed for people with COPD, particularly in the EU and North America (although the updated GOLD 2017 guidance may impact on this). This applies not just to people with COPD in GOLD categories C and D (Drivenes 2014; Price 2014; Suissa 2009; White 2013). However, the effectiveness of LABA+ICS even for these high-risk group of people with COPD is questionable for several reasons. First, although LABA+ICS has been repeatedly evaluated in many trials, few trials assessed the efficacy and safety of single-agent ICS. Thus, the benefits of adding ICS to LABA when treating stable COPD has not yet been sufficiently clarified (Suissa 2009). Second,

there is no plausible explanation for the efficacy of adding ICS over LABA to treat COPD. Unlike asthma caused by eosinophilic inflammation, COPD is mainly caused by neutrophilic inflammation (Suissa 2009). Even though some experts have repeatedly warned of the risks of using ICS for stable COPD (Barnes 2010; Suissa 2009), pharmaceutical promotions (Table 2) and GOLD guidelines (GOLD 2016) have continued to recommend the use of LABA+ICS for stable COPD. According to Nannini's review, LABA+ICS is surely effective compared to placebo (Nannini 2013). Nonetheless, superiority of LABA+ICS over LABA monotherapy was still questionable (Nannini 2012). The superiority of LABA+ICS over LABA monotherapy in preventing exacerbations was observed but was supported by low quality evidence (Nannini 2012). They observed an increased risk of pneumonia with LABA+ICS, which is compatible with our analysis (Nannini 2012).

Limitations

We identified some limitations of the current studies. Although we tried to extract data for exacerbations of any severity, some trials counted only moderate to severe exacerbations. In addition, some outcomes such as exacerbation and adverse effects were dependent on the threshold judged by researchers of the original articles. Concerning a cross-over study by Magnussen and colleagues, CIs might be wider in our analysis due to a unit-of-analysis error introduced by cross-over design (Magnussen 2012). Nevertheless, an error with this would make our results conservative. Additional limitations are lack of long-term follow-up data, the inclusion of category A/B participants for whom LABA+ICS is not currently recommended, and heterogeneous design among studies.

Quality of the evidence

The quality of evidence is summarised in Summary of findings for the main comparison.

Among the 11 included studies, one study with the smallest number of participants did not have any commercial sponsorship (Hoshino 2015). The other 10 studies had a COI involving a sponsoring manufacturer (Table 2). Stakeholders need not be excluded from medical studies. However, their involvement should be properly justified with independency, transparency, democracy, and compassion toward participants (Cluzeau 2012).

Even though most studies were rated as having a risk of bias due to a COI, the included studies were well designed and had a sufficient number of participants. Except for the SGRQ total score change from the baseline, the LAMA+LABA subgroup analysis, fixed-effect-model-based sensitivity analysis, and sensitivity analysis excluding unblinded studies confirmed the robustness of each pooled outcome.

LAMA+LABA therapies were associated with significantly better results for exacerbation rates, trough FEV_1, pneumonia, and SGRQ total score change more than minimal clinically important difference. These findings were also supported by biological plausibility. It is reasonable to assume that the dual bronchodilator therapy had a larger bronchodilating effect than LABA+ICS, which could lead to improved quality of life. In addition, ICS diminishes the local immunity of the airway and increase the risk of pneumonia and viral infection.

We observed a strong heterogeneity in the results for SGRQ total score change from the baseline. This heterogeneity was mainly introduced by an open-label study by Hoshino 2015 (Figure 7). The pooled MD of this outcome was not sufficiently reliable.

Potential biases in the review process

We included two unpublished studies, for which we extracted data from the ClinicalTrial.gov website (Beeh 2016; Vogelmeier 2016). Publication of the full-length articles at a later date could affect these results.

We also found two additional ongoing studies (NCT02497001; NCT02516592). The results from these studies may affect our results when this review is updated.

Concerning a cross-over study by Magnussen and colleagues, CIs might be wider in our analysis (Magnussen 2012).

Agreements and disagreements with other studies or reviews

We conducted a systematic review and meta-analysis on the same subject in 2015 that included eight studies consisting of 4392 participants (Horita 2015b). The study revealed that LAMA+LABA was associated with a larger improvement in trough FEV_1, as well as fewer occurrences of exacerbations and pneumonia. The frequency of SAEs, all-cause death, and SGRQ change from the baseline were not different between treatment arms. The current review generally confirms the results obtained in the previous review. Oba and colleagues published similar meta-analysis (Oba 2016). They concluded that, compared to LABA+ICS, LAMA+LABA was associated with greater improvement of FEV_1, fewer episodes of pneumonia, and similar risk of exacerbation (Oba 2016). The key discrepancy between our analysis and their analysis is effect on exacerbations. Our study has more power as we included the recently published large trial (Wedzicha 2016).

AUTHORS' CONCLUSIONS

Implications for practice

For the treatment of chronic obstructive pulmonary disease (COPD), long-acting muscarinic antagonists plus long-acting beta-agonists (LAMA+LABA) are associated with fewer exacerbations, larger improvement of forced expiratory volume in one second (FEV_1), reduced risk of pneumonia, and more frequent St. George's Respiratory Questionnaire (SGRQ) total score improvement exceeding the minimal clinically important difference (4 points or greater). These data were supported by low or moderate quality of evidence generated from mainly people with moderate to severe COPD in heterogeneous trials with observation period less than one year. The findings of the review support the recently updated Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidance, which favours LAMA+LABA over long-acting beta-agonists plus inhaled corticosteroids (LABA+ICS).

Implications for research

Further research is indicated to clarify the relative positions of LABA +ICS and LAMA+LABA in the COPD treatment guidelines. Trialists should seek to define and report exacerbations consistently and, if possible, provide disaggregated data for participants in different COPD severity groups. Longer-term follow-up data would be

beneficial, especially to identify any impact on serious adverse events or mortality. Results from future or ongoing trials evaluating newly developed bronchodilators are awaited. Meta-analyses that access the data for each combined medication separately are also anticipated.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Beeh 2016

Methods	Design: randomised, double-blind, cross-over, double-dummy, placebo-controlled 4-period 4-arm trial. Countries: 8 countries (mainly EU countries). Site: 29 centres. Study duration: 6 weeks × 4 time periods. Study start: October 2013. Run-in period: unclear.
Participants	Key inclusion criteria: %pred FEV_1 30% to 80%, without recent exacerbation. Numbers of randomised and consequent-treatment completed cases: 229 and 202. Age: 63.6 (SD 7.6) years. Male/female: 148/81. %pred FEV_1: unclear
Interventions	LAMA/LABA: tiotropium/olodaterol (2.5/5 µg) or tiotropium/olodaterol (5/5 µg).

Beeh 2016 *(Continued)*

	LABA/ICS: salmeterol/fluticasone (50/250 µg) twice daily or salmeterol/fluticasone (50/500 µg) twice daily.
Outcomes	Primary outcome: change from baseline FEV_1 AUC (0-12 h) after 6 weeks of treatment. Tiotropium/olodaterol (2.5/5 µg): 0.295 (SE 0.014). Tiotropium/olodaterol (5/5 µg): 0.317 (SE 0.014). Salmeterol/fluticasone (50/250 µg): 0.192 (SE 0.015). Salmeterol/fluticasone (50/500 µg): 0.188 (SE 0.014).
Notes	Registration: NCT01969721. COI: sponsored by Boehringer Ingelheim.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study was double-blinded. Performance bias was not suspected.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Study was double-blinded. Detection bias was not suspected.
Incomplete outcome data (attrition bias) All outcomes	Low risk	202/229 participants completed the study. Considerable attrition bias was not suspected because attrition was < 20%. Attrition was 6.9% with T+O 2.5/5 > T+O 5/5 > F+S 250/50 > F+S 500/50, 17.4% with T+O 5/5 > F+S 500/50 > T+O 2.5/5 > F+S 250/50, 10.0% with F+S 250/50 > T+O 2.5/5 > F+S 500/50 > T+O 5/5, and 11.5% with F+S 500/50 > F+S 250/50 > T+O 5/5 > T+O 2.5/5 Note: This was four-arm crossover study. Each arm used four consecutive treatments. For example, patients in the first arm were treated by T+O2.5/5, then treated by T+O5/5, then treated by F+S 250/50, then F+S 500/50.
Selective reporting (reporting bias)	Low risk	Study was registered and the prespecified outcomes were appropriately described.
Other bias	High risk	COI: sponsored by Boehringer Ingelheim.

Donohue 2015a

Methods	Design: randomised, double-blind, parallel-group, double-dummy, placebo-controlled trial. Countries: 7 countries (US and European countries).

Donohue 2015a *(Continued)*

	Site: 63 centres. Study duration: 12 weeks. Study start: March 2013. Run-in period: 7 to 14 days.
Participants	Key inclusion criteria: %pred FEV_1 30% to 70%, mMRC ≥ 2, no recent exacerbation. Numbers of randomised and completed cases: 707 and 634. Age: 62.8 (SD 9.0) years. Male/female: 497/213. %pred FEV_1: 49.4% (SD 10.9).
Interventions	LAMA/LABA: umeclidinium/vilanterol (62.5/25 µg). LABA/ICS: salmeterol/fluticasone (50/250 µg) twice daily.
Outcomes	Primary endpoint: change from baseline in 24-h weighted-mean serial FEV_1 on day 84. Umeclidinium/vilanterol (62.5/25 µg): 0.165 (SE 0.0130). Salmeterol/fluticasone (50/250 µg) twice daily: 0.091 (SE 0.0131).
Notes	Registration: NCT01817764, GSK-DB2114930. COI: sponsored by GlaxoSmithKline.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central randomisation schedule was generated using a validated computer system (RanAll, GSK).
Allocation concealment (selection bias)	Low risk	Centred randomisation prevented the foreknowledge of intervention assignments by neither researchers nor participants.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study was double-blinded. Performance bias was not suspected.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Study was double-blinded. Detection bias was not suspected.
Incomplete outcome data (attrition bias) All outcomes	Low risk	634/707 participants completed the study. Considerable attrition bias was not suspected because attrition was < 20%. Attrition was 9.6% in umeclidinium/vilanterol arm and 10.8% in salmeterol/fluticasone arms.
Selective reporting (reporting bias)	Low risk	Study was registered and the prespecified outcomes were appropriately described.

Donohue 2015a *(Continued)*

Other bias	High risk	COI: sponsored by GlaxoSmithKline.

Donohue 2015b

Methods	Design: randomised, double-blind, parallel-group, double-dummy, placebo-controlled trial. Countries: 7 countries (US and European countries and Russia). Site: 71 centres. Study duration: 12 weeks. Study start: June 2013. Run-in period: 7 to 14 days.
Participants	Key inclusion criteria: %pred FEV_1 30% to 70%, mMRC ≥ 2, no recent exacerbation. Numbers of randomised and completed cases: 700 and 638. Age: 63.6 (SD 8.9) years. Male/female: 528/169. %pred FEV_1: 49.5% (SD 10.9).
Interventions	LAMA/LABA: umeclidinium/vilanterol (62.5/25 µg). LABA/ICS: salmeterol/fluticasone (50/250 µg) twice daily.
Outcomes	Primary endpoint: Change from baseline in 24-h weighted-mean serial FEV_1 on treatment day 84. Umeclidinium/vilanterol (62.5/25 µg): 0.213 (SE 0.0137). Salmeterol/fluticasone (50/250 µg) twice daily: 0.112 (SE 0.0139).
Notes	Registration: NCT01879410, GSK-DB2114951. COI: sponsored by GlaxoSmithKline.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central randomisation schedule was generated using a validated computer system (RanAll, GSK).
Allocation concealment (selection bias)	Low risk	Centralised randomisation prevented the foreknowledge of intervention assignments by neither researchers nor participants.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study was double-blinded. Performance bias was not suspected.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Study was double-blinded. Detection bias was not suspected.

Donohue 2015b *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	638/700 participants completed the study. Considerable attrition bias was not suspected because attrition was < 20%. Attrition was 6.9% in umeclidinium/vilanterol arm and 10.9% in salmeterol/fluticasone arm.
Selective reporting (reporting bias)	Low risk	Study was registered and the prespecified outcomes were appropriately described.
Other bias	High risk	COI: sponsored by GlaxoSmithKline.

Hoshino 2015

Methods	Design: randomised, parallel-group, open-label trial. Countries: 1 country (Japan). Site: 1 centre. Study duration: 16 weeks. Study start: unclear. Run-in period: 21 days.
Participants	Key inclusion criteria: %pred FEV_1 30% to 80%, without recent exacerbation. Numbers of randomised and completed cases: 46 and 43. Age: LAMA/LABA, 72 years (SD 7); LABA/ICS, 69 years (SD 6). Male/female: 36/7. %pred FEV_1: LAMA/LABA, 61.9% (SD 16.3%); LABA/ICS, 60.8% (SD 16.4%).
Interventions	LAMA/LABA: tiotropium/indacaterol (18/150 µg). LABA/ICS: salmeterol/fluticasone (50/250 µg) twice daily.
Outcomes	Primary outcomes: Effects on airway dimensions. Tiotropium plus indacaterol significantly increased CT-indices including Ai corrected for body surface area (Ai/BSA), and decreased WA/BSA, WA/Ao and T/√BSA compared with Advair($p < 0.05$, respectively).
Notes	Registration: none. COI: none.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Not described.

Hoshino 2015 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Performance bias was suspected due to open-label study design.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Detection bias was suspected due to open-label study design.
Incomplete outcome data (attrition bias) All outcomes	Low risk	43/46 participants completed the study. Considerable attrition bias was not suspected because attrition was < 20%. Attrition was 8.3% in tiotropium/indacaterol arm and 4.5% in salmeterol/fluticasone arm.
Selective reporting (reporting bias)	High risk	Reporting bias could not be denied because this trial was not registered.
Other bias	Low risk	Authors found no risk of other bias.

Magnussen 2012

Methods	Design: randomised, double-blind, cross-over, double-dummy, placebo-controlled trial. Countries: 7 countries. Site: 40 centres. Study duration: 8 weeks twice daily. Study start: September 2007. Run-in period: 15 days.
Participants	Key inclusion criteria: %pred FEV_1 ≤ 65%, without recent exacerbation. Numbers of randomised and completed cases: 344 and 300. Age: 61.0 years (SD 7.6). Male/female: 247/97. %pred FEV_1: 47% (SD 12%).
Interventions	LAMA/LABA: tiotropium/salmeterol (18/50 µg) twice daily. LABA/ICS: salmeterol/fluticasone (50/500 µg) twice daily.
Outcomes	Co-primary endpoints 1: post-dose thoracic gas volume (functional residual capacity) (after 8 weeks). Mean difference -0.087 (SE 0.044). Co-primary endpoints 2: endurance time (after 8 weeks). Mean difference 3.0 (95% CI -9.5 to 27.5).
Notes	Registration: NCT00530842.

Magnussen 2012 *(Continued)*

	COI: sponsored by Boehringer Ingelheim and Pfizer.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centralised randomisations of 4 blocks stratified according to sites.
Allocation concealment (selection bias)	Low risk	Centralised randomisations of 4 blocks stratified according to sites.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study was double-blinded. Performance bias was not suspected.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Study was double-blinded. Detection bias was not suspected.
Incomplete outcome data (attrition bias) All outcomes	Low risk	300/344 participants completed the study. Considerable attrition bias was not suspected because attrition was < 20%. Attrition was 13.4% in tiotropium/salmeterol > salmeterol/fluticasone arm and 12.2% in salmeterol/fluticasone > tiotropium/salmeterol arms.
Selective reporting (reporting bias)	Low risk	Study was registered and the prespecified outcomes were appropriately described. Authors found no risk of reporting bias.
Other bias	High risk	COI: sponsored by Boehringer Ingelheim and Pfizer.

Rabe 2008

Methods	Design: randomised, double-blind, parallel-group, double-dummy, placebo-controlled trial. Countries: 8 countries, mainly EU. Site: multi-centre. Study duration: 6 weeks. Study start: November 2003. Run-in period: 2 to 4 weeks.
Participants	Key inclusion criteria: %pred FEV_1 ≤ 65% without recent exacerbation. Numbers of randomised and completed cases: 605 and unclear. Age: 62 years (SD 9). Male/female: 414/191. %pred FEV_1: 55% (SD 13%).

Rabe 2008 *(Continued)*

Interventions	LAMA/LABA: tiotropium/formoterol (18 µg/24 µg) twice daily. LABA/ICS: salmeterol/fluticasone propionate (50 µg/500 µg) twice daily.
Outcomes	Co-primary endpoints 1: FEV_1 AUC (0 to 12 h) after 6 weeks of treatment. Mean difference 78 mL (95% CI 34 to 122) higher in tiotropium/formoterol arm. Co-primary endpoints 2: peak FEV_1 measured after 6 weeks of treatment. Mean difference 103 mL (95% CI 55 to 150) higher in tiotropium/formoterol arm.
Notes	Registration: NCT00239421. COI: sponsored by Boehringer and Pfizer.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Peak FEV_1 measured after 6 weeks of treatment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study was double-blinded. Performance bias was not suspected.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Study was double-blinded. Detection bias was not suspected.
Incomplete outcome data (attrition bias) All outcomes	Low risk	592/605 participants completed the study. Considerable attrition bias was not suspected because attrition was < 20%. Attrition was 2.3% in tiotropium/formoterol arms and 2.0% in salmeterol/fluticasone propionate arms.
Selective reporting (reporting bias)	Low risk	Study was registered and the prespecified outcomes were appropriately described. Authors found no risk of reporting bias.
Other bias	High risk	COI: sponsored by Boehringer and Pfizer.

Singh 2015

Methods	Design: randomised, double-blind, parallel-group, double-dummy, placebo-controlled trial. Countries: 8 countries (mainly EU). Site: 79 centres. Study duration: 12 weeks.

Singh 2015 *(Continued)*

	Study start: April 2013. Run-in period: 7 to 14 days.
Participants	Key inclusion criteria: %pred FEV_1 30% to 70%, mMRC ≥ 2, without recent exacerbation. Numbers of randomised and completed cases: 717 and 674. Age: 61.6 years (SD 8.0). Male/female: 515/201. %pred FEV_1: 50.6% (SD 10.7%).
Interventions	LAMA/LABA: umeclidinium/vilanterol (62.5/25 µg). LABA/ICS: salmeterol/fluticasone (50/500 µg) twice daily.
Outcomes	Primary outcome: change from baseline in 0 to 24 h weighted mean serial FEV_1 at day 84. Mean difference 0.080 L (95% CI 0.046 to 0.113) (P < 0.001).
Notes	Registration: NCT01822899, GSK-DB2116134. COI: sponsored by GlaxoSmithKline.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Validated computer system (RandAll) was used to generate central randomisation.
Allocation concealment (selection bias)	Low risk	Validated computer system (RandAll) was used to generate central randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study was double-blinded. Performance bias was not suspected.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Study was double-blinded. Detection bias was not suspected.
Incomplete outcome data (attrition bias) All outcomes	Low risk	674/717 participants completed the study. Considerable attrition bias was not suspected because attrition was < 20%. Attrition was 6.7% in umeclidinium/vilanterol arm and 5.0% in salmeterol/fluticasone arm.
Selective reporting (reporting bias)	Low risk	Study was registered and the prespecified outcomes were appropriately described. Authors found no risk of reporting bias.
Other bias	High risk	COI: sponsored by GlaxoSmithKline.

Vogelmeier 2013

Methods	Design: randomised, double-blind, parallel-group, double-dummy, placebo-controlled trial. Countries: 10 countries (mainly EU). Site: 92 centres. Study duration: 26 weeks. Study start: March 2011. Run-in period: 14 days.
Participants	Key inclusion criteria: stage II/III, without recent exacerbation. Numbers of randomised and completed cases: 523 and 432. Age: LAMA/LABA, 63.2 years (SD 8.2); LABA/ICS, 63.4 years (SD 7.7). Male/female: LAMA/LABA, 181/77; LABA/ICS, 189/75. %pred FEV_1: LAMA/LABA, 60.5% (SD 10.5%); LABA/ICS, 60.0% (SD 10.7%).
Interventions	LAMA/LABA: indacaterol/glycopyrronium (110/50 µg). LABA/ICS: salmeterol/fluticasone (50/500 µg) twice daily.
Outcomes	Primary outcome: FEV_1 AUC (0 to 12 h). LAMA/LABA: 1.69 (SE 0.027). LABA/ICS: 1.56 (SE 0.026).
Notes	Registration: NCT01315249. COI: sponsored by Novartis. Study name: ILLUMINATE.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Investigators used an automated, interactive response technology to assign randomisation numbers to participants.
Allocation concealment (selection bias)	Low risk	Investigators used an automated, interactive response technology to assign randomisation numbers to participants.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study was double-blinded. Performance bias was not suspected.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Study was double-blinded. Detection bias was not suspected.
Incomplete outcome data (attrition bias) All outcomes	Low risk	432/523 participants completed the study. Considerable attrition bias was not suspected because attrition was < 20%.

Vogelmeier 2013 *(Continued)*

		Attrition was 17.0% in indacaterol/glycopyrronium arm and 17.0% in salmeterol/fluticasone arms.
Selective reporting (reporting bias)	Low risk	Study was registered and the prespecified outcomes were appropriately described.
Other bias	High risk	COI: sponsored by Novartis.

Vogelmeier 2016

Methods	Design: randomised, double-blind, parallel-group, double-dummy, placebo-controlled trial. Countries: 14 countries (mainly EU). Site: 126 centres. Study duration: 24 weeks. Study start: September 2013. Run-in period: unclear.
Participants	Key inclusion criteria: %pred FEV_1 < 80%, CAT ≥ 10, without recent exacerbation. Numbers of randomised and completed cases: 933 and 788. Age: 63.4 years (SD 7.8). Male/female: 607/326.
Interventions	LAMA/LABA: aclidinium/formoterol (400/12 µg) twice daily. LABA/ICS: salmeterol/fluticasone (50/500 µg) twice daily.
Outcomes	Primary outcome: peak FEV_1 at week 24. LAMA/LABA: 1.655 (SE 0.011). LABA/ICS: 1.562 (SE 0.011).
Notes	Registration: NCT01908140, EudraCT 2013-000116-14. COI: sponsored by AstraZeneca.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study was double-blinded. Performance bias was not suspected.

Vogelmeier 2016 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Study was double-blinded. Detection bias was not suspected.
Incomplete outcome data (attrition bias) All outcomes	Low risk	788/933 participants completed the study. Considerable attrition bias was not suspected because attrition was < 20%. Attrition was 14.1% in aclidinium/formoterol arm and 17.0% in salmeterol/fluticasone arm.
Selective reporting (reporting bias)	Low risk	Study was registered and the prespecified outcomes were appropriately described. Authors found no risk of reporting bias.
Other bias	High risk	COI: sponsored by AstraZeneca.

Wedzicha 2016

Methods	Design: randomised, double-blind, parallel-group, double-dummy, placebo-controlled trial. Countries: 43 countries. Site: 496 centres. Study duration: 52 weeks. Study start: July 2013. Run-in period: 4 weeks.
Participants	Key inclusion criteria: %pred FEV_1 25% to 60%, mMRC ≥ 2, with recent exacerbation. Numbers of randomised and completed cases: 3362 and 2760. Age: 64.6 years (SD 7.8). Male/female: 2557/805. %pred FEV_1: 44.1% (SD 9.5%).
Interventions	LAMA/LABA: indacaterol/glycopyrronium (110/50 µg). LABA/ICS: salmeterol/fluticasone (50/500 µg) twice daily.
Outcomes	Primary outcome: rate of COPD exacerbations per year. LAMA/LABA: 3.59 (95% CI 3.28 to 3.94). LABA/ICS: 4.03 (95% CI 3.68 to 4.41).
Notes	Registration: NCT01782326. COI: sponsored by Novartis. Study name: FLAME.

Risk of bias

Wedzicha 2016 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised via Interactive Response Technology to 1 of the treatment arms.
Allocation concealment (selection bias)	Low risk	Participants were randomised via Interactive Response Technology to 1 of the treatment arms.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study was double-blinded. Performance bias was not suspected.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Study was double-blinded. Detection bias was not suspected.
Incomplete outcome data (attrition bias) All outcomes	Low risk	2760/3362 participants completed the study. Considerable attrition bias was not suspected because attrition was < 20%. Attrition was 16.6% in indacaterol/glycopyrronium arm and 19.0% in salmeterol/fluticasone arm.
Selective reporting (reporting bias)	Low risk	Study was registered and the prespecified outcomes were appropriately described.
Other bias	High risk	COI: sponsored by Novartis.

Zhong 2015

Methods	Design: randomised, double-blind, parallel-group, double-dummy, placebo-controlled trial. Countries: 4 countries (recruited mainly in China). Site: 56 centres. Study duration: 26 weeks. Study start: November 2012. Run-in period: 14 days.
Participants	Key inclusion criteria: stage II/III mMRC ≥ 2, without recent exacerbation. Numbers of randomised and completed cases: 744 and 676. Age: LAMA/LABA 64.8 years (SD 7.8); LABA/ICS 65.3 years (SD 7.9). Male/female: 672/69. %pred FEV_1: LAMA/LABA 51.6% (SD 12.8%), LABA/ICS 52.0% (SD 12.9%).
Interventions	LAMA/LABA: indacaterol/glycopyrronium (110/50 µg). LABA/ICS: salmeterol/fluticasone (50/500 µg) twice daily.
Outcomes	Primary outcome: trough FEV_1 following 26 weeks of treatment to demonstrate the non-inferiority of indacaterol/glycopyrronium to salmeterol/fluticasone.

Zhong 2015 *(Continued)*

	LAMA/LABA: 1.248 L (SE 0.0173). LABA/ICS: 1.176 L (SE 0.0172).
Notes	Registration: NCT01709903. COI: sponsored by Novartis. Study name: LANTERN.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised via Interactive Response Technology to 1 of the treatment arms.
Allocation concealment (selection bias)	Low risk	Participants were randomised via Interactive Response Technology to 1 of the treatment arms.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study was double-blinded. Performance bias was not suspected.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Study was double-blinded. Detection bias was not suspected.
Incomplete outcome data (attrition bias) All outcomes	Low risk	676/744 participants completed the study. Considerable attrition bias was not suspected because attrition was < 20%. Attrition was 7.8% in indacaterol/glycopyrronium arm and 10.4% in salmeterol/fluticasone arm.
Selective reporting (reporting bias)	Low risk	Study was registered and the prespecified outcomes were appropriately described.
Other bias	High risk	COI: sponsored by Novartis.

%pred FEV_1: % predicted forced expiratory volume in one second; AUC: area under curve; CAT: chronic obstructive pulmonary disease assessment test; CI: confidence interval; COI: conflicts of interest; COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in one second; h: hour; ICS: inhaled corticosteroid; LABA: long-acting beta-agonist; LAMA: long-acting muscarinic antagonist; mMRC: modified Medical Research Council dyspnoea scale; SD: standard deviation; SE: standard error.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bruhn 2003	Not comparing LAMA+LABA vs LABA+ICS. (Comparing LABA+ICS (salmeterol/fluticasone propionate) vs LABA (salmeterol) vs ICS (fluticasone propionate).)
Calverley 2007	Not comparing LAMA+LABA vs LABA+ICS. (Comparing LABA+ICS (salmeterol/fluticasone propionate) vs LAMA (tiotropium).)

Study	Reason for exclusion
Knobil 2004a	Not comparing LAMA+LABA vs LABA+ICS. (Comparing LABA+ICS (salmeterol/fluticasone propionate) vs ipratropium/albuterol. Ipratropium is not LAMA.)
Knobil 2004b	Not comparing LAMA+LABA vs LABA+ICS. (Comparing LABA+ICS (salmeterol/fluticasone propionate) vs ipratropium/albuterol. Ipratropium is not LAMA.)
NCT00120978	Not comparing LAMA+LABA vs LABA+ICS. (Comparing LABA+ICS (salmeterol/fluticasone propionate) vs ICS (fluticasone propionate).)
Price 2014	Cost-effectiveness analysis using previously published data. (Cost-effectiveness of the LABA/LAMA (indacaterol/glycopyrronium.)
Sciurba 2004	Not comparing LAMA+LABA vs LABA+ICS. (Comparing LABA+ICS (salmeterol/fluticasone propionate) vs ipratropium/albuterol. Ipratropium is not LAMA.)

ICS: inhaled corticosteroids; LABA: long-acting beta-agonist; LAMA: long-acting muscarinic antagonist.

Characteristics of ongoing studies *[ordered by study ID]*

NCT02497001

Trial name or title	A Randomized, Double-blind, Parallel-Group, 24-Week, Chronic-Dosing, Multi-center Study to Assess the Efficacy and Safety of PT010, PT003, and PT009 Compared with Symbicort® Turbuhaler® (Kronos).
Methods	Design: randomised, double-blind, parallel-group, double-dummy, placebo-controlled trial. Countries: 2 countries (US and Canada). Site: 94 centres. Study duration: 24 weeks. Study start: July 2015. Run-in period: unclear.
Participants	Key inclusion criteria: %pred FEV_1 < 80%. Estimated enrolment: 1800.
Interventions	4-arm trial. Budesonide + glycopyrronium + formoterol fumarate inhalation aerosol (MDI, 320/14.4/9.6 µg, PT010). Glycopyrronium + formoterol fumarate inhalation aerosol (MDI, 14.4/9.6 µg, PT003). Budesonide + formoterol fumarate inhalation aerosol (MDI, 320/9.6 µg, PT009). Budesonide + formoterol fumarate inhalation powder (Turbuhaler)
Outcomes	Change from baseline in morning pre-dose trough FEV_1 after follow-up.
Starting date	July 2015.
Contact information	Raul Lima, 862-777-8094.
Notes	Completion date: March 2017. Registration: NCT02497001.

NCT02497001 *(Continued)*

	COI: Sponsored by Pearl Therapeutics, Inc.

NCT02516592

Trial name or title	Assessment of Switching from Salmeterol/Fluticasone to Indacaterol/Glycopyrronium in a Symptomatic COPD Patient Cohort (FLASH).
Methods	Design: randomised, double-blind, parallel-group, double-dummy, placebo-controlled trial. Countries: 11 countries. Site: 55 centres. Study duration: 12 weeks. Study start: October 2015. Run-in period: unclear.
Participants	%pred FEV_1 30% to 80%, CAT ≥ 10, without recent exacerbation. Estimated enrolment: 492.
Interventions	Will investigate whether switching people with symptomatic COPD from a fixed-dose combination of salmeterol/fluticasone 50/500 µg twice daily to a fixed-dose combination of indacaterol/glycopyrronium 110/50 µg once daily. LAMA/LABA: switching from salmeterol/fluticasone (50/500 µg) twice daily to indacaterol/glycopyrronium (110/50 µg). LABA/ICS: continuing salmeterol/fluticasone (50/500 µg) twice daily.
Outcomes	Change from baseline in trough pre-dose FEV_1 in both arms after follow-up.
Starting date	October 2015.
Contact information	Novartis Pharmaceuticals +41613241111.
Notes	Completion date: August 2016. Registration: NCT02516592. COI: Sponsored by Novartis.

%pred FEV_1: % predicted forced expiratory volume in one second; CAT: chronic obstructive pulmonary disease assessment test; COI: conflicts of interest; COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in one second; ICS: inhaled corticosteroids; LABA: long-acting beta-agonist; LAMA: long-acting muscarinic antagonist; MDI: metered dose inhaler.

DATA AND ANALYSES

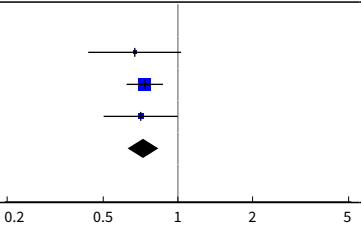
Comparison 1. Long-acting muscarinic antagonist (LAMA) plus long-acting beta-agonist (LABA) versus LABA plus inhaled corticosteroid (ICS)

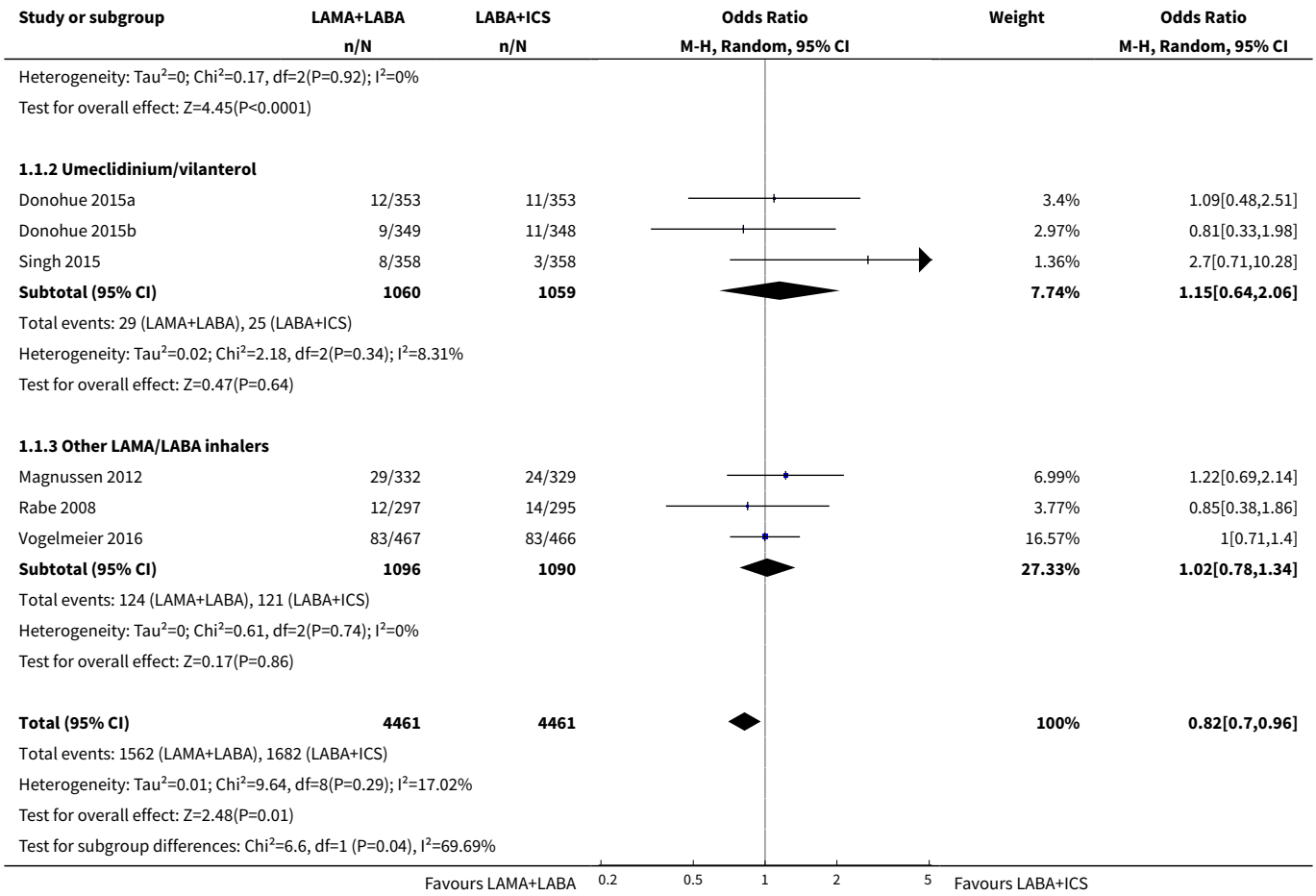
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Exacerbation	9	8922	Odds Ratio (M-H, Random, 95% CI)	0.82 [0.70, 0.96]
1.1 Indacaterol/glycopyrronium	3	4617	Odds Ratio (M-H, Random, 95% CI)	0.72 [0.63, 0.83]
1.2 Umeclidinium/vilanterol	3	2119	Odds Ratio (M-H, Random, 95% CI)	1.15 [0.64, 2.06]
1.3 Other LAMA/LABA inhalers	3	2186	Odds Ratio (M-H, Random, 95% CI)	1.02 [0.78, 1.34]
2 Serious adverse effect	10	9793	Odds Ratio (M-H, Random, 95% CI)	0.91 [0.79, 1.05]
2.1 Indacaterol/glycopyrronium	3	4621	Odds Ratio (M-H, Random, 95% CI)	0.82 [0.61, 1.10]
2.2 Umeclidinium/vilanterol	3	2119	Odds Ratio (M-H, Random, 95% CI)	1.00 [0.43, 2.31]
2.3 Other LAMA/LABA inhalers	4	3053	Odds Ratio (M-H, Random, 95% CI)	1.10 [0.77, 1.57]
3 St. George's Respiratory Questionnaire (SGRQ) total score change from the baseline (mean difference)	6	5858	Mean Difference (Random, 95% CI)	-1.22 [-2.52, 0.07]
3.1 Indacaterol/glycopyrronium	2	3693	Mean Difference (Random, 95% CI)	-1.29 [-2.08, -0.50]
3.2 Umeclidinium/vilanterol	3	2119	Mean Difference (Random, 95% CI)	-0.08 [-1.34, 1.18]
3.3 Other LAMA/LABA inhalers	1	46	Mean Difference (Random, 95% CI)	-5.0 [-7.35, -2.65]
4 Trough forced expiratory volume in 1 second (FEV_1) change from the baseline	6	7277	Mean Difference (Random, 95% CI)	0.08 [0.06, 0.09]
4.1 Indacaterol/glycopyrronium	2	4291	Mean Difference (Random, 95% CI)	0.08 [0.04, 0.12]
4.2 Umeclidinium/vilanterol	3	2119	Mean Difference (Random, 95% CI)	0.09 [0.07, 0.11]
4.3 Other LAMA/LABA inhalers	1	867	Mean Difference (Random, 95% CI)	0.05 [0.02, 0.08]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 Pneumonia	8	8540	Odds Ratio (M-H, Random, 95% CI)	0.57 [0.42, 0.79]
5.1 Indacaterol/glycopyrronium	3	4621	Odds Ratio (M-H, Random, 95% CI)	0.50 [0.25, 1.00]
5.2 Umeclidinium/vilanterol	3	2119	Odds Ratio (M-H, Random, 95% CI)	0.37 [0.11, 1.29]
5.3 Other LAMA/LABA inhalers	2	1800	Odds Ratio (M-H, Random, 95% CI)	0.40 [0.09, 1.76]
6 All-cause death	8	8200	Odds Ratio (M-H, Random, 95% CI)	1.01 [0.61, 1.67]
6.1 Indacaterol/glycopyrronium	3	4621	Odds Ratio (M-H, Random, 95% CI)	1.02 [0.59, 1.78]
6.2 Umeclidinium/vilanterol	3	2120	Odds Ratio (M-H, Random, 95% CI)	0.78 [0.19, 3.18]
6.3 Other LAMA/LABA inhalers	2	1459	Odds Ratio (M-H, Random, 95% CI)	1.59 [0.20, 12.96]
7 SGRQ total score improvement from the baseline (≥ 4 units)	2	3192	Odds Ratio (M-H, Random, 95% CI)	1.25 [1.09, 1.44]
7.1 Indacaterol/glycopyrronium	2	3192	Odds Ratio (M-H, Random, 95% CI)	1.25 [1.09, 1.44]
8 Total SGRQ change from the baseline (excluding unblinded studies)	5	6360	Mean Difference (Random, 95% CI)	-0.70 [-1.58, 0.18]
8.1 Indacaterol/glycopyrronium	2	4241	Mean Difference (Random, 95% CI)	-1.29 [-2.08, -0.50]
8.2 Umeclidinium/vilanterol	3	2119	Mean Difference (Random, 95% CI)	-0.08 [-1.34, 1.18]

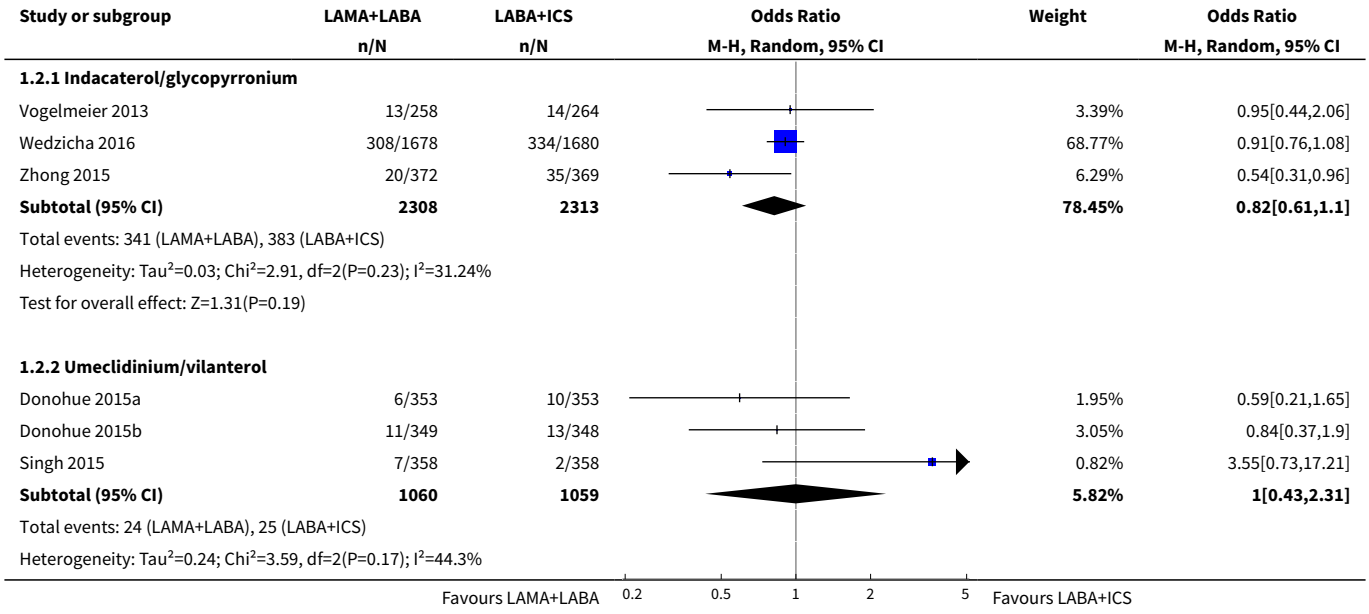
Analysis 1.1. Comparison 1 Long-acting muscarinic antagonist (LAMA) plus long-acting beta-agonist (LABA) versus LABA plus inhaled corticosteroid (ICS), Outcome 1 Exacerbation.

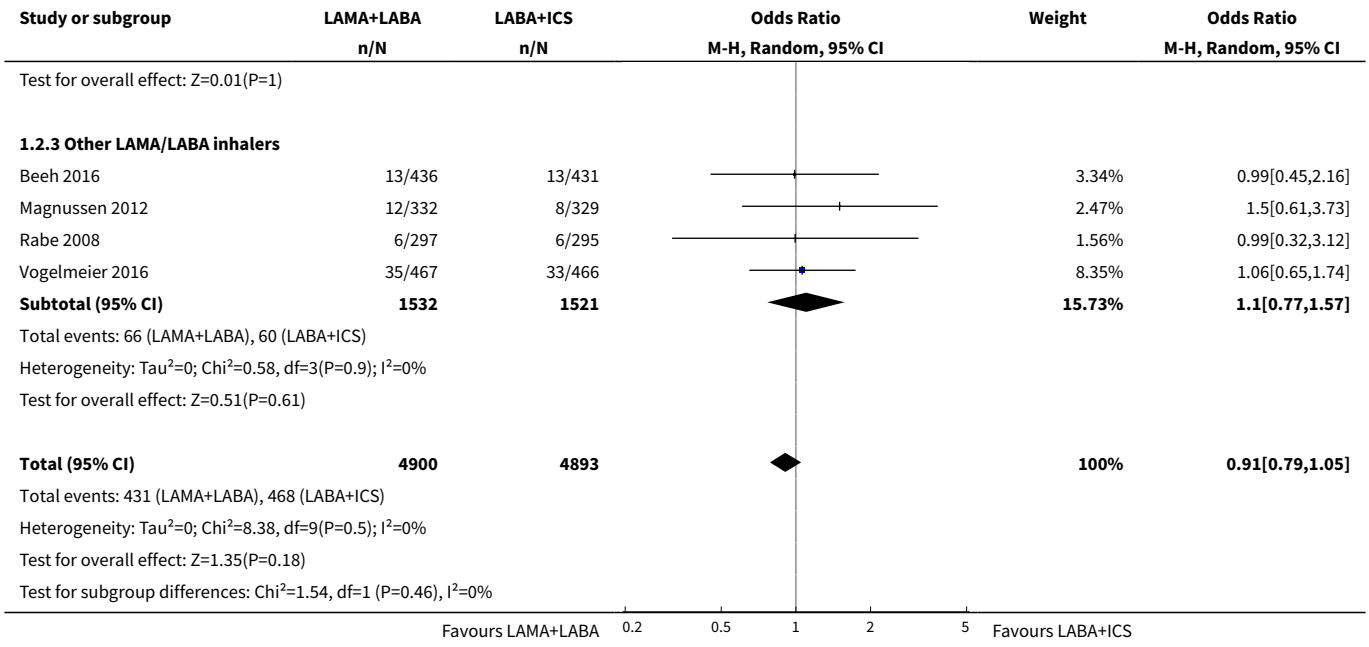
Study or subgroup	LAMA+LABA n/N	LABA+ICS n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
1.1.1 Indacaterol/glycopyrronium					
Vogelmeier 2013	44/258	62/264		11.11%	0.67[0.44,1.03]
Wedzicha 2016	1290/1675	1377/1679		37.82%	0.73[0.62,0.87]
Zhong 2015	75/372	97/369		16.01%	0.71[0.5,1]
Subtotal (95% CI)	**2305**	**2312**		**64.94%**	**0.72[0.63,0.83]**
Total events: 1409 (LAMA+LABA), 1536 (LABA+ICS)					



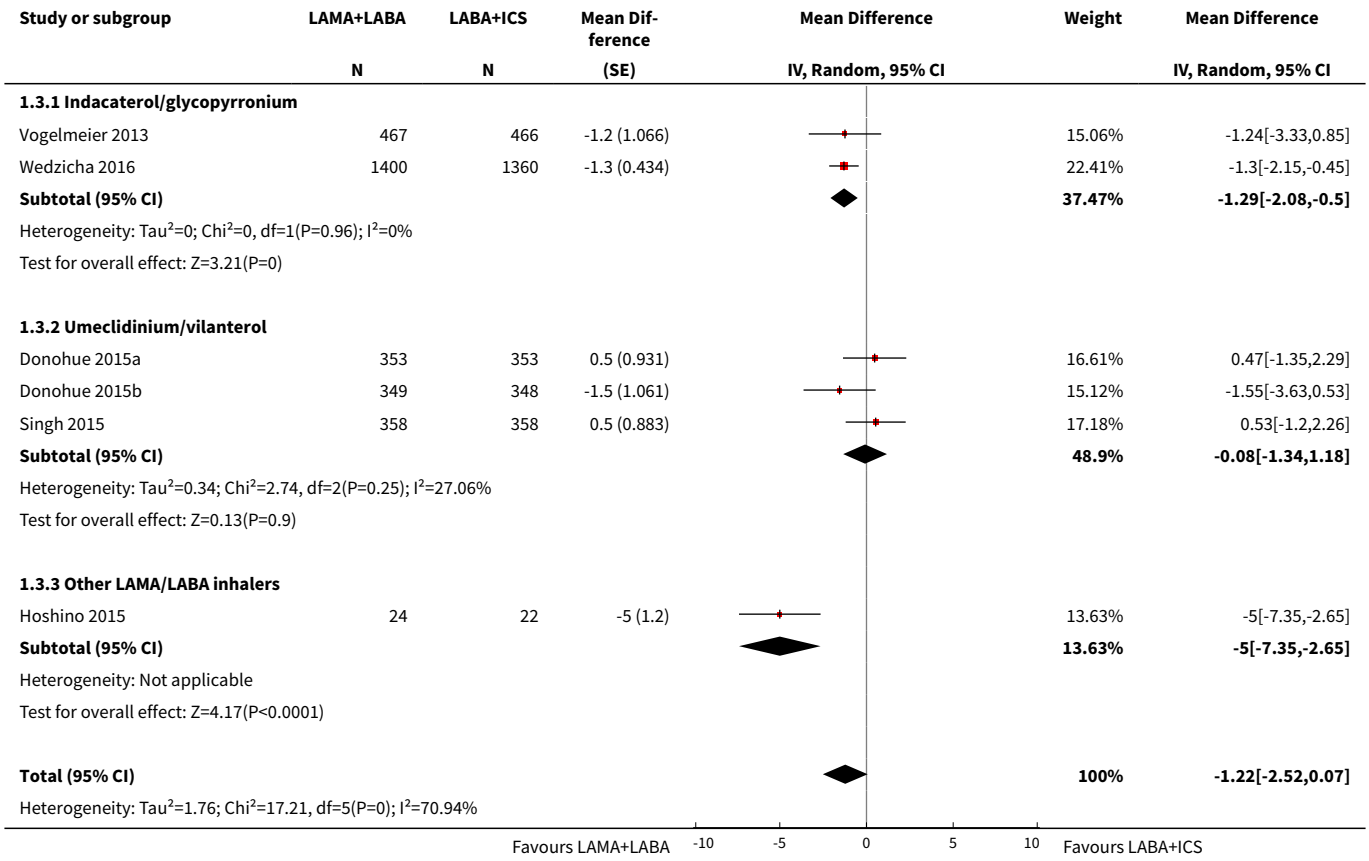


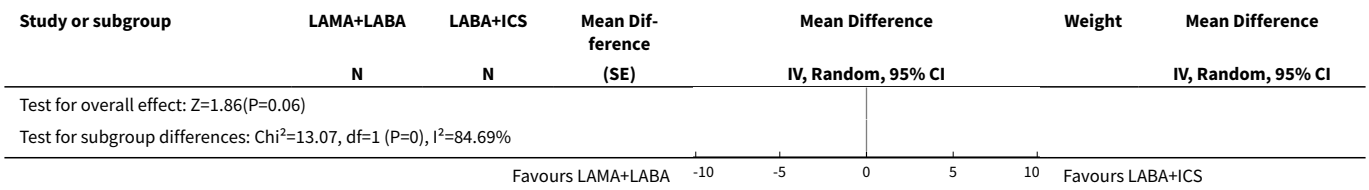
Analysis 1.2. Comparison 1 Long-acting muscarinic antagonist (LAMA) plus long-acting beta-agonist (LABA) versus LABA plus inhaled corticosteroid (ICS), Outcome 2 Serious adverse effect.



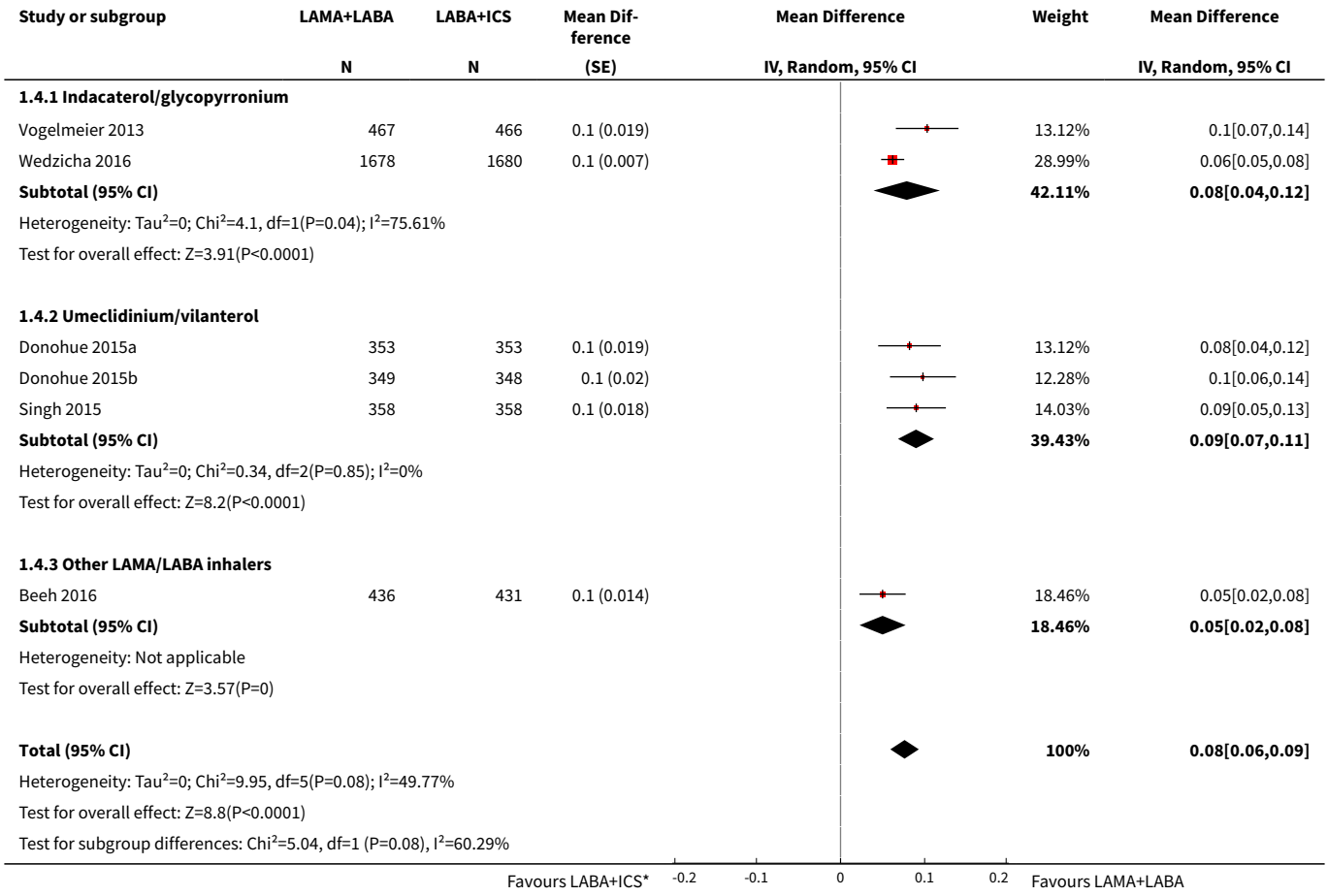


Analysis 1.3. Comparison 1 Long-acting muscarinic antagonist (LAMA) plus long-acting beta-agonist (LABA) versus LABA plus inhaled corticosteroid (ICS), Outcome 3 St. George's Respiratory Questionnaire (SGRQ) total score change from the baseline (mean difference).

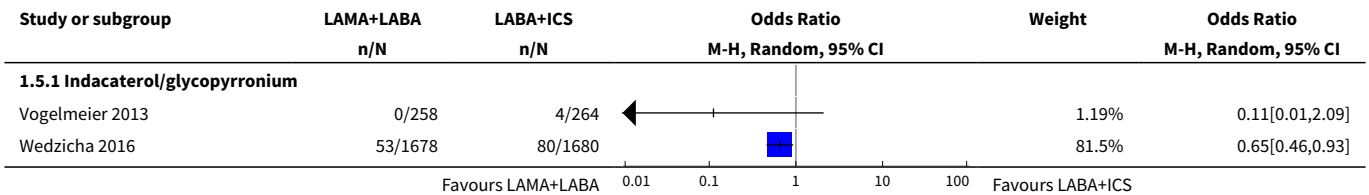


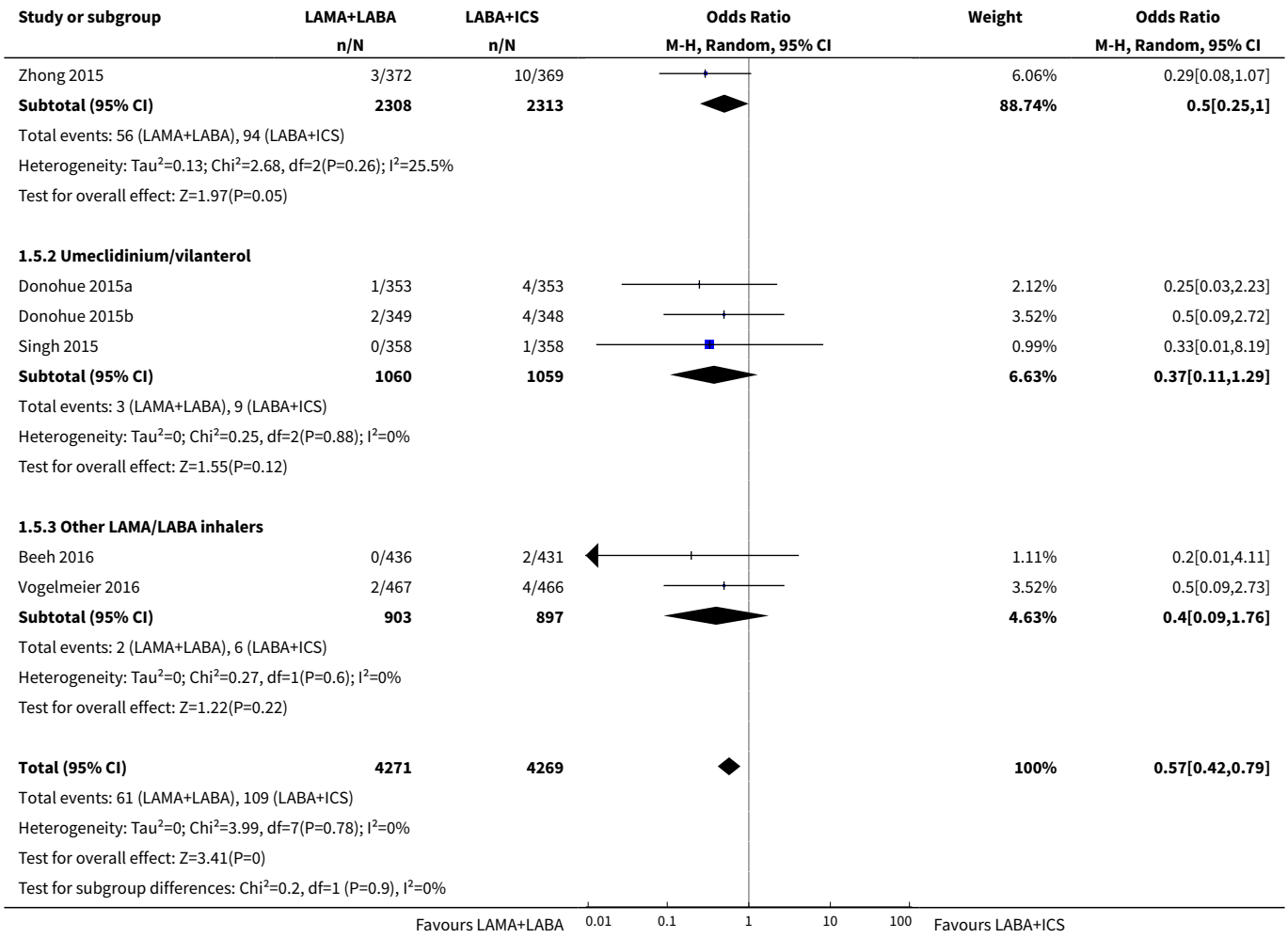


Analysis 1.4. Comparison 1 Long-acting muscarinic antagonist (LAMA) plus long-acting beta-agonist (LABA) versus LABA plus inhaled corticosteroid (ICS), Outcome 4 Trough forced expiratory volume in 1 second (FEV_1) change from the baseline.

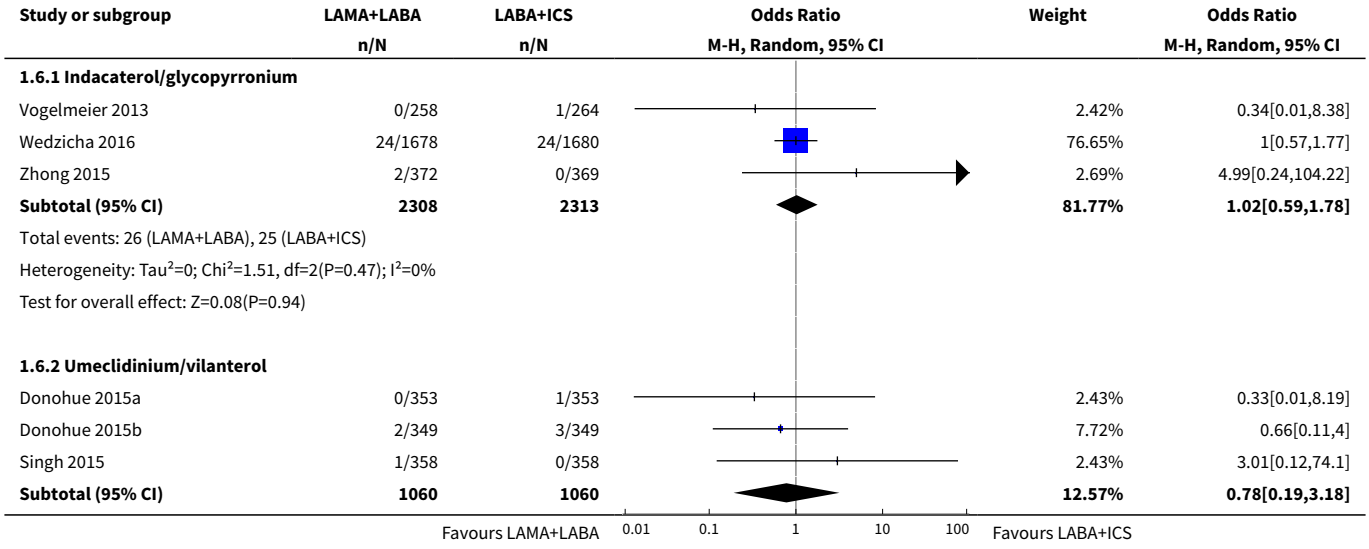


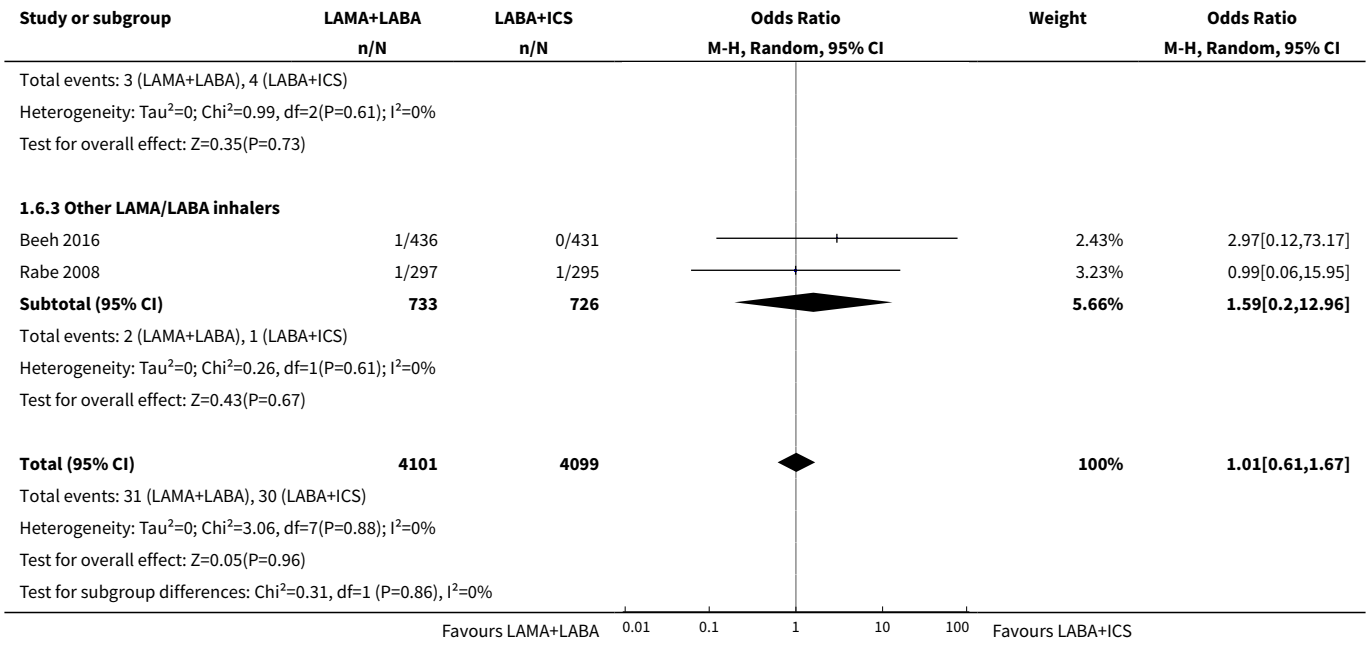
Analysis 1.5. Comparison 1 Long-acting muscarinic antagonist (LAMA) plus long-acting beta-agonist (LABA) versus LABA plus inhaled corticosteroid (ICS), Outcome 5 Pneumonia.



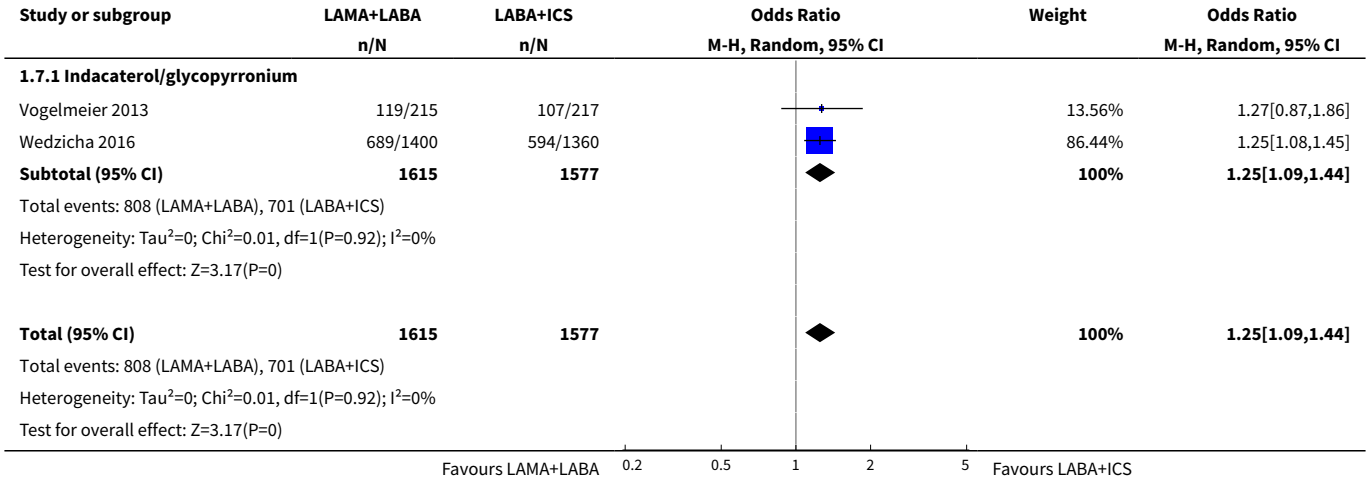


Analysis 1.6. Comparison 1 Long-acting muscarinic antagonist (LAMA) plus long-acting beta-agonist (LABA) versus LABA plus inhaled corticosteroid (ICS), Outcome 6 All-cause death.

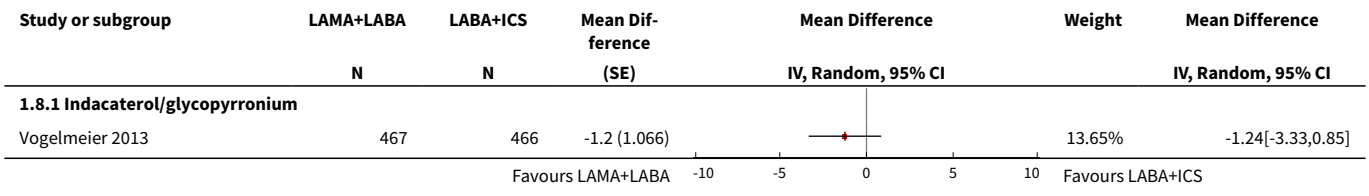


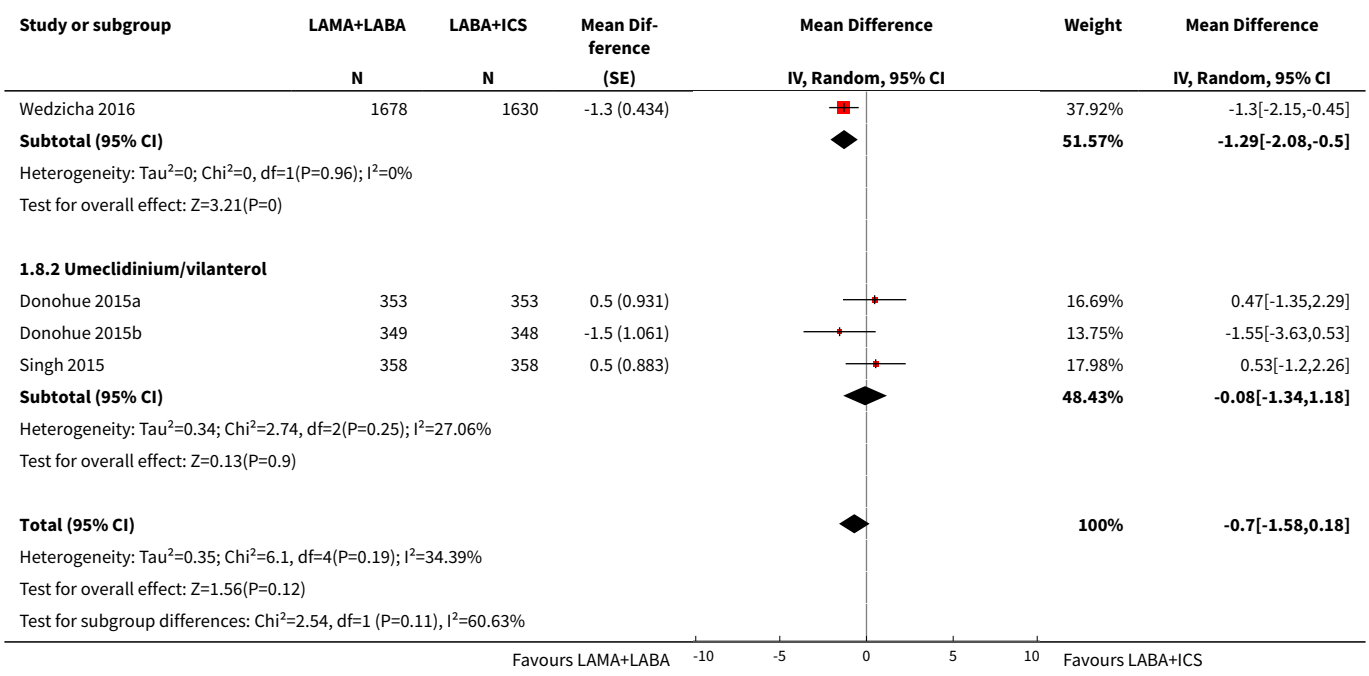


Analysis 1.7. Comparison 1 Long-acting muscarinic antagonist (LAMA) plus long-acting beta-agonist (LABA) versus LABA plus inhaled corticosteroid (ICS), Outcome 7 SGRQ total score improvement from the baseline (≥ 4 units).



Analysis 1.8. Comparison 1 Long-acting muscarinic antagonist (LAMA) plus long-acting beta-agonist (LABA) versus LABA plus inhaled corticosteroid (ICS), Outcome 8 Total SGRQ change from the baseline (excluding unblinded studies).





ADDITIONAL TABLES

Table 1. Summary of characteristics of included studies

Study	LAMA+LABA	LABA+ICS	Key inclusion criteria	Follow-up duration (weeks)	Mean/median age (years)	Number randomised
Beeh 2016	Tiotropium/olodaterol (2.5/5 µg) or tiotropium/olodaterol (5/5 µg)	Salmeterol/fluticasone (50/250 µg) twice daily or salmeterol/fluticasone (50/500 µg) twice daily.	%pred FEV_1 30% to 80% Ex(-)	6 × 4 time periods (cross-over)	64	229
Donohue 2015a	Umeclidinium/vilanterol (62.5/25 µg)	Salmeterol/fluticasone (50/250 µg) twice daily	%pred FEV_1 30% to 70%, mMRC ≥ 2, Ex(-)	12	63	707
Donohue 2015b	Umeclidinium/vilanterol (62.5/25 µg)	Salmeterol/fluticasone (50/250 µg) twice daily	%pred FEV_1 30% to 70%, mMRC ≥ 2, Ex(-)	12	64	700
Hoshino 2015	Tiotropium/indacaterol (18/150 µg)	Salmeterol/fluticasone (50/250 µg) twice daily	%pred FEV_1 30% to 80%, Ex(-)	16	71	46
Magnussen 2012	Tiotropium/salmeterol (18/50 µg) twice daily	Salmeterol/fluticasone (50/500 µg) twice daily	%pred FEV_1 ≤ 65%, Ex(-)	8 x 2 time periods (cross-over)	61	344
Rabe 2008	Tiotropium/formoterol (18/24 µg) twice daily	Salmeterol/fluticasone (50/500 µg) twice daily	%pred FEV_1 ≤ 65%, Ex(-)	6	62	605

Table 1. Summary of characteristics of included studies *(Continued)*

Singh 2015	Umeclidinium/vilanterol (62.5/25 µg)	Salmeterol/fluticasone (50/500 µg) twice daily	%pred FEV_1 30% to 70%, mMRC ≥ 2, Ex(-)	12	62	717
Vogelmeier 2013	Indacaterol/glycopyrronium bromide (110/50 µg)	Salmeterol/fluticasone (50/500 µg) twice daily	Stage II/III, Ex(-)	26	63	523
Vogelmeier 2016	Aclidinium/formoterol (400/12 µg) twice daily	Salmeterol/fluticasone (50/500 µg) twice daily	%pred FEV_1 < 80%, CAT ≥ 10, Ex(-)	24	63	933
Wedzicha 2016	Indacaterol/glycopyrronium bromide (110/50 µg)	Salmeterol/fluticasone (50/500 µg) twice daily	%pred FEV_1 25% to 60%, mMRC ≥ 2, Ex(+)	52	65	3362
Zhong 2015	Indacaterol/glycopyrronium bromide (110/50 µg)	Salmeterol/fluticasone (50/500 µg) twice daily	Stage II/III, mMRC ≥ 2, Ex(-)	26	65	744

%pred FEV_1: % predicted forced expiratory volume in one second; CAT: chronic obstructive pulmonary disease assessment test; Ex(-): without recent exacerbation; Ex(+): with recent exacerbation; LABA: long-acting beta-agonist; LAMA: long-acting muscarinic antagonist; mMRC: modified Medical Research Council dyspnoea scale.

Table 2. Sponsor list for chronic obstructive pulmonary disease studies

Sponsor	Record count	% of 1723
GlaxoSmithKline	134	7.78
Novartis	128	7.43
AstraZeneca	122	7.08
Boehringer Ingelheim	113	6.56
Pfizer	84	4.88
Nycomed	49	2.84
GSK	45	2.61
Chiesi	41	2.38
Almirall	36	2.09
Merck	30	1.74

Web of Science Core Collection, advanced search for "TI=(COPD) AND TS=(inhal*)" without any restriction hit 1723 reports as of 13 June 2016. "Results analysis" > "Source Titles" output the table above.

APPENDICES

Appendix 1. Sources and search methods for the Cochrane Airways Group Specialised Register (CAGR)

Electronic searches: core databases

Database	Frequency of search
MEDLINE (Ovid)	Weekly
Embase (Ovid)	Weekly
CENTRAL	Monthly
PsycINFO (Ovid)	Monthly
CINAHL (EBSCO)	Monthly
AMED (EBSCO)	Monthly

Handsearches: core respiratory conference abstracts

Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 onwards
American Thoracic Society (ATS)	2001 onwards
Asia Pacific Society of Respirology (APSR)	2004 onwards
British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards
European Respiratory Society (ERS)	1992, 1994, 2000 onwards
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards

MEDLINE search strategy used to identify trials for the CAGR

Condition search

1. Lung Diseases, Obstructive/

2. exp Pulmonary Disease, Chronic Obstructive/

3. emphysema$.mp.

4. (chronic$ adj3 bronchiti$).mp.

5. (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).mp.

6. COPD.mp.

7. COAD.mp.

8. COBD.mp.

9. AECB.mp.

10. or/1-9

Filter to identify randomised controlled trials

1. exp "clinical trial [publication type]"/

2. (randomised or randomised).ab,ti.

3. placebo.ab,ti.

4. dt.fs.

5. randomly.ab,ti.

6. trial.ab,ti.

7. groups.ab,ti.

8. or/1-7

9. Animals/

10. Humans/

11. 9 not (9 and 10)

12. 8 not 11

The MEDLINE strategy and RCT filter are adapted to identify trials in other electronic databases

Appendix 2. Search strategy to identify relevant trials from the Cochrane Airways Group Specialised Register (CAGR)

#1 MeSH DESCRIPTOR Pulmonary Disease, Chronic Obstructive Explode All

#2 MeSH DESCRIPTOR Bronchitis, Chronic

#3 (obstruct*) near3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)

#4 COPD:MISC1

#5 (COPD OR COAD OR COBD OR AECOPD):TI,AB,KW

#6 #1 OR #2 OR #3 OR #4 OR #5

#7 MeSH DESCRIPTOR Muscarinic Antagonists

#8 muscarinic* NEXT antagonist*

#9 LAMA:ti,ab

#10 tiotropium*

#11 Spiriva

#12 glycopyrronium*

#13 NVA237

#14 Seebri

#15 umeclidinium*

#16 GSK573719

#17 Incruse

#18 aclidinium*

#19 LAS34273

#20 Turdorza

#21 Eklira

#22 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21

#23 MeSH DESCRIPTOR Adrenergic beta-2 Receptor Agonists

#24 long* NEAR beta* NEAR agonist*

#25 salmeterol*

#26 *formoterol*

#27 indacaterol*

#28 QAB149

#29 vilanterol*

#30 GW642444

#31 olodaterol*

#32 "BI 1744 CL"

#33 #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32

#34 MeSH DESCRIPTOR Adrenal Cortex Hormones Explode All

#35 inhal* NEAR (corticosteroid* or steroid* or glucocorticoid*)

#36 fluticasone*

#37 budesonide*

#38 beclomethasone*

#39 ciclesonide*

#40 flunisolide*

#41 mometasone*

#42 triamcinolone*

#43 #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42

#44 #6 AND #22 AND #33 AND #43

#45 Ultibro

#46 QVA149

#47 Stiolto

#48 Anoro

#49 #45 or #46 or #47 or #48

#50 Symbicort

#51 Viani

#52 Seretide

#53 Advair

#54 Atmadisc

#55 Adoair

#56 Foster or Fostair

#57 Inuvair

#58 Dulera

#59 Flutiform

#60 Breo

#61 #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60

#62 #49 AND #61

#63 #49 AND #43

#64 #61 AND #22

#65 (#62 or #63 or #64) AND #6

#66 #44 or #65

[Note: in search line #4, MISC1 denotes the field in the record where the reference has been coded for condition, in this case, COPD]

Appendix 3. Search strategy to identify relevant trials from the ClinicalTrials.gov

Search term: (COPD OR chronic obstructive lung disease) AND (glycopyrrolate OR umeclidinium OR tiotropium OR aclidinium OR olodaterol OR QVA149) AND (indacaterol OR formoterol OR vilanterol OR salmeterol OR QVA149) AND (fluticasone OR budesonide)
Study type: Intervention

Appendix 4. Search strategy to identify relevant trials from the World Health Organization search portal

Title search: (COPD OR chronic obstructive lung disease) AND (glycopyrrolate OR umeclidinium OR tiotropium OR aclidinium OR olodaterol OR QVA149) AND (indacaterol OR formoterol OR vilanterol OR salmeterol OR QVA149) AND (fluticasone OR budesonide)

Appendix 5. Search strategy to identify relevant trial (7 September 2016 update)

PubMed
#1: (COPD OR COAD OR COBD OR AECOPD OR emphysema OR "Chronic obstructive pulmonary disease")
#2: (muscarinic OR LAMA OR tiotropium OR Spiriva OR glycopyrronium OR NVA237 OR Seebri OR umeclidinium OR GSK573719 OR Incruse OR aclidinium OR LAS34273 OR Turdorza OR Eklira)
#3: ((long* NEAR beta* NEAR agonist*) OR salmeterol OR *formoterol OR indacaterol OR QAB149 OR vilanterol OR GW642444 OR olodaterol)
#4: ((inhal* NEAR corticosteroid*) OR fluticasone OR budesonide OR beclomethasone OR ciclesonide OR flunisolid OR mometasone OR triamcinolone)
#5: (Ultibro OR QVA149 OR Stiolto OR Anoro)
#6: (Symbicort OR Viani OR Seretide OR Advair OR Atmadisc OR Adoair OR Foster or Fostair OR Inuvair OR Dulera OR Flutiform OR Breo)
#7: #1 AND ((#2 AND #3 AND #4) OR (#2 AND #6) OR (#4 AND #5))
date: 2016/Feb/1 to 2016/June/30
Results 11

Web of Science
#1: TS=(COPD OR COAD OR COBD OR AECOPD OR emphysema OR "Chronic obstructive pulmonary disease")
#2: TS=(muscarinic OR LAMA OR OR tiotropium OR Spiriva OR glycopyrronium OR NVA237 OR Seebri OR umeclidinium OR GSK573719 OR Incruse OR aclidinium OR LAS34273 OR Turdorza OR Eklira)
#3: TS=((long* NEAR beta* NEAR agonist*) OR salmeterol OR *formoterol OR indacaterol OR QAB149 OR vilanterol OR GW642444 OR olodaterol)

#4: TS=((inhal* NEAR corticosteroid*) OR fluticasone OR budesonide OR beclomethasone OR ciclesonide OR flunisolid OR mometasone OR triamcinolone)
#5: TS=(Ultibro OR QVA149 OR Stiolto OR Anoro)
#6: TS=(Symbicort OR Viani OR Seretide OR Advair OR Atmadisc OR Adoair OR Foster or Fostair OR Inuvair OR Dulera OR Flutiform OR Breo)
#7: #1 AND ((#2 AND #3 AND #4) OR (#2 AND #6) OR (#4 AND #5))
date: 2016 to 2016

>>ENERGITO

F E E D B A C K

Interpretation of SGRQ data and missing data, 20 March 2017

Summary

My colleagues and I thank Dr. Horita and colleagues for their efforts on their Cochrane Review (1). With the recent publication of the FLAME trial (2) that compared the utility of indacaterol-glycopyrronium versus salmeterol-fluticasone for chronic obstructive pulmonary disease (COPD) and its potential to change our current standard of care, we appreciate their work in evaluating the results of this trial and putting this evidence into perspective.

As we reviewed the manuscripts presented in the article, we focused on the applicability of the evidence. The authors reported that for the treatment of COPD, combination LAMA+LABA was associated with more frequent St. George's Respiratory Questionnaire (SGRQ) total score improvement exceeding the minimal clinically important difference (4 points or greater).(1) Respectively, after critically appraising the data presented, we have reservations about the conclusions made regarding the impact of LABA+LAMA on the SGRQ. Please refer to our additional letter regarding the outcomes of rate of exacerbations and serious adverse events.

In this review, the outcome of SGRQ total score improvement (≥4 points) was based on two trials with the FLAME trial driving the results (Analysis 1.7).(1) We are concerned that the data set used for this outcome from FLAME is incomplete. Rather than using the modified intention to treat (mITT) population (N=3354) or even the per protocol population (N=3084), it appears that only patients who completed 52 weeks of treatment were included (N=2760).(2) It is possible that the exclusion of these 594 patients may have skewed the results of this analysis. Furthermore, it is unclear where the data used for this outcome came from, as neither the FLAME publication nor the supplemental appendices identify the SGRQ results for this population of patients who completed 52 weeks of treatment. This information is also not available through clinicaltrials.gov. In Figure 6 of this review, the outcome of mean difference in SGRQ from baseline was also driven by this same population.(1) Therefore, this begs the question of whether it is fair to base conclusions regarding the effects of LABA+LAMA versus LABA+ICS on SGRQ on the results of only two trials especially given that the larger trial's data set does not appear to be complete.

In summary, with greater transparency and citation of the original data used for analyses, we believe that our conclusions potentially could align more closely with those identified by the Cochrane review authors. At present, perhaps the conclusions regarding the impact of these interventions on SGRQ could incorporate a greater sense of uncertainty and/or acknowledgement of the limitations of the available evidence. Overall, aside from the clarification of the data reported in the Cochrane review, we agree with the authors that a call for more research is warranted to ascertain the relative position of LAMA+LABA and LABA+ICS for COPD treatment and disaggregated data for participants in different COPD severity groups.

We hope that you will consider our constructive feedback and look forward to hearing from you soon.

References:

1. Horita N, Goto A, Shibata Y, Ota E, Nakashima K, Nagai K, Kaneko T. Long-acting muscarinic antagonist (LAMA) plus long-acting beta-agonist (LABA) versus LABA plus inhaled corticosteroid (ICS) for stable chronic obstructive pulmonary disease (COPD). Cochrane Database Syst Rev. 2017 Feb 10;2:CD012066.

2. Wedzicha JA, Banerji D, Chapman KR, Vestbo J, Roche N, Ayers RT, Thach C, Fogel R, Patalano F, Vogelmeier CF, FLAME Investigators. Indacaterol-Glycopyrronium versus Salmterol-Fluticasone for COPD. N Engl J Med. 2016 Jun 9;374(23):2222-34.

Reply

Cochrane Airways awaits a final response from the author team.

Contributors

Stephanie Garland, BSc. Pharm, Pharmacy Resident
Andrea Wan, BSc. Pharm, Pharmacy Resident
Anna Yee, BSc. Pharm, Pharmacy Resident
Grant Gill, BSc. Pharm, Pharmacy Resident
Aaron Tejani, BSc. Pharm, PharmD

Exacerbations and missing data, 13 April 2017

Summary

With the recent publication of the FLAME trial (1) and its potential to change clinical practice, we would like to thank Dr. Horita and colleagues for their efforts in evaluating the results of this trial and putting this evidence into perspective in their Cochrane Review (2). The authors reported that for the treatment of COPD, combination LAMA+LABA was associated with fewer exacerbations, and a non-significant decrease in serious adverse events (SAE) (2). Respectively, we have reservations in making similar claims and would like to address our chief concerns below.

First, we would like to focus on the reported reduction in the rate of COPD exacerbations and the implications based on the data set analyzed. As illustrated in Figure 3, the FLAME trial was a primary driver of this finding, and the only trial to show a statistically significant reduction in the number of exacerbations.(2) When examining the FLAME data set, we were concerned that the data used to make this conclusion was incomplete. Of the 598 patients who did not complete 52 weeks of treatment, only 192 patients were continually followed with respect to exacerbations and adverse events (1). Thus, 406 patients were unaccounted for in both groups combined that may have experienced an exacerbation and unbalanced the intervention and control groups. Without delineating how these patients may have skewed the results, we are less confident that the results observed were the true effect. Moreover, of the 1680 patients randomized to indacaterol-glycopyrronium and 1682 patients randomized to salmeterol-fluticasone, 152 and 126 patients were unaccounted for in each group respectively in the per protocol analysis (1). Interestingly, the data from the per protocol analysis was used to quantify the primary outcomes in the FLAME trial, which complicates whether the observed effects are reliable. Additionally, when comparing the results of FLAME to those reported in this review, we found a discrepancy in exacerbation reporting. In Figure 3, 1290/1675 and 1377/1679 exacerbation events were reported in the LAMA+LABA and LABA+ICS groups respectively (2). However, it is unclear where this data originated from, as neither the FLAME publication, the supplemental appendices, nor the data from clinicaltrials.gov provided these exact results. Regarding the generalizability of the outcome data, patients in the FLAME trial experienced an average of 3.59 or 4.09 exacerbations during the 52 weeks of indacaterol-glycopyrronium and salmeterol-fluticasone treatment respectively, and these rates were primarily driven the total number of *mild* exacerbations recorded (1). Thus, it would be difficult to meaningfully apply this data to patients with chronic COPD who experience moderate to severe exacerbations. Given the potentially incomplete data from FLAME, the discrepancy in the data used, and the limited applicability of the primary outcome results, it is difficult to draw a definitive conclusion about the effects of LAMA+LABA compared to LABA+ICS on reducing the rate of COPD exacerbations at this time.

Second, despite the reduction in COPD exacerbations and the risk of pneumonia in patients randomized to the LAMA+LABA group, these differences failed to translate into statistically significant reductions in SAE and adverse events (AE), and produced no change in all cause mortality between the two treatment modalities. These discordant findings raise further questions about the validity of the data being meta-analyzed. Predictably, we have identified the FLAME trial as a contributor to these potentially skewed results due to its ambiguous reporting of outcome data that does not outline the proportion of SAE, AE, or mortality following early discontinuation of study drugs and early withdrawal. As mentioned above, 406 patients were unaccounted for and without information on whether these patients may have experienced additional SAE or AE, it is difficult to interpret and make conclusions about the true effect.

In summary, with greater transparency and citation of the original data used for analyses, and acknowledgement of the limitations in the demographics of the studied patient population and reporting of primary outcomes, we believe that our conclusions could potentially more closely align with those identified by the Cochrane review authors. Acutely, perhaps the conclusions originally stated could incorporate a greater sense of uncertainty, and/or caveats to the generalizations provided. To close, we agree with the authors that a call for more research to ascertain the relative position of LAMA+LABA and LABA+ICS for COPD treatment and disaggregated data for participants in different COPD severity groups is warranted.

We hope that you will consider our constructive feedback and look forward to hearing from you soon.

The authors of this letter have no known conflicts of interest to declare.

References:

1. Wedzicha JA, Banerji D, Chapman KR, Vestbo J, Roche N, Ayers RT, Thach C, Fogel R, Patalano F, Vogelmeier CF, FLAME Investigators. Indacaterol-Glycopyrronium versus Salmterol-Fluticasone for COPD. N Engl J Med. 2016 Jun 9;374(23):2222-34.
2. Horita N, Goto A, Shibata Y, Ota E, Nakashima K, Nagai K, Kaneko T. Long-acting muscarinic antagonist (LAMA) plus long-acting beta-agonist (LABA) versus LABA plus inhaled corticosteroid (ICS) for stable chronic obstructive pulmonary disease (COPD). Cochrane Database Syst Rev. 2017 Feb 10;2:CD012066.

Reply

Cochrane Airways awaits a final response from the author team.

Contributors

Andrea Wan, BSc. Pharm, Pharmacy Resident
Anna Yee, BSc. Pharm, Pharmacy Resident

Grant Gill, BSc. Pharm, Pharmacy Resident
Stephanie Garland, BSc. Pharm, Pharmacy Resident
Aaron Tejani, BSc. Pharm, PharmD

Questioning the pooling of exacerbation data, 18 December 2017

Summary

I read with great interest the systematic review on Long-acting muscarinic antagonist (LAMA) plus long-acting beta-agonist (LABA) versus LABA plus inhaled corticosteroid (ICS) for stable chronic obstructive pulmonary disease (COPD) (1). The review is illustrated with a forest plot of the association of combined therapy with COPD exacerbation. This figure shows that indacaterol/glycopyrronium is the only combination able to prevent exacerbations.

The first step when a reader goes through a systematic review is to assess its credibility. In the case of this forest plot, this credibility is questioned when we inspect the rate of events. The indacaterol/glycopyrronium trials had a 66.4% of events in the control group, meanwhile it was 2.4% in the umeclidinium/vilanterol trials and 11.1% in the other inhalers. Although there is no statistically significant heterogeneity according to Cochrane Q test or I^2, it is questionable to construct a forest plot in the presence of significant clinical heterogeneity (e.g. trials with exacerbation rates ranging between 2.4 to 66.4%).

The FLAME trial (2) was the only one designed to assess COPD exacerbations. This trial included patients with recent exacerbations and followed them for 52 weeks. In contrast, the other trials included patients without recent COPD exacerbations and followed them for only 6 to 12 weeks. It is nearly impossible to draw conclusions about the role of LAMA/LABA in the prevention of COPD exacerbation with these last trial designs. Neither the population, nor the follow-up period were adequate to assess the prevention of COPD exacerbation. The importance of the follow-up length could be illustrated in figure 2 of the own FLAME trial (2), where there were no differences in the rate of severe exacerbations until week 32.

We can be fairly confident about indacaterol/glycopyrronium preventing COPD exacerbations for patients with frequent exacerbations, but we do not have either enough evidence about the role of the others LABA/LAMA combinations to prevent COPD exacerbations, or the role of indacaterol/glycopyrronium in patients without frequent exacerbations.

In my opinion, the forest plot in question is misleading due its combination of apples and oranges.

Luis Corral-Gudino

Reference

1. Horita N, Goto A, Shibata Y, Ota E, Nakashima K, Nagai K, Kaneko T. Long-acting muscarinic antagonist (LAMA) plus long-acting beta-agonist (LABA) versus LABA plus inhaled corticosteroid (ICS) for stable chronic obstructive pulmonary disease (COPD). Cochrane Database Syst Rev. 2017 Feb 10;2:CD012066.
2. Wedzicha JA, Banerji D, Chapman KR, Vestbo J, Roche N, Ayers RT, Thach C, Fogel R, Patalano F, Vogelmeier CF. Indacaterol–glycopyrronium versus salmeterol–fluticasone for COPD. N Engl J Med. 2016 Jun 9;2016(374):2222-34.

Reply

We appreciate Dr. Corral-Gudino's comments concerning the exacerbation forest plot in our review [1].

As correctly mentioned, the subgroup analysis of the exacerbation forest plot shows non-negligible discrepancy. This planned subgroup analysis is impressive. While indacaterol/glycopyrronium clearly decreased the risk of exacerbation, medications in the other two subgroups did not. I^2 for subgroup difference is as high as 69.7% with significant P value of 0.04. We agree with Dr. Corral-Gudino that only indacaterol/glycopyrronium seemed to prevent exacerbations, which we discussed in the 'Overall Completeness and Applicability of Evidence' section of our review [1]. Given some limitations, the GRADE quality of evidence related to the outcome of exacerbations was downgraded to 'low.'[1]

Dr. Corral-Gudino rightly commented that the study designs of included studies varied greatly. Thus, the between-study heterogeneity should be assessed. It is reasonable to evaluate the heterogeneity using Cochrane Q test (P value = 0.29) and I^2 statics (17%), which dispelled considerable inconsistency (Figure 1) [1].

The frequencies of exacerbation were indeed different between studies. Absolute risk reduction and number needed to treatment are meaningless if event frequencies are largely different among studies. However, odds ratios are known to be robust even when exacerbation frequencies vary greatly. For example, the incidence of exacerbations in Vogelmeier's, Wedzicha's and Zhong's studies were (44+62)/(258+264)=20%, (1290+1377)/(1675/1679)=80%, and (75+97)/(372/369)=23%, respectively. Yet the corresponding odds ratios were 0.67, 0.73, and 0.71 [1]. Compared to patients who were treated by control medication, those treated by indacaterol/glycopyrronium had a 30% lower chance of exacerbation regardless of absolute risk. As long as odds ratios are calculated, inconsistent frequencies between studies is not a considerable problem.

While Wedzicha's trial included patients with recent exacerbation, Vogeleier's and Zhong's trials included patients without recent exacerbation. Dr. Corral-Gudino insists we do not have enough evidence about the role of indacaterol/glycopyrronium in patients without frequent exacerbations. However, our analysis clearly shows that the medication constantly decreased the risk of exacerbation in the three trials, with an odds ratio of approximately 0.7 without heterogeneity (I^2=0%, P for heterogeneity = 0.92) regardless of recent exacerbations.

As Dr. Corral-Gudino pointed out, observed exacerbations in each study were not sufficient in all studies, except Wedzicha's, due to small sample size, inclusion of patients without recent exacerbation, and short follow-up periods. This is exactly why meta-analysis *is* needed. A meta-analysis can integrate many studies that do not have statistical power.

Reference

1. Horita N, Goto A, Shibata Y, Ota E, Nakashima K, Nagai K, Kaneko T. Long-acting muscarinic antagonist (LAMA) plus long-acting beta-agonist (LABA) versus LABA plus inhaled corticosteroid (ICS) for stable chronic obstructive pulmonary disease (COPD). Cochrane Database Syst Rev. 2017 Feb 10;2:CD012066.

Contributors

Feedback submitter

Luis Corral-Gudino PhD MD, Internal Medicine Department. Hospital El Bierzo, Ponferrada Leon.

Do you have any affiliation with or involvement in any organisation with a financial interest in the subject matter of your comment?

I do not have any affiliation with or involvement in any organisation with a financial interest in the subject matter of my comment

Authors

Nobuyuki Horita, Atsushi Goto, Yuji Shibata, Erika Ota, Kentaro Nakashima, Kenjiro Nagai, Takeshi Kaneko

WHAT'S NEW

Date	Event	Description
5 February 2018	Feedback has been incorporated	Response to feedback added.

HISTORY

Protocol first published: Issue 2, 2016
Review first published: Issue 2, 2017

Date	Event	Description
17 January 2018	Amended	Feedback added.
14 June 2017	Feedback has been incorporated	Two pieces of feedback added to the review. Cochrane Airways awaits a full response from the author team.

CONTRIBUTIONS OF AUTHORS

NH conducted the study search, data extraction, analysis, study quality assessment, and drafting as a principal investigator.

AG provided statistical advice.

YS conducted the study search, study quality assessment, and data extraction.

EO managed editing of the full review as a Cochrane methodologist.

KN, KN, and TK contributed to the conception, study design, interpretation of the data, and critical revision as pulmonologists.

DECLARATIONS OF INTEREST

TK: received grants or lecture fees (or both) from GlaxoSmithKline, Boehringer Ingelheim, Pfizer, Meiji, AstraZeneca, and Novartis from 2013 to 2016. This review was not funded by any pharmaceutical companies.

HN, GA, SY, OE, NK, and NK: none known.

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External sources

- Japan Agency for Medical Research and Development, Japan.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Yuji Shibata was added as the third review author.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Inhalation; Adrenal Cortex Hormones [*administration & dosage]; Adrenergic beta-2 Receptor Agonists [adverse effects] [*therapeutic use]; Cause of Death; Disease Progression; Drug Therapy, Combination [adverse effects]; Forced Expiratory Volume; Muscarinic Antagonists [adverse effects] [*therapeutic use]; Pneumonia [etiology]; Pulmonary Disease, Chronic Obstructive [*drug therapy]; Quality of Life; Randomized Controlled Trials as Topic

MeSH check words

Humans