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Once-daily long-acting beta₂-agonists/inhaled corticosteroids combined inhalers versus inhaled long-acting muscarinic antagonists for people with chronic obstructive pulmonary disease (Review)

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[Intervention Review]

Once-daily long-acting beta₂-agonists/inhaled corticosteroids combined inhalers versus inhaled long-acting muscarinic antagonists for people with chronic obstructive pulmonary disease

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ABSTRACT

Background

Three classes of inhaler medication are used to manage chronic obstructive pulmonary disease (COPD): long-acting beta₂-agonists (LABA); long-acting muscarinic antagonists (LAMA); and inhaled corticosteroids (ICS). To encourage patient adherence, two classes of medication are often combined in a single medication device; it seems that once-daily dosing offers greatest convenience to patients and may markedly influence adherence.

Objectives

To compare a once-daily combination of inhaled corticosteroid and long-acting beta₂-agonist inhalers (ICS/LABA) versus inhaled long-acting muscarinic antagonists alone (LAMA) for people with chronic obstructive pulmonary disease (COPD).

Search methods

We performed an electronic search of the Specialised Register of the Cochrane Airways Group (14 May 2018), ClinicalTrials.gov (14 May 2018), and the World Health Organization International Clinical Trials Registry Platform (20 September 2017), then a search of other resources, including reference lists of included studies and manufacturers' trial registers (10 October 2017). Two pairs of review authors screened and scrutinised selected articles.

Selection criteria

We included randomised controlled trials (RCTs) comparing once-daily administered ICS/LABA and LAMA in adults with COPD.

Data collection and analysis

Two review authors independently extracted data and assessed risk of bias in each study. We analysed dichotomous data as random-effects odds ratios (ORs) and continuous data as mean differences (MDs), both with 95% confidence intervals (95% CIs), using Review Manager 5.

Main results

We included two studies with 880 participants. We identified one ongoing trial with planned recruitment of 80 participants. Included studies enrolled participants with both partially reversible and non-reversible COPD and baseline mean per cent predicted (%pred) forced expiratory volume in one second (FEV₁) of 43.4 to 49.6. Both studies lasted 12 weeks. Both studies used the same combination of inhaled ICS/LABA (fluticasone furoate and vilanterol 100/25 mcg once daily; FF/VI) versus LAMA (18 mcg tiotropium; TIO). They were published as full articles, and neither study was at low risk of bias in all domains.

Compared to the TIO arm, results for pooled primary outcomes for the FF/VI arm were as follows: mortality: OR 0.20, 95% CI 0.02 to 1.73, 880 participants (deaths reported only in the TIO arm), very low-quality evidence; COPD exacerbation (requiring short-burst oral corticosteroids or antibiotics, or both): OR 0.72, 95% CI 0.35 to 1.50, 880 participants, very low-quality evidence; pneumonia: reported in both studies only during treatment with FF/VI: OR 6.12, 95% CI 0.73 to 51.24, 880 participants, very low-quality evidence; and total serious adverse events: OR 0.96, 95% CI 0.50 to 1.83, 880 participants, very low-quality evidence. None of the pneumonias were fatal. Compared to the TIO arm, we found no statistically significant difference for pooled secondary outcomes, including St George's Respiratory Questionnaire (SGRQ) mean total score change; hospital admissions (all-cause); disease-specific adverse events; mean weekly rescue medication use (results available from only one of the studies); and mean weekly percentage of rescue-free days for FF/VI. We found no statistically significant differences between ICS/LABA and LAMA for improvement in symptoms measured by the COPD Assessment Test (CAT score) nor for FEV₁ (change from baseline trough in 24-hour weighted mean on treatment day 84). Many pooled estimates lacked precision. Data for other endpoints such as exacerbations leading to intubation and physical activity measures were not available in included trials.

Authors' conclusions

Based on analysis of primary and secondary outcomes, we are uncertain whether once-daily ICS/LABA, combined in one inhaler, has a different efficacy or adverse effect profile compared to LAMA for treatment of people with COPD. However, the current review is based on only two trials with the main focus on primary outcomes other than those considered in this review. The short follow-up period and the very low quality of evidence limit our confidence in the result and increase uncertainty. Further trials of longer duration are needed. Current evidence is not strong enough to demonstrate important differences between inhalers in terms of effects, nor to establish that once-daily fluticasone/vilanterol 100/25 mcg and tiotropium 18 mcg are equivalent.

PLAIN LANGUAGE SUMMARY

Is once-daily ICS/LABA combined in one inhaler more beneficial than inhaled LAMA for treatment of people with COPD?

Background

Chronic obstructive pulmonary disease (COPD) is a lung disease that includes chronic bronchitis and/or emphysema. Symptoms include breathlessness and long-term cough. COPD cannot be cured, but its symptoms are treatable.

Three classes of inhaler medication are used to manage COPD, each acting in a different way: long-acting beta₂-agonists (LABA, e.g. vilanterol); long-acting muscarinic antagonists (LAMA, e.g. tiotropium); and inhaled corticosteroids (ICS, e.g. fluticasone). To try to make it easier for people to take their medications, inhalers that combine treatments have been developed. We wanted to find out if using a combined inhaler containing ICS and LABA once a day is better or worse than taking a LAMA inhaler alone.

Study characteristics

We found two studies involving 880 participants that compared the benefits and harms of once-daily inhaled ICS/LABA combined in one inhaler versus inhaled LAMA for treatment of adults with COPD. These studies lasted 12 weeks. Participants were men and women aged 40 or older who had COPD with various degrees of severity.

Key results

No consistent differences were found between the two different types of inhalers included in this review. Researchers reported no major differences in death rate, numbers of COPD exacerbations, lung inflammation, or other serious unwanted events. People receiving both inhalers showed similar improvements in quality of life, symptoms, and lung function tests.

Quality of the evidence

Overall, we assessed the evidence presented in this review to be of very low quality, which means we have very little confidence in the findings. The main reasons for such judgement include the small number of identified studies and the fact that these studies were not focused on the outcomes of interest for this review. Also, both studies had a short observation time, which means that most of the undesired events may have occurred after the observation period was over.

Bottom line

From this review, we did not find evidence strong enough to demonstrate major differences between inhalers or to establish that these inhalers have the same effect.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Once-daily ICS/LABA combined inhalers compared to once-daily LAMA for people with chronic obstructive pulmonary disease

Once-daily ICS/LABA combined inhalers compared to once-daily LAMA for people with chronic obstructive pulmonary disease

Patient or population: people with chronic obstructive pulmonary disease

Setting: studies were conducted at 102 medical centres in 11 countries (Canada, Czech Republic, Germany, Poland, Romania, USA, Argentina, France, Italy, Norway, Russian Federation, Ukraine)

Intervention: once-daily inhaled corticosteroids/long-acting beta₂-agonists combined inhalers (FF/VI)

Comparison: inhaled long-acting muscarinic antagonist (TIO)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with inhaled long-acting muscarinic antagonist (TIO)	Risk with once-daily long-acting beta ₂ -agonists/inhaled corticosteroids combined inhalers (FF/VI)				
Mortality (all-cause) Follow-up: 12 weeks	9 per 1000		OR 0.20 (0.02 to 1.73)	880 (2 RCTs)	⊕⊕⊕⊕ VERY LOW ^{a,b}	
Any COPD exacerbation that requires short-burst oral corticosteroids or antibiotics, or both Follow-up: 12 weeks	41 per 1000	30 per 1000 (15 to 60)	OR 0.72 (0.35 to 1.50)	880 (2 RCTs)	⊕⊕⊕⊕ VERY LOW ^{a,c}	
Pneumonia Follow-up: 12 weeks	0 per 1000	0 per 1000 (0 to 0)	OR 6.12 (0.73 to 51.24)	880 (2 RCTs)	⊕⊕⊕⊕ VERY LOW ^{a,b}	
Quality of life assessed with SGRQ Mean change from baseline, scale 0-100, low on the scale is better QoL Follow-up: 12 weeks.	Mean change from baseline in quality of life was -4.97 in one study	MD 1.29 lower (3.01 lower to 0.42 higher)	-	779 (2 RCTs)	⊕⊕⊕⊕ VERY LOW ^{a,d}	Only 1 study provided information on mean change from baseline in each group; the other study reported only differences between groups
Hospital admissions (all-cause)	41 per 1000	39 per 1000	OR 0.96	880	⊕⊕⊕⊕	

Follow-up: 12 weeks	(20 to 74)	(0.49 to 1.89)	(2 RCTs)	VERY LOW ^{a,d}
Exacerbations leading to intubation	Not reported -	-	-	-
Physical activity measure (e.g. 6MWT)	Not reported -	-	-	-

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI)

6MWT: 6-Minute Walking Test; CI: confidence interval; COPD: chronic obstructive pulmonary disease; FF: fluticasone furoate; ICS: inhaled corticosteroids; LABA: long-acting beta₂-agonists; LAMA: long-acting muscarinic antagonists; OR: odds ratio; QoL: quality of life; RCT: randomised controlled trial; SGRQ: St George's Respiratory Questionnaire; TIO: tiotropium; VI: vilanterol

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

^aWe downgraded for risk of bias by one level because both studies had unclear risk of bias for blinding and incomplete outcome data and one study did not provide information on methods of randomisation and concealment

^bWe downgraded for imprecision by two levels because very low number of events leads to wide 95% CIs, and the number of events was too low to reliably calculate optimal information size

^cWe downgraded for imprecision by two levels because the optimal information size criterion is not met and the 95% CI is wide including significant benefit and harm

^dWe downgraded for imprecision by two levels owing to very wide 95% CIs including significant benefit and harm

BACKGROUND

Description of the condition

Chronic obstructive pulmonary disease (COPD) is a disorder of the respiratory system that is characterised by significant mortality and morbidity worldwide. In 2012, COPD was the fourth leading cause of death in the world (Guerra 2008). The World Health Organization (WHO) has reported more than three million deaths (WHO 2005), equivalent to 6% of deaths from all causes globally, and it is predicted that COPD will become the third leading cause of death worldwide by 2030 (Mathers 2006). COPD is a chronic, progressive, and incurable condition that is usually caused by cigarette smoking. The underlying mechanism is associated with an enhanced chronic inflammatory response in the airways and within the lung to noxious particles or gases (GOLD 2018). Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines describe COPD as a combination of obstructive bronchitis and emphysema (previously known as independent disease entities). The diagnosis of COPD is based on clinical manifestations, history of exposure to risk factors, and spirometry. GOLD 2018 decided to include individual patient symptoms as assessed by questionnaires such as the COPD Assessment Test (CAT) and the modified MRC Dyspnoea Scale (mMRC). Spirometry, which is required to establish a diagnosis of COPD, measures airflow limitation by post-bronchodilator forced expiratory volume in one second (FEV₁)/forced vital capacity (FVC) ≤ 0.7 (independent of reference values) (GOLD 2018). On the basis of symptoms and risks of exacerbation, patients are divided into four groups (A, B, C, and D). Patients in GOLD C or D categories may be at greater risk for hospital admission and death (GOLD 2018).

Description of the intervention

The efficacy of COPD pharmacological management is rated by spirometry (FEV₁) and by an individualised assessment of disease course, which includes reduction in current symptoms and in future risks of exacerbation (GOLD 2018). None of the medications available for COPD have been shown to modify the long-term decline in lung function in a significant way (Anthonisen 1994; Burge 2000; GOLD 2018; Pauwels 1999; Vestbo 1999). Bronchodilators are used as first-line medication for control of breathlessness. For group A patients, a short-acting beta₂-agonist (SABA) or a short-acting anticholinergic agent (SAMA) may be recommended as first-choice treatment (GOLD 2018). In the case of persistent and worsening breathlessness (group B), long-acting bronchodilators are used. Long-acting beta₂-agonists (LABA) are more effective than long-acting anticholinergic agents (LAMA) if symptoms and health-related quality of life are considered the primary outcomes, whereas use of LAMA is preferable among those with frequent exacerbations (Cazzola 2014). The choice of LABA or LAMA is dependent on patients' perception of symptom relief; for those with severe breathlessness, the alternative treatment is a combination of LAMA and LABA. Anti-inflammatory interventions using oral corticosteroids should be restricted for the management of COPD exacerbations (GOLD 2018). Inhaled corticosteroids (ICS) can be considered if the risk of recurrent exacerbations is high. GOLD 2018 recommends a combination of ICS and either LABA or LAMA for patients within the GOLD C category (Barr 2005; Calverley 2003; Calverley 2007; Niewoehner 2005; Spencer 2011). The combination of two long-acting bronchodilators or the combination of ICS and LAMA can be used as an alternative choice (GOLD 2018). For group D patients, treatment recommendations

include a combination of ICS plus LABA or LAMA or a combination of all three classes of drugs together; however, this guidance is based mostly on the findings of short-term studies (GOLD 2018).

How the intervention might work

Inhaled LABA, such as salmeterol or formoterol, improve FEV₁ and lead to a better health status and fewer exacerbations compared with placebo or short-acting bronchodilators (Stockley 2006). LABA with a 24-hour duration of action, such as indacaterol, vilanterol, and olodaterol, provide sustained bronchodilation compared with twice-daily dosing with either salmeterol or formoterol, together with some reduction in use of rescue therapy or intensity of breathlessness, or both (Dahl 2010; Korn 2011).

Results of the Prevention of Exacerbations with Tiotropium (POET) in COPD study indicate that in patients with moderate to very severe COPD, LAMA (tiotropium) were significantly more effective than LABA (salmeterol) in preventing exacerbations (Vogelmeier 2011). Decramer 2013 observed similar results when comparing once-daily LABA (indacaterol) versus tiotropium. The new LAMA agents (aclidinium, glycopyrronium, and umeclidinium) have at least comparable efficacy to tiotropium, and choice of treatment depends on physician and patient preference (Ismaila 2015).

ICS have been used in COPD treatment for many years. The benefits of ICS treatment for patients with COPD may be similar to those of LABA, but long-term monotherapy with ICS is not recommended. Consistent evidence indicates that long-term use of fluticasone-based ICS is associated with increased risk of pneumonia (Calverley 2007; Wedzicha 2008), as well as pulmonary tuberculosis (Kim 2013). Compared to placebo, ICS such as fluticasone propionate and budesonide as monotherapy reduce exacerbations by up to 20% and in combination with LABA by up to 30%. The combination of ICS and LABA is better than its components and placebo in improving lung function and health status as well (Calverley 2003; Calverley 2007). When compared with once-daily tiotropium, the twice-daily combination of salmeterol and fluticasone propionate (SFC) had a similar effect on the overall exacerbation rate (Wedzicha 2008). The only approved once-daily fixed combination of vilanterol and fluticasone furoate produced greater improvement in lung function than its components separately and is as effective as the other twice-daily administered combinations of ICS and LABA in preventing exacerbations (Martinez 2015; Styne 2015). On the other hand, the Effect of Indacaterol-Glycopyrronium Versus Fluticasone-Salmeterol on COPD Exacerbations (FLAME) study confirmed that once-daily indacaterol-glycopyrronium is more effective than twice-daily salmeterol-fluticasone in preventing exacerbations among patients with a history of exacerbations during the previous year (Wedzicha 2016). Finally, recently published results of the Inpatient Mortality Prediction Algorithm Clinical Trial (IMPACT) trial reveal that triple therapy with fluticasone furoate, umeclidinium, and vilanterol in a single inhaler resulted in lower rates of moderate to severe COPD exacerbation than were seen with fluticasone furoate-vilanterol or umeclidinium-vilanterol in the same population (Lipson 2018).

Why it is important to do this review

This Cochrane Review will be the first to directly compare once-daily ICS/LABA combined in one inhaler versus inhaled LAMA. Patients with COPD, as others with chronic diseases, experience problems in adhering to treatment (Rand 1995). Even though it

is not a single factor, dosing frequency has been suggested to influence therapy (Bourbeau 2008; Charles 2010). It seems that once-daily dosing offers greater convenience to patients and may markedly influence their adherence to treatment. Previous reviews have focused on twice-daily ICS/LABA inhalers and have covered the following comparisons: ICS/LABA combined inhalers versus ICS alone (Nannini 2013); ICS/LABA combined inhalers in addition to tiotropium versus tiotropium (Welsh 2013), or combination alone (Karner 2011); and ICS/LABA combined inhalers versus long-acting beta₂-agonists (Nannini 2012). One review performed a network meta-analysis to compare LABA, LAMA, ICS, and ICS/LABA (Kew 2014). None of these systematic reviews separated the different LAMA agents. Thus, our proposed systematic review is original and may be informative for COPD management. Moreover, this review will form part of a suite of reviews on various combinations of LABA, LABA, and ICS for treatment of people with COPD.

OBJECTIVES

To compare a once-daily combination of inhaled corticosteroid and long-acting beta₂-agonist inhalers (ICS/LABA) versus inhaled long-acting muscarinic antagonists alone (LAMA) in people with chronic obstructive pulmonary disease (COPD).

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) with a parallel or cross-over group design of at least 12 weeks' duration. We included studies reported as full-text articles, those published as abstracts only, and those with unpublished data.

Types of participants

We included adults (over 21 years old) with a diagnosis of COPD confirmed by an external set of criteria for this condition, such as those provided by the Global Initiative for chronic Obstructive Lung Disease (GOLD 2018), the American Thoracic Society (ATS), the British Thoracic Society (BTS), or the Thoracic Society of Australia and New Zealand (TSANZ).

Types of interventions

We included studies that compared participants randomised to receive any fixed combination of ICS/LABA once daily (in one inhaler) versus inhaled LAMA.

We included participants with COPD who were taking co-mediations provided that the co-mediations were not part of the randomised treatment.

Types of outcome measures

Primary outcomes

1. Mortality, all-cause
2. Any COPD exacerbation that requires short-burst oral corticosteroids or antibiotics, or both
3. Pneumonia and other serious adverse events

Secondary outcomes

1. Quality of life (measured with a validated scale for COPD, e.g. St George's Respiratory Questionnaire (SGRQ), Chronic Respiratory Disease Questionnaire)
2. Hospital admissions, all-cause and due to exacerbation
3. Exacerbations leading to intubation
4. Disease-specific adverse events other than pneumonia
5. Physical activity measure (e.g. results of six-minute walk test (6MWT))
6. Improvement in symptoms
7. Use of rescue medications
8. FEV₁

We defined adverse events as serious and non-serious according to International Conference on Harmonisation (ICH) Guideline definitions (ICH-GCP 1996) (i.e. a serious fatal or non-fatal adverse event is any event that leads to death, is life-threatening, requires in-patient hospitalisation or prolongs existing hospitalisation, or results in persistent or significant disability, and any important medical event that may have jeopardised the participant or requires intervention to prevent its effects). We defined any other adverse events as non-serious.

Reporting in a study one or more of the outcomes listed above was not an inclusion criterion for this review.

Search methods for identification of studies

Electronic searches

We identified studies from the Cochrane Airways Trials Register, which is maintained by the Information Specialist for the Group. The Cochrane Airways Trials Register contains studies identified from several sources.

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL), through the Cochrane Register of Studies Online (crso.cochrane.org) (inception to date).
2. Weekly searches of MEDLINE Ovid SP (1946 to date).
3. Weekly searches of Embase Ovid SP (1974 to date).
4. Monthly searches of PsycINFO Ovid SP (1967 to date).
5. Monthly searches of the Cumulative Index to Nursing and Allied Health Literature (CINAHL) EBSCO (1937 to date).
6. Monthly searches of the Allied and Complementary Medicine Database (AMED) EBSCO (all years to date).
7. Handsearches of the proceedings of major respiratory conferences.

Studies contained in the Trials Register are identified through search strategies based on the scope of Cochrane Airways. Details of these strategies, as well as a list of handsearched conference proceedings, are provided in Appendix 1. See Appendix 2 for search terms used to identify studies for this review.

We searched all databases from their inception to 14 May 2018, and we imposed no restriction on language of publication.

We conducted a search of ClinicalTrials.gov (<http://ClinicalTrials.gov>) and the WHO International Clinical Trials Registry Platform (<http://who.int/ictrp/en/>) (20 September 2017).

The Information Specialist of the Cochrane Airways Group suggested the search methods for identification of studies.

Searching other resources

We checked the reference lists of all primary studies, review articles, guidelines, and Health Technology Assessment (HTA) reports identified through our searches. We contacted experts in the field and authors of identified studies to ask about unpublished data. We searched relevant manufacturers' websites for trial information and contacted them to request information about unpublished trials. Also we checked <http://www.clinicaltrials.gov/> and websites of the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for unpublished data.

We searched for errata or retractions from included studies published in full text on PubMed (www.ncbi.nlm.nih.gov/pubmed), but we identified none.

Data collection and analysis

Selection of studies

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 eliminated duplicate records of the same study using reference management software. Two pairs of review authors (MJ, AS, IGS, RN, MS, MMB) independently screened titles and abstracts for inclusion of all potential studies that we identified as a result of the search and coded them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. Each pair consisted of a content expert and an experienced methodologist. We resolved discrepancies by discussion and, if the two review authors could not resolve discrepancies, a third review author (MMB) acted as arbiter. We retrieved the full-text study reports/publications of studies in the 'retrieve' category. Two groups of review authors (MJ, AS, IGS, RN, MS, MMB) independently screened the full-text articles, identified studies for inclusion, and identified and recorded reasons for exclusion of ineligible studies. We resolved any disagreement through discussion or, if required, we consulted a third review author (MMB). We recorded the selection process in sufficient detail to complete a PRISMA flow diagram and a [Characteristics of excluded studies](#) table (Moher 2009).

Data extraction and management

We used a data collection form to record study design, methods, population, intervention, outcomes, and results. If sufficient flexibility was available, we used Covidence software for data extraction (Covidence 2016); if not, we used a Microsoft Excel spreadsheet. We first tested a data collection form and made adjustments. Two pairs of review authors (MJ and RN; IGS and MS) extracted data from the included studies. We discussed disagreements, and a third review author (MMB) acted as arbiter if necessary. We extracted the following study characteristics.

1. Methods: study design, total duration of study, details of any 'run-in' period, number of study centres and locations, study settings, withdrawals, and date of study.
2. Participants: N, mean age, age range, gender, severity of condition, diagnostic criteria, baseline lung function, smoking history, inclusion criteria, and exclusion criteria.

3. Interventions: intervention, comparison, concomitant medications, and excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.
5. Notes: funding for study, and notable conflicts of interest of study authors.

Assessment of risk of bias in included studies

Two pairs of review authors (MJ and RN; IGS/MMB and MS) independently assessed the risk of bias for each included study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*, and followed advice from this source document for each of the 'Risk of bias' domains (Higgins 2011). We resolved disagreements by discussion or by involving another review author (MMB, AS). We assessed risk of bias according to the following domains.

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other bias.

We graded each potential source of bias as 'high', 'low', or 'unclear', and provided a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. We summarised 'Risk of bias' judgements across different studies for each of the domains listed and separately for objective and subjective outcomes.

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

We classified studies as having low risk of bias if they were at low risk of bias in all domains. Otherwise, we classified studies as having high risk of bias.

Assessment of bias in conducting the systematic review

We conducted the review according to the published protocol and reported any deviations from it in the [Differences between protocol and review](#) section of the systematic review.

Measures of treatment effect

We analysed dichotomous data as odds ratios (ORs) and continuous data as mean differences (MDs) if the scale used in the studies was the same, or as standardised mean differences (SMDs) if the scales used by study authors differed. We used adjusted results, estimated from the model with the highest number of covariates. When adjusted results were unavailable, we extracted both change from baseline and final score and used the former in the analysis (in the same meta-analysis as the adjusted results). If the included studies reported results only as mean difference values with standard error or 95% confidence intervals (CIs), we pooled them using the generic inverse variance (GIV) method and the calculator available in Review Manager (RevMan) (RevMan 2014).

If the numbers of participants within an event were unavailable, we analysed count data as time-to-event or rate ratios, as reported. We planned to pool rate ratios after transforming them to log values using the GIV option in RevMan (RevMan 2014).

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 narratively described skewed data reported as medians and interquartile ranges.

When a single trial reported multiple trial arms, we planned to include only the relevant trial arms. If we had identified a trial with two relevant intervention arms that we combined in a single meta-analysis, we planned to halve the control group to avoid double-counting.

We used the end of the study as a measurement point for all included studies.

Unit of analysis issues

In the case of dichotomous data, the unit of analysis was the participant. In the case of included studies using count data, we analysed them as rate ratios or time-to-event data. In the case of included studies in which rate ratios were reported, we used these values in the analysis. We did not identify any cross-over trials.

Dealing with missing data

We contacted investigators to verify and obtain missing data such as key study characteristics and numerical outcome data; however we received no response from the study authors. When we did not consider the data to be missing at random, we planned to analyse them as treatment failures and to test this approach in a sensitivity analysis.

Assessment of heterogeneity

We used the χ^2 test and the I^2 statistic to measure heterogeneity among the studies in each analysis. We did not identify substantial heterogeneity (as defined as a rough estimate in the Cochrane Handbook: $I^2 > 50\%$) and thus did not explore possible causes with our prespecified subgroup analysis (Higgins 2011).

Assessment of reporting biases

To minimise reporting bias, we planned to search multiple sources and to create and examine a funnel plot to explore possible small-study and publication biases, but we included only two studies; therefore this was not possible.

Data synthesis

We used a random-effects model and planned to perform a sensitivity analysis with a fixed-effect model. If, owing to heterogeneity, pooling of data was not possible, we summarised the findings using tables, figures, and text. If results of a single study are presented on a forest plot, then a fixed-effect model is displayed.

'Summary of findings' table

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 as it relates to

studies that contribute data to the meta-analyses for prespecified outcomes. We used methods and recommendations described in Sections 8.6 ('Presentation of assessments of risk of bias') and 11.5 ('Summary of findings' tables) of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), and we used GRADEpro Guideline Development Tool (GDT) software (GRADEpro GDT). We justified all decisions to downgrade or upgrade the quality of the evidence by using footnotes, and we made comments to aid the reader's understanding of the review when necessary. We included the following outcomes in the 'Summary of findings' table: mortality, any COPD exacerbation, pneumonia, hospital admission, COPD exacerbation leading to intubation, quality of life, and physical fitness.

Subgroup analysis and investigation of heterogeneity

Comparisons of treatment effects might be influenced by patient-related and disease- or management-associated modifiers, such as patient age or gender (Mannino 2002); smoking status (Kohansal 2009); co-morbidities (cardiovascular, metabolic, etc.) (Agusti 2010; Holguin 2005; Mannino 2008); severity of airflow limitation (FEV₁) (Decramer 2009; Hurst 2010); number of exacerbations in the prior 12 months (≤ 1 vs ≥ 2) (Hurst 2010); and type, dose, and delivery mode of studied, concomitant, and previous COPD medications (Al-Showair 2009; Chrystyn 1988; Kim 1997). However, those data were not available at the study level.

We planned to analyse studies within the following a priori subgroups, using the formal test for subgroup interactions in Review Manager (RevMan) (RevMan 2014).

1. Type and dose (mean or defined by primary studies protocols) of LABA.
2. Type and dose (mean or defined by protocols) of LAMA.
3. Type and dose (mean or defined by protocols) of ICS used.
4. Number of exacerbations in prior 12 months (mean at baseline or according to inclusion criteria: ≤ 1 vs ≥ 2).
5. Severity of airflow limitation (mean at baseline or according to inclusion criteria: FEV₁ $> 80\%$ vs 50 to 80% vs $< 50\%$ predicted).
6. Prior therapy: inhaled ICS + LABA; inhaled LAMA (dichotomised as yes/no according to inclusion criteria).
7. Concomitant medication: theophylline (dichotomised as yes/no according to inclusion criteria).
8. Smoking status (current smokers dichotomised as yes/no according to inclusion criteria).
9. Co-morbidity (cardiac, vascular, metabolic (diabetes), etc.; dichotomised as yes/no according to inclusion criteria).
10. Study duration (less than six months, $\geq$ six months).
11. Open and double-blind trial design.

However, owing to lack of required data, we did not carry out these analyses.

Sensitivity analysis

We planned to perform sensitivity analyses with regard to missing data (best-best; worst-worst, and risk of bias low and high). Again, the small number of studies and the paucity of data precluded these analyses. Because events in cases of mortality and pneumonia were rare, we conducted additional post hoc sensitivity analysis using the Peto odds ratio.

RESULTS

Description of studies

Results of the search

We performed our searches on 14 May 2018 and identified 475 records after removal of duplicates. See [Figure 1](#) for an overview

of literature search results, their assessment, and inclusion and exclusion of studies in the review. We have reported reasons for exclusions under [Characteristics of excluded studies](#). Finally we included two studies that fulfil the criteria of our review ([Covelli 2016](#), [Pepin 2014](#)). In addition, we identified one ongoing trial ([NCT02546297](#)).

Figure 1. Study flow diagram.

Included studies

The two included studies were described as randomised controlled trials (RCTs) and as double-blind studies ([Covelli 2016](#), [Pepin 2014](#)). We present detailed information on the methods used in each study under [Characteristics of included studies](#).

Participants

Both studies recruited in total 880 participants (50% were men) aged ≥ 40 years (mean age, 63 years) with a diagnosis of COPD

confirmed by an external set of criteria for this condition and a history of ≥ 10 pack-years of smoking, with partially reversible or non-reversible airflow limitation and mean percent predicted (%pred) FEV₁ of 45.4. In each study, follow-up lasted 12 weeks.

In both studies, a high proportion of participants had cardiovascular co-morbidities; the most common were hypertension (75% and 84%), hypercholesterolaemia (41% and 44%), and coronary artery disease (32% and 44%).

Location and setting

The included studies were co-ordinated in Germany (at the Lung Clinic in the Medical University of Göttingen, per [Pepin 2014](#)) and in the USA (at Kootenai Health, Coeur d'Alene, Idaho, per [Covelli 2016](#)).

Patients were recruited at 102 medical centres (outpatient clinics) in 11 countries (Argentina, Canada, Czech Republic, France, Germany, Italy, Norway, Poland, Romania Russian Federation, Ukraine, and the USA) ([Covelli 2016](#) [Pepin 2014](#)).

Interventions

In the included studies, the combination inhaled ICS/LABA was fluticasone and vilanterol 100/25 mcg once daily in [Covelli 2016](#) and [Pepin 2014](#), respectively, versus 18 mcg tiotropium. Each participant was instructed to self-administer the blinded study drug. Dosage of the combined preparation and of the separate medications remained stable throughout the studies. Concomitant therapy permitted was as-needed short-acting beta₂-agonist (salbutamol) or oral steroids or antibiotics, or both, in the case of exacerbations.

Outcomes

Both studies reported any COPD exacerbation that required short-burst oral corticosteroids or antibiotics or hospitalisation. Both studies reported mortality, but only as fatal adverse events.

Each study measured and reported pneumonia and other serious adverse events. Both studies reported lung function as FEV₁, and one study reported change from baseline in 24 hours weight mean FEV₁ at week 12 as a primary endpoint ([Covelli 2016](#)). Both studies reported quality of life assessment by St George's Respiratory Questionnaire (SGRQ)-COPD, as well as improvement in symptoms assessment by the COPD Assessment Test (CAT). Only [Pepin 2014](#) used the EuroQoL Group Quality of Life Questionnaire based on five dimensions (EQ-5D). Studies also reported vital signs (blood pressure and pulse rate), spirometry parameters, and clinical laboratory tests (hematology and chemistry). The primary outcome in one study was mean change from baseline (BL) in aortic pulse wave velocity (aPWV) at the end of the 12-week treatment period (day 84) ([Pepin 2014](#)).

Excluded studies

We provide reasons for exclusion under [Characteristics of excluded studies](#).

Risk of bias in included studies

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 present details for each study under [Characteristics of included studies](#). [Figure 2](#) shows the overall risk of bias in each domain for studies in this review. Risk of bias by trial can be seen in [Figure 3](#).

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

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias): objective outcomes	Blinding of participants and personnel (performance bias): subjective outcomes	Blinding of outcome assessment (detection bias): objective outcomes	Blinding of outcome assessment (detection bias): subjective outcomes	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Covelli 2016	+	+	+	?	+	?	?	+	+
Pepin 2014	?	?	+	?	+	?	?	+	+

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Both included studies were published in full articles, and neither study was at low risk of bias in all domains (Covelli 2016 Pepin 2014).

Allocation

Both studies were randomised trials, and we gave neither study high risk ratings for either of the selection bias domains. One study described the method of randomisation, and thus we rated this study as having low risk of bias (Covelli 2016).

One study described the method of allocation concealment (interactive voice response system), and we rated this study as having low risk of bias (Covelli 2016). The second study did not explicitly describe its methods; therefore we rated this study as having unclear risk of bias.

Blinding

Both studies were double-blind, which was understood to pertain to at least participants and personnel; therefore we gave both studies a low risk rating for performance and detection bias for objective outcomes. However, for both trials, we rated the risk of bias for subjective outcomes as unclear in performance and detection domains, as capsules in one of the groups had trade markings, but it was not clear if participants noted the difference.

Incomplete outcome data

Both studies described withdrawals, but not all participants were included in the analyses of secondary outcomes, and it was not clear how studies dealt with missing data for those outcomes. We

therefore rated both trials as having unclear risk of bias in the incomplete outcome data domain.

Selective reporting

Both trials could be linked to a prospectively registered protocol for cross-checking of reported outcomes (on clinicaltrials.gov). Both studies reported named outcomes well in published articles, and a subset had additionally posted results summaries on clinicaltrials.gov, warranting a low risk rating.

Other potential sources of bias

Both studies did not report any important concerns about bias not addressed in the other domains in the tool.

Effects of interventions

See: [Summary of findings for the main comparison Once-daily ICS/LABA combined inhalers compared to once-daily LAMA for people with chronic obstructive pulmonary disease](#)

Mortality

In both studies, death was reported only in patients receiving TIO (four participants). Overall, the main analysis did not demonstrate statistically significant differences in the number of deaths between fluticasone furoate (FF)/vilanterol (VI) and tiotropium (TIO) (OR 0.20, 95% CI 0.02 to 1.73; 880 participants; [Analysis 1.1](#); [Figure 4](#)). However, because events were so rare, we performed an additional sensitivity analysis using the Peto OR, which showed some benefit of FF/VI as compared with TIO (Peto OR 0.14, 95% CI 0.02 to 0.97; 880 participants; [Analysis 2.1](#)).

Figure 4. Forest plot of comparison: 1 Once-daily long-acting beta₂-agonists/inhaled corticosteroids combined inhalers (FF/VI) versus inhaled long-acting muscarinic antagonists (TIO), outcome: 1.1 Mortality all-cause.

Mortality was not analysed as a primary outcome in the included studies.

Any COPD exacerbation

Both studies did not provide a definition of COPD exacerbation, and both reported severe exacerbations (exacerbation leading to hospitalisation) as a safety endpoint. One study presented a definition of exacerbation history (Covelli 2016), which we accepted as the definition of COPD exacerbations during the

study ("exacerbation requiring oral corticosteroid and/or antibiotic treatment and/or hospitalisation"). In Pepin 2014, data for COPD worsening or exacerbation were reported together and only as adverse events. We combined these two endpoints in a single analysis of exacerbations. The total number of people experiencing one or more exacerbations in both studies was 13 in the FF/VI group and 18 in the TIO group (OR 0.72, 95% CI 0.35 to 1.50; 880 participants; Analysis 1.2; Figure 5). None of the COPD exacerbations were fatal.

Figure 5. Forest plot of comparison: 1 Once-daily long-acting beta₂-agonists/inhaled corticosteroids combined inhalers (FF/VI) versus inhaled long-acting muscarinic antagonists (TIO), outcome: 1.2 Any COPD exacerbation that requires short-burst oral corticosteroids or antibiotics, or both.

Pneumonia and other serious adverse events

Both studies observed pneumonia only in the FF/VI group, but the difference versus the TIO group was not statistically significant in the main analysis (OR 6.12, 95% CI 0.73 to 51.24; 880 participants;

Analysis 1.3; Figure 6). However, because events were so rare, we performed an additional sensitivity analysis using the Peto OR, which showed increased risk of pneumonia in the FF/VI group as compared with the TIO group (Peto OR 7.56, 95% CI 1.30 to 43.75; 880 participants; Analysis 2.2).

Figure 6. Forest plot of comparison: 1 Once daily long-acting beta₂-agonists/inhaled corticosteroids combined inhalers (FF/VI) versus inhaled long-acting muscarinic antagonists(TIO), outcome: 1.3 Pneumonia.

In total, studies reported five pneumonias, none of which were fatal. One study radiologically confirmed pneumonia and treated patients with antibiotics in each case (n = 3; [Covelli 2016](#)). Two of the three participants were hospitalised. In the other study, pneumonia was not defined but was reported as a serious adverse event (n = 2; [Pepin 2014](#)), and all participants with pneumonia were hospitalised.

All studies evaluated serious adverse events (SAEs) at 12 weeks' observation. Researchers reported no significant differences in the number of SAEs between groups (OR 0.96, 95% CI 0.50 to 1.83; 880 participants; [Analysis 1.4](#); [Figure 7](#)). We gathered data on other SAEs as reported according to *Medical Dictionary for Regulatory Activities* (MedDRA) terminology in [Table 1](#).

Figure 7. Forest plot of comparison: 1 Once-daily long-acting beta₂-agonists/inhaled corticosteroids combined inhalers (FF/VI) versus inhaled long-acting muscarinic antagonists (TIO), outcome: 1.4 Total, serious adverse events.

Quality of life

Both included studies looked at changes in quality of life using the SGRQ, and both showed improvement in quality of life (with respect to all COPD-specific (SGRQ-C) components: symptoms, impacts, activity) in both groups ([Covelli 2016](#), [Pepin 2014](#)). Lower scores indicate better quality of life.

In [Pepin 2014](#), data for SGRQ change after 12 weeks were available for each group, and [Covelli 2016](#) provided information about mean change differences between groups. Therefore, with Review Manager (RevMan) ([RevMan 2014](#)), we calculated the mean change difference between FF/VI and TIO groups at day 84 using data available in the e-Appendix of [Pepin 2014](#).

The mean change difference between groups in total SGRQ was not significant (MD -1.29, 95% CI -3.01 to 0.42; 779 participants; [Analysis 1.5](#)).

[Covelli 2016](#) performed a responder analysis for the total SGRQ-C score. Study authors reported that 48% and 42% of participants achieved the minimal clinically important difference (MCID) of -4 units after 12 weeks of treatment with FF/VI and TIO, respectively. Using percentages reported by authors and total numbers of participants, we calculated the number of responders in each group, which did not show significant differences between groups (OR 1.27, 95% CI 0.93 to 1.74; 313 participants; [Analysis 1.6](#)).

Hospital admissions: all-cause and due to exacerbation

Studies included in this review did not explicitly report the number of participants hospitalised; therefore we assumed that the total number of SAEs was equivalent to the number of hospitalisations for any reason. Study data were available for comparison of the rate of hospitalisation due to a COPD exacerbation versus pneumonia ([Covelli 2016](#) [Pepin 2014](#)). Those studies observed no significant differences in hospitalisation for any reason between FF/VI and TIO groups (OR 0.96, 95% CI 0.49 to 1.89; 880 participants; [Analysis 1.7](#)).

Exacerbations leading to intubation

Included studies did not report this outcome.

Disease-specific adverse events other than pneumonia

Both studies, which enrolled 880 participants in total, reported adverse events related to COPD ([Covelli 2016](#) [Pepin 2014](#)). Authors of both studies reported cardiovascular events (n = 35), lower respiratory tract infection excluding pneumonia (n = 8), local steroid effects (n = 31), bone disorders/fractures (n = 5), and ocular effects/glaucoma (n = 2). They reported no significant differences between treated groups (FF/VI vs TIO) for any of the analysed disease-specific adverse events ([Analysis 1.8](#)). In addition, analysis of any adverse events (not including serious) showed no differences between two treatment groups (OR 0.99, 95% CI 0.62 to 1.57; 880 participants; [Analysis 1.8](#)). We gathered the data on other adverse events reported in [Table 2](#).

Physical activity measure (e.g. results of six-minute walk test (6MWT))

The included studies did not report this outcome.

Improvement in symptoms

Both studies used the CAT score to assess severity of symptoms over the entire 12-week treatment period. Lower scores indicate fewer symptoms. However, one study reported least squares mean change differences between groups (Covelli 2016), and the other study reported CAT values at 84 days (Pepin 2014). Because data were insufficient for pooling of results of both studies, we have presented them narratively. In Covelli 2016, least squares mean change differences between groups in total CAT score at 12 weeks was -0.4 (95% CI -1.3 to 0.5; 565 participants), and in Pepin 2014, the difference in CAT scores between FF/VI and TIO groups at 12 weeks was 0.6 (95% CI -1.31 to 2.51; 257 participants) (Analysis 1.9). On the basis of available data, we could calculate only mean change in both groups from baseline, which was -3 in the FF/VI group and -2.5 in the TIO group, with a difference of -0.5.

Use of rescue medications

Analyses for mean weekly rescue medication use of albuterol/salmeterol over the 12-week course of the study were available for only one study (Covelli 2016). Researchers reported a significant difference between groups (FF/VI vs TIO) in mean weekly use of SABA/LABA (-0.37 inhalations, 95% CI -0.55 to -0.19; 565 participants) and in mean weekly percentage of rescue-free days (9.1%, 95% CI 4.0 to 14.2; 565 participants). Albuterol use was measured as occasions used per day.

FEV₁

Both studies measured change from baseline in trough FEV₁ at the end of the study (12 weeks). We have presented the results for 268 and 249 participants available for analysis in FF/VI and TIO groups in one study (Covelli 2016) and for 112 and 112 participants available for analysis in the second study (Pepin 2014). Because both studies reported least squares mean change difference with 95% CI, we calculated the standard error from available data and pooled mean differences. As a result, we found no significant differences between FF/VI and TIO groups (MD 0.01, 95% CI -0.02 to 0.04; 741 participants; Analysis 1.10).

In addition, Covelli 2016 presented dichotomous improvement for a change in FEV₁ $\geq$ 100 mL from baseline within four hours post dose on treatment day 1. An increase $\geq$ 100 mL was not met for 21% and 18% of participants receiving FF/VI and TIO, respectively; however the change from baseline $\geq$ 100 mL within five minutes was achieved by 36% of participants receiving FF/VI and by 23% of those receiving TIO.

DISCUSSION

Summary of main results

We reviewed data from two randomised trials (880 participants) comparing efficacy and safety of a once-daily combination of inhaled corticosteroid and long-acting beta₂-agonist (ICS/LABA) in one inhaler versus inhaled long-acting muscarinic antagonist alone (LAMA) in patients with chronic obstructive pulmonary disease (COPD). In both studies, assessment of cardiovascular events was the main objective, follow-up lasted 12 weeks, the combination

ICS/LABA was fluticasone and vilanterol 100/25 mcg once daily, and the LAMA was tiotropium 18 mcg once daily. We also identified one ongoing trial comparing budesonide/formoterol and tiotropium in patients with COPD and bronchiectases.

Both included trials reported mortality. Deaths occurred only in the tiotropium group (four participants in total). In the main analysis, we did not demonstrate or exclude any differences between groups in mortality, but in an additional sensitivity analysis using the Peto odds ratio (OR), undertaken because deaths were a rare event, we showed that the difference favoured fluticasone/vilanterol. However, we have very low confidence in this effect estimate. Of note, death was not a primary endpoint in any of the included trials, and these studies might be underpowered to detect differences in mortality.

Both included studies also assessed COPD exacerbations, pneumonia, and other serious adverse events (mainly of cardiovascular origin). Pneumonia was observed only in the fluticasone/vilanterol group (five participants in total), and in the main analysis we did not demonstrate or exclude any differences between groups, but as above, in an additional sensitivity analysis using the Peto OR, we showed the difference in favour of tiotropium. As for mortality, evidence of very low quality greatly reduces our certainty in this finding. Differences for COPD exacerbations and other serious events could neither be demonstrated nor excluded. All these endpoints were not assessed as primary in the included trials; therefore the population may have been too small to show statistically significant differences.

Included studies assessed quality of life using St George's Respiratory Questionnaire (SGRQ) and noted improvement in all SGRQ components among both groups. However, the mean change difference between groups in total SGRQ was not significant. It is also uncertain whether improvement in symptoms measured by the COPD Assessment Test (CAT score; data available only in Pepin 2014), in hospital admissions (due to pneumonia, COPD exacerbation, or any reason), and in forced expiratory volume in one second (FEV₁) (change from baseline trough in 24-hour weighted mean on treatment day 84) differs between compared treatment options. Only one study assessed the use of rescue medication (Covelli 2016), which was less in the ICS/LABA group. The included trials were not powered to detect differences in aforementioned outcomes, except for FEV₁, which was the primary outcome in one study (Covelli 2016).

Included trials did not provide data for other prespecified endpoints (exacerbations leading to intubation and physical activity measure; e.g. results of six-minute walk test (6MWT)).

In conclusion, our review shows neither major differences between ICS/LABA and LAMA nor equivalence of these treatments in patients with COPD, and a high degree of uncertainty is associated with evidence of very low quality for all assessed outcomes.

Overall completeness and applicability of evidence

Participants and reported outcomes are typical for patients with COPD, except for the arterial stiffness parameter (aortic pulse wave velocity (aPWV) in one study - Pepin 2014), and the requirement for all participants to have either a history of a cardiovascular disease (CVD) event, or at least one additional CVD risk factor (one study - Covelli 2016). However, included trials were focused

on and were powered for surrogate outcomes (FEV₁ in [Covelli 2016](#), and aPWV in [Pepin 2014](#)), and their aims differed from the aims of this review. In addition, follow-up lasted only 12 weeks in both trials. This limits the practical value of evidence related to clinically important (patient-centred) outcomes. Data on mortality are most strongly affected, in that mortality was obviously low during such a short time. Twelve weeks' follow-up also impairs the applicability of evidence for COPD exacerbations, hospital admissions, pneumonia, and other serious adverse events. Follow-up prolonged to at least six months, preferably with annualised results, would be more appropriate for these rarer endpoints. In addition, data synthesis was limited by lack of common data for some outcomes, namely, use of rescue medication and some adverse events. Moreover, assessments of some other endpoints important for patients with COPD, such as admissions to intensive care units (exacerbations leading to intubation) and measures of physical activity (e.g. 6MWT), are lacking. Finally, lack of data prevented us from performing planned subgroup and sensitivity analyses. For future reviews involving more studies, a priori subgroups might also include, for example, peripheral blood eosinophil count.

Quality of the evidence

We assessed the overall quality of evidence as very low for all outcomes. Both included trials were industry sponsored. We downgraded quality by one level for risk of bias because of some limitations for multiple criteria that are sufficient to lower confidence in the estimate of effect despite the absence of high risk ratings. Specifically, selection bias was unclear in one study owing to lack of information on methods of random sequence generation and allocation concealment ([Pepin 2014](#)). Moreover, we assessed risk of performance and detection bias in both studies as unclear for subjective outcomes because imperfect methods of blinding were reported ([Covelli 2016](#); [Pepin 2014](#)). Finally, we judged risk of attrition bias as unclear in both trials despite intention-to-treat analyses of their primary outcomes, because secondary outcome results were not described for all participants, and it is not clear how researchers handled missing data.

Because typical patients with COPD participated in both included trials, the quality of evidence was not influenced by indirectness. We also did not detect significant heterogeneity (inconsistency) between studies. However, the quality of evidence was strongly affected by imprecision for all outcomes, and we lowered the ratings by two levels because small numbers of events and limited numbers of participants resulted in wide (or very wide) confidence intervals, including significant benefits and harms, and/or the optimal information size criterion was not met (or numbers of events were too low for reliable calculation of optimal information size).

We were not able to assess publication bias using funnel plots owing to the small number (only two) of included trials. Paucity of studies also precluded subgroup analyses and sensitivity analysis for risk of bias, which we had pre-planned in the protocol of our review ([Sliwka 2016](#)).

Potential biases in the review process

We performed an exhaustive search of the published and unpublished literature for potentially relevant clinical trials by applying a systematic search strategy. Trial selection and

data extraction followed a prespecified protocol and were independently conducted by two review authors ([Sliwka 2016](#)). Despite all these efforts, additional unidentified trials may exist.

Agreements and disagreements with other studies or reviews

Our review is the first to compare a once-daily combination of inhaled corticosteroid and long-acting beta₂-agonist inhalers (ICS/LABA) versus inhaled long-acting muscarinic antagonists alone (LAMA) in people with chronic obstructive pulmonary disease (COPD).

A previous Cochrane Review compared the combination of inhaled steroid and long-acting beta₂-agonist taken twice daily versus tiotropium ([Welsh 2013](#)). This review was based mainly on the Investigating New Standards for Prophylaxis in Reducing Exacerbations (INSPIRE) trial, and review authors were unable to reach any definitive conclusions. According to the INSPIRE trial, twice-daily combinations of salmeterol and fluticasone propionate when compared with once-daily tiotropium seemed to have a similar effect on the overall exacerbation rate, although fewer dropouts and deaths and a better health status were recorded in the combination group ([Wedzicha 2008](#)). However, withdrawal rates were high (as is usual for COPD trials lasting longer than six months) and were unbalanced between arms, and people who dropped out were not followed up. This reduced the certainty of the effect; therefore the efficacy and safety of combined ICS/LABA compared to tiotropium remained uncertain. In our review, the combination of vilanterol trifenate and fluticasone furoate in comparison to tiotropium alone did not improve health-related quality of life but reduced the use of rescue medication.

Three other Cochrane Reviews may bring us indirect comparisons of treatment efficacy. A network meta-analysis of long-acting inhaled therapies for COPD including beta₂-agonists, anticholinergics, and steroids included a node for combination of ICS and LABA administered twice daily ([Kew 2014](#)). Review authors found the ICS/LABA combination as the most likely treatment strategy to bring the greatest improvement to quality of life and lung function at six months and ranked LAMA second at this time point, which is compatible with our observations according to quality of life.

Nannini et al reviewed 19 randomised controlled trials (RCTs) assessing the efficacy and safety of combined inhaled steroids and long-acting beta₂-agonists versus placebo for treatment of COPD ([Nannini 2013](#)). Combined therapy reduced the rate of moderate exacerbations, but it did not translate to a significant reduction in hospitalisation rate. Also, small benefit over placebo in effects on health-related quality of life, symptoms, lung function, and use of rescue medication was reported. Adverse effects, particularly pneumonia, were more common in the treatment groups than in the placebo groups, but exclusion of the Towards a Revolution in COPD Health (TORCH) trial showed that an excess of pneumonia was seen only with fluticasone propionate/salmeterol - not with the other combined inhalers. ICS alone could be responsible for an increased mortality rate, as was shown in the TORCH fluticasone monotherapy arm versus the ICS/LABA combination arm at the end of the trial ([Calverley 2007](#)). This finding is concordant with the observations of our review because in an additional sensitivity analysis using the Peto odds ratio (OR) due to rare events, we showed statistically significantly increased risk of pneumonia in the

fluticasone/vilanterol group and no differences in other non-fatal serious adverse events as compared with the tiotropium group.

Rojas-Reyes et al reviewed six RCTs with low risk of bias that compared tiotropium in addition to ICS/LABA combination versus tiotropium alone (Rojas-Reyes 2016). Review authors found no statistically significant differences in mortality between treatments nor in all-cause hospitalisations. Health-related quality of life and lung function tests showed significant improvement in the combination treatment group as compared with the tiotropium alone group. At the same time, review authors found no significant differences in adverse events, serious adverse events, or pneumonia due to rare events between treatment groups, which is compatible with our observations, except for mortality and pneumonia in the additional sensitivity analysis based on Peto ORs.

AUTHORS' CONCLUSIONS

Implications for practice

Only two relevant randomised controlled trials (RCTs) have been published to date. Both compared the combination of inhaled corticosteroids (ICS)/long-acting beta₂-agonists (LABA) - fluticasone and vilanterol 100/25 mcg once daily - versus a long-acting muscarinic antagonist (LAMA) - 18 mcg tiotropium; both trials were of short duration and focused on different primary outcomes than were included in our review.

Very low-quality evidence does not allow us to be certain that there are important differences, or equivalence, in effects between once-daily ICS/LABA combined inhalers and long-acting LAMA in patients with chronic obstructive pulmonary disease (COPD). Our confidence is reduced primarily by the imprecision of effect estimates and concerns about the methodological quality of the included studies. However the included trials were not powered to detect differences in clinically important outcomes, such as mortality, hospital admissions, exacerbations, and other undesirable effects or quality of life; therefore more trials with longer follow-up that are focused on patient-important outcomes are needed.

Implications for research

RCTs with complete follow-up of at least 12 months are required to compare once-daily combination ICS/LABA inhalers versus inhaled LAMA in people with COPD. It is suggested that future studies should be designed to take into account the primary and secondary patient-centred outcomes typical for COPD (e.g. mortality, COPD exacerbation, pneumonia, other serious adverse events as primary outcomes; quality of life, hospital admissions, exacerbations leading to intubation, disease-specific adverse events as secondary outcomes). Given that the aims of included studies were not directly dedicated to assessment of effects of the active substance on primary endpoints important in COPD, a comparative study of fluticasone and vilanterol 100/25 mcg once daily versus tiotropium 18 mcg once daily would be valuable. However, in view of the rapid advances in pharmacology dedicated to this group of patients, it is important to take into account what active substances and concentrations will be applied in inhalers used once a day.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Covelli 2016

Methods	<p>Design: randomised, multi-centre, double-blind, parallel-group study</p> <p>Duration: 12 weeks</p> <p>Date of study: April to December 2012</p> <p>Location: the study took place at 56 centres in 6 countries</p> <p>Objectives: to compare the efficacy and safety of once-daily FF/VI and TIO for COPD treatment over a 12-week period, and to investigate if they would differ between patients with CVD and those at risk for CVD</p>
Participants	<p>Population: 623 participants who received either FF/VT (n = 310) or TIO (n = 313)</p> <p>Baseline characteristics</p> <p>Mean age (years): FF/VI/TIO, 62.9 (SD = 8.1)/62.3 (SD = 8.0)</p> <p>Smoking history: FF/VI: current/former smoker, n = 161/149 (% 52/48); pack-years 43.2 (SD 24.5); TIO: current/former smoker, n = 161/152 (% 51/49); pack-years 45.6 (SD 25.2)</p> <p>% Reversibility: FF/VI/TIO, 33/31</p> <p>% FEV₁ predicted: FF/VI/TIO, 49.4 (10.5)/49.7 (11.1)</p> <p>Cardiovascular co-morbidities FF/VT/TIO</p> <p>Hypertension 81%/87%</p> <p>Hypercholesterolaemia 43%/46%</p> <p>Coronary artery disease 27%/26%</p> <p>Diabetes 17%/23%</p> <p>Myocardial infarction 10%/8%</p> <p>Arrhythmia 5%/9%</p> <p>Congestive heart failure 5%/5%</p> <p>Cerebrovascular accident 4%/1%</p> <p>Inclusion criteria: Both sexes (women were postmenopausal or were using effective contraception) aged ≥ 40 years with a clinical diagnosis of COPD, positive smoker status (current or former ≥ 10 pack-years), postbronchodilator FEV₁ range 30% to 70%, FEV₁/FVC ratio ≤ 70% at screening, positive history of CVD event, or at least 1 current CV risk factor (hypertension, hypercholesterolaemia, or treated diabetes)</p> <p>Exclusion criteria: diagnosis of asthma or respiratory disorders other than COPD, recent (≤ 12 months) lung volume reduction surgery, clinically significant abnormalities not due to COPD detected by chest X-ray/CT scan/Holter/ECG/laboratory tests, hospitalisation for poorly controlled COPD within 12 weeks or acute worsening of COPD (treated with corticosteroids or antibiotics) within 6 weeks of screening, long-term or nocturnal oxygen therapy (> 12 hours/d), carcinoma not in complete remission for at least 5 years</p>
Interventions	<p>Drug: fluticasone furoate/vilanterol 100/25 mcg, once daily</p> <p>Tiotropium bromide 18 mcg, once daily</p>

Covelli 2016 (Continued)

Each morning (approximately 6 to 10 am) take 1 inhalation from the NDPI followed by 2 inhalations of the contents of 1 capsule administered via the HandiHaler
In FF/VI group: NDPI with FF/VI and HandiHaler with placebo
In TIO group: NDPI with placebo and HandiHaler with TIO

Co-medication:

Allowed medications: rescue medication (albuterol) and mucolytics (constant dosage)
Excluded medications: systemic/oral/parenteral corticosteroids (recent: ≤ 6 weeks), ICS or ICS/LABA combinations (recent: ≤ 4 weeks), anticholinergics long-acting (1 week before screening and thereafter)/short-acting (4 hours before screening and thereafter), oral PDEI-4 (1 week before screening and thereafter), LABA (within 48 hours before screening and thereafter)

Outcomes	<p>Lung function: FEV₁ (change from baseline trough in 24-hour weighted mean FEV₁ on treatment day 84)</p> <p>Adverse events: fatal serious adverse events; pneumonia; any COPD exacerbation that requires short-burst oral corticosteroids or antibiotics, or both; hospital admissions due to exacerbations and due to pneumonia</p> <p>Other: quality of life (SGRQ-COPD), improvement in symptoms measured, time (calculated over 0 to 4 hours post dose) to an increase of 100 mL from baseline in FEV₁, change from baseline in trough FEV₁ at treatment day 84 (average of day 84 values minus baseline value), changes from baseline and week 12 for 7 biomarkers (hsCRP, CCL-18, SP-D, fibrinogen, IL-6, CC-16, and BNP), pulse rate, heart rate, QTc intervals, ECG, Holter monitoring, clinical chemistry, and hematology results</p>
Notes	<p>Funding: GlaxoSmithKline</p> <p>Sample size: an estimate based on historical data - 271 participants per treatment arm required for 90% power to detect a 60-mL difference between FF/VI and TIO for 24-hour weighted mean FEV₁ at week 12 (SD of 215 mL and significance at the 2-sided 5% level), but to allow for a 10% withdrawal rate, at least 300 participants were to be randomised per treatment arm</p> <p>Withdrawal rate: 19 participants (6.13%) in the FF/VI group and 39 (12.46%) in the TIO group</p> <p>Study number: 115805</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned to the 2 groups in balanced blocks using a validated computerised system and communicated via a validated computerised voice response system
Allocation concealment (selection bias)	Low risk	Intervention: using the Registration and Medication Ordering System when the investigative site called to randomise a participant
Blinding of participants and personnel (performance bias) objective outcomes	Low risk	Double-blind, double-dummy: "TIO and placebo capsules were closely matched in colour, but TIO capsules had trade markings that were not present on the placebo capsules"; not clear if participants noted the difference, HandiHaler covered with label; no information on masking of FF/VI placebo; staff blinded; no influence on objective outcomes
Blinding of participants and personnel (performance bias) subjective outcomes	Unclear risk	Double-blind, double-dummy: "TIO and placebo capsules were closely matched in colour, but TIO capsules had trade markings that were not present on the placebo capsules"; not clear if participants noted the difference, HandiHaler covered with label; no information on masking of FF/VI placebo; staff blinded; unclear influence on subjective outcomes
Blinding of outcome assessment (detection bias) objective outcomes	Low risk	Double-blind, double-dummy: Outcomes were assessed by patients, who were blinded: "TIO and placebo capsules were closely matched in colour, but TIO capsules had trade markings that were not present on the placebo capsules"; not clear if participants noted the difference, HandiHaler covered with label;

Covelli 2016 (Continued)

		no information on masking of FF/VI placebo; staff blinded; no influence on objective outcomes
Blinding of outcome assessment (detection bias) subjective outcomes	Unclear risk	Double-blind, double-dummy: "TIO and placebo capsules were closely matched in colour, but TIO capsules had trade markings that were not present on the placebo capsules"; not clear if participants noted the difference, Hand-ihlaer covered with label; no information on masking of FF/VI placebo; staff blinded; unclear influence on subjective outcomes
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Nineteen participants (6.13%) withdrew from the FF/VI group and 39 (12.46%) from the TIO group Withdrawal rates were described for all outcomes together; ITT was reported for primary outcome; for secondary outcomes, results described were not for all participants; no information on dealing with missing outcome data for those outcomes
Selective reporting (reporting bias)	Low risk	Comparison of protocol with article and methods vs results within article
Other bias	Low risk	None

Pepin 2014

Methods	Design: randomised, multi-centre, double-blind, parallel-group study Duration: 12 weeks + 2 weeks run-in period Date of study: June 2011 to August 2012 Location: Study took place at 46 centres in 7 countries Objectives: to evaluate the effect of treatment with once-daily FF/VI compared with once-daily TIO on arterial stiffness measured as aPWV in patients with COPD and aPWV > 11.0 m/s
Participants	Population: 257 participants who received either fluticasone furoate/vilanterol (FF/VI) (127) or tiotropium (TIO) (130) Baseline characteristics Mean age (years): FF/VI/TIO, 66.7 (SD = 7.20)/67.7 (SD = 7.34) Smoking history: FF/VI, current/former smoker, n = 59 (% = 46); pack-years, 42.6 (SD = 19.82); TIO, current/former smoker, n = 58 (% = 45); pack-years, 44.6 (SD = 24.97) % Reversibility: FF/VI/TIO, 8.5 (11.12)/8.5 (13.86) % postbronchodilator FEV ₁ predicted: FF/VI/TIO, 45.6 (14.49)/47.4 (13.80) Cardiovascular co-morbidities FF/VI/TIO Any cardiovascular risk factor 84%/89% Hypertension 76%/75% Hypercholesterolaemia 41%/41% Coronary artery disease 33%/31%

Pepin 2014 (Continued)

Diabetes 9%/15%

Myocardial infarction 7%/12%

Arrhythmia 7%/5%

Congestive heart failure 18%/15%

Cerebrovascular accident < 1%/4%

Inclusion criteria: male or non-pregnant female aged ≥ 40 years with current or prior history of COPD, history of ≥ 10 pack-years of smoking; post-albuterol/salbutamol $FEV_1 \leq 70\%$ of predicted normal; $FEV_1/FVC \leq 0.7$; $aPWV \geq 11.0$ m/s

Exclusion criteria: active lung disease other than COPD, poorly controlled COPD or clinical instability due to other causes; use of prohibited medications

Interventions	<p>Drug</p> <p>Fluticasone furoate/vilanterol 100/25 mcg, once daily Tiotropium bromide 18 mcg, once daily</p> <p>Each participant was instructed to self-administer blinded study drug Each morning, take 1 inhalation from the NDPI followed by 2 inhalations of the contents of 1 capsule administered via the HandiHaler</p> <p>In FF/VI group: NDPI with FF/VI and HandiHaler with placebo In TIO group: NDPI with placebo and HandiHaler with TIO</p> <p>Co-medication</p> <p>Allowed medications: ACE inhibitors, anticoagulants, calcium channel blockers, statins, antidiabetics, beta-blockers</p> <p>Excluded medications: LABA, ICS other than FF/VI, TIO</p>
Outcomes	<p>Lung function: FEV_1</p> <p>Adverse events: pneumonia, hand fracture, bronchitis, cataract, any COPD exacerbation that requires short-burst oral corticosteroids or antibiotics, or both; cardiovascular event; using local steroid</p> <p>Other: quality of life (CAT, EQ-5D, SGRQ), improvement in symptoms measured, mean change from baseline $aPWV$ at the end of the 12-week treatment period (day 84); vital signs (blood pressure and pulse rate), spirometry parameters, and clinical laboratory test (haematology and chemistry) results</p>
Notes	<p>Funding: GlaxoSmithKline</p> <p>Sample size: based on a 2-sample, 2-sided t test - 102 participants per treatment group - to provide 90% power to detect a treatment difference of 1 m/s in change from baseline in $aPWV$ after 12 weeks ($P = 0.05$)</p> <p>Study number: 115247</p> <p>We contacted study authors to ask about the definition of exacerbation and the transmission of unpublished data, but study authors did not respond to our query. Also we asked the authors of Pepin 2014 about the number of participants who responded with a fall of at least 4 units in SGRQ in each group, but study authors have not replied yet</p> <p>Withdrawal rate: 15 participants (11.81%) in the FF/VI group and 17 (13.08%) in the TIO group</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details

Pepin 2014 (Continued)

Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) objective outcomes	Low risk	Double-blind, double-dummy: "Blinding of TIO was imperfect, however, because the TIO capsules had trade markings but the placebo capsules, while closely matched in colour, did not have trade markings"; staff blinded; no influence on objective outcomes
Blinding of participants and personnel (performance bias) subjective outcomes	Unclear risk	Double-blind, double-dummy: "Blinding of TIO was imperfect, however, because the TIO capsules had trade markings but the placebo capsules, while closely matched in colour, did not have trade markings"; staff blinded; unclear influence on subjective outcomes
Blinding of outcome assessment (detection bias) objective outcomes	Low risk	Double-blind, double-dummy: "Blinding of TIO was imperfect, however, because the TIO capsules had trade markings but the placebo capsules, while closely matched in colour, did not have trade markings"; staff blinded; no influence on objective outcomes
Blinding of outcome assessment (detection bias) subjective outcomes	Unclear risk	Double-blind, double-dummy: "Blinding of TIO was imperfect, however, because the TIO capsules had trade markings but the placebo capsules, while closely matched in colour, did not have trade markings"; staff blinded; unclear influence on subjective outcomes
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Fifteen participants (11.81%) withdrew from the FF/VI group and 17 (13.08%) from the TIO group Withdrawal balanced between groups in numbers and reasons, reported as ITT, but not clear how missing data were dealt with for COPD outcomes as for secondary outcome results described but not for all participants
Selective reporting (reporting bias)	Low risk	Reported as stated in the protocol
Other bias	Low risk	None

ACE: angiotensin-converting enzyme; aPWV: aortic pulse wave velocity; BNP: brain natriuretic peptide; CAT: COPD Assessment Test; CC-16: Clara cell secretory protein; CCL-18: CC chemokine ligand 18; COPD: chronic obstructive pulmonary disease; CT: computed tomography; CV: cardiovascular; CVD: cardiovascular disease; ECG: electrocardiography; EQ-5D: EuroQol five-dimensional questionnaire; FEV₁: forced expiratory volume in one second; FF: fluticasone furoate; FVC: forced vital capacity; h: hours; hsCRP: high-sensitivity C-reactive protein; ICS: inhaled corticosteroid; IL-6: interleukin-6; LABA: long-acting beta-adrenoceptor agonist; NDPI: novel dry powder inhaler; PDEI-4: phosphodiesterase type 4 inhibitor; SD: standard deviation; SGRQ: St George's Respiratory Questionnaire; SP-D: surfactant protein D; TIO: tiotropium; VI: vilanterol.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Bateman 2008	Wrong intervention
Berbecaru Iovan 2015	Wrong intervention
Biscione 2009a	Wrong intervention
Cazzola 2007a	Wrong intervention
Horita 2015	Wrong intervention

Study	Reason for exclusion
INSPIRE 2008	Wrong intervention
Leidy N 2014	Wrong intervention
Malerba 2016	Wrong study design
Maltais 2012	Wrong intervention
NCT01124422	Wrong intervention
Perng 2009	Wrong intervention
Santus 2006	Wrong intervention
Sarac 2013	Wrong dose
Singh 2008B	Wrong comparator
Tricco 2015	Wrong study design

Characteristics of studies awaiting assessment *[ordered by study ID]*

[Hara 2007](#)

Methods	Randomised, single-blind cross-over study
Participants	Patients with COPD
Interventions	Tiotropium vs salmeterol/fluticasone propionate
Outcomes	FEV ₁ , SGRQ
Notes	Frequency of dosing not reported - conference abstract

COPD: chronic obstructive pulmonary disease; FEV₁: forced expiratory volume in one second; SGRQ: St George's Respiratory Questionnaire.

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

[NCT02546297](#)

Trial name or title	Comparisons of inhaled LAMA or ICS + LABA for COPD with bronchiectasis
Methods	Design: randomised, double-blind, cross-over phase 4 Duration: ongoing
Participants	Population: planned sample size (80 participants) will be randomly assigned to budesonide/formoterol and tiotropium Inclusion criteria: 18 years of age or older with diagnosis of COPD group C and bronchiectasis Exclusion criteria: active tuberculosis; severe respiratory disease (such as lung cancer, ARDS, pulmonary encephalopathy, respiratory failure); uncontrollable diabetes; hypersensitivity to any components of ICS/LABA or LAMA

NCT02546297 (Continued)

Interventions	Budesonide/formoterol Tiotropium
Outcomes	Lung function: FEV ₁ Adverse events: pneumonia and other serious adverse events; any COPD exacerbation that requires short-burst oral corticosteroids or antibiotics, or both Other: quality of life (SGRQ, LCQ, CAT, mMRC)
Starting date	January 2015
Contact information	Shanghai Pulmonary Hospital, Shanghai, China Contact: Ke Fei, MD, PhD; +86 21 65115006
Notes	Funding: Shanghai Pulmonary Hospital, Shanghai, China Study number: 20150717

ARDS: acute respiratory distress syndrome; CAT: COPD Assessment Test; COPD: chronic obstructive pulmonary disease; FEV₁: forced expiratory volume in one second; ICS: inhaled corticosteroid; LABA: long-acting beta-adrenoceptor agonist; LAMA: long-acting muscarinic antagonist; LCQ: Leicester Cough Questionnaire; mMRC: modified Medical Research Council; SGRQ: St George's Respiratory Questionnaire.

DATA AND ANALYSES

Comparison 1. Once-daily long-acting beta₂-agonists/inhaled corticosteroids combined inhalers (FF/VI) versus inhaled long-acting muscarinic antagonists (TIO)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality all-cause	2	880	Odds Ratio (M-H, Random, 95% CI)	0.20 [0.02, 1.73]
2 Any COPD exacerbation that requires short-burst oral corticosteroids or antibiotics, or both	2	880	Odds Ratio (M-H, Random, 95% CI)	0.72 [0.35, 1.50]
2.1 Exacerbation	1	623	Odds Ratio (M-H, Random, 95% CI)	0.73 [0.29, 1.83]
2.2 Exacerbation or worsening	1	257	Odds Ratio (M-H, Random, 95% CI)	0.72 [0.22, 2.33]
3 Pneumonia	2	880	Odds Ratio (M-H, Random, 95% CI)	6.12 [0.73, 51.24]
4 Total, serious adverse events	2	880	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.50, 1.83]
5 Quality of life: SGRQ	2	779	Mean Difference (Random, 95% CI)	-1.29 [-3.01, 0.42]
6 Quality of life: improvement by the MCID after 12 weeks	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7 Hospital admissions	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Pneumonia	2	880	Odds Ratio (M-H, Random, 95% CI)	5.14 [0.60, 44.21]
7.2 Exacerbation COPD	2	880	Odds Ratio (M-H, Random, 95% CI)	0.95 [0.13, 6.79]
7.3 Hospitalisation for any reason	2	880	Odds Ratio (M-H, Random, 95% CI)	0.96 [0.49, 1.89]
8 Disease-specific adverse events other than pneumonia	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 Lower respiratory tract infection	2	880	Odds Ratio (M-H, Random, 95% CI)	0.97 [0.25, 3.80]
8.2 Cardiovascular effects	2	880	Odds Ratio (M-H, Random, 95% CI)	0.85 [0.43, 1.67]
8.3 Local steroid effects/candidiasis	2	880	Odds Ratio (M-H, Random, 95% CI)	1.76 [0.83, 3.72]
8.4 Bone disorders/fractures	2	880	Odds Ratio (M-H, Random, 95% CI)	3.06 [0.48, 19.54]
8.5 Ocular effects/glaucoma	2	880	Odds Ratio (M-H, Random, 95% CI)	1.02 [0.11, 9.82]
8.6 Any adverse events (not including serious)	2	880	Odds Ratio (M-H, Random, 95% CI)	0.99 [0.62, 1.57]
9 CAT score difference at 12 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
10 Trough FEV1	2	741	Mean Difference (Random, 95% CI)	0.01 [-0.02, 0.04]

Analysis 1.1. Comparison 1 Once-daily long-acting beta₂-agonists/inhaled corticosteroids combined inhalers (FF/VI) versus inhaled long-acting muscarinic antagonists (TIO), Outcome 1 Mortality all-cause.

Study or subgroup	FF/VI n/N	TIO n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
Test for overall effect: $Z=1.46(P=0.14)$					
Favours FF/VI 0.005 0.1 1 10 200 Favours TIO					

Analysis 1.2. Comparison 1 Once-daily long-acting beta₂-agonists/inhaled corticosteroids combined inhalers (FF/VI) versus inhaled long-acting muscarinic antagonists (TIO), Outcome 2 Any COPD exacerbation that requires short-burst oral corticosteroids or antibiotics, or both.

Study or subgroup	FF/VI n/N	TIO n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
1.2.1 Exacerbation					
Covelli 2016	8/310	11/313		61.75%	0.73[0.29,1.83]
Subtotal (95% CI)	310	313		61.75%	0.73[0.29,1.83]
Total events: 8 (FF/VI), 11 (TIO)					
Heterogeneity: Not applicable					
Test for overall effect: $Z=0.68(P=0.5)$					
1.2.2 Exacerbation or worsening					
Pepin 2014	5/127	7/130		38.25%	0.72[0.22,2.33]
Subtotal (95% CI)	127	130		38.25%	0.72[0.22,2.33]
Total events: 5 (FF/VI), 7 (TIO)					
Heterogeneity: Not applicable					
Test for overall effect: $Z=0.55(P=0.58)$					
Total (95% CI)	437	443		100%	0.72[0.35,1.5]
Total events: 13 (FF/VI), 18 (TIO)					
Heterogeneity: $\tau^2=0$; $\chi^2=0$, $df=1(P=0.99)$; $I^2=0\%$					
Test for overall effect: $Z=0.87(P=0.38)$					
Test for subgroup differences: $\chi^2=0$, $df=1(P=0.99)$, $I^2=0\%$					
Favours FF/VI 0.01 0.1 1 10 100 Favours TIO					

Analysis 1.3. Comparison 1 Once-daily long-acting beta₂-agonists/inhaled corticosteroids combined inhalers (FF/VI) versus inhaled long-acting muscarinic antagonists (TIO), Outcome 3 Pneumonia.

Study or subgroup	FF/VI n/N	TIO n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
Pepin 2014	2/127	0/130		48.69%	5.2[0.25,109.37]
Covelli 2016	3/310	0/313		51.31%	7.14[0.37,138.74]
Total (95% CI)	437	443		100%	6.12[0.73,51.24]
Total events: 5 (FF/VI), 0 (TIO)					
Heterogeneity: $\tau^2=0$; $\chi^2=0.02$, $df=1(P=0.88)$; $I^2=0\%$					
Test for overall effect: $Z=1.67(P=0.09)$					
Favours FF/VI 0.005 0.1 1 10 200 Favours TIO					

Analysis 1.4. Comparison 1 Once-daily long-acting beta₂-agonists/inhaled corticosteroids combined inhalers (FF/VI) versus inhaled long-acting muscarinic antagonists (TIO), Outcome 4 Total, serious adverse events.

Analysis 1.5. Comparison 1 Once-daily long-acting beta₂-agonists/inhaled corticosteroids combined inhalers (FF/VI) versus inhaled long-acting muscarinic antagonists (TIO), Outcome 5 Quality of life: SGRQ.

Analysis 1.6. Comparison 1 Once-daily long-acting beta₂-agonists/inhaled corticosteroids combined inhalers (FF/VI) versus inhaled long-acting muscarinic antagonists (TIO), Outcome 6 Quality of life: improvement by the MCID after 12 weeks.

Analysis 1.7. Comparison 1 Once-daily long-acting beta₂-agonists/inhaled corticosteroids combined inhalers (FF/VI) versus inhaled long-acting muscarinic antagonists (TIO), Outcome 7 Hospital admissions.

Analysis 1.8. Comparison 1 Once-daily long-acting beta₂-agonists/inhaled corticosteroids combined inhalers (FF/VI) versus inhaled long-acting muscarinic antagonists (TIO), Outcome 8 Disease-specific adverse events other than pneumonia.

Analysis 1.9. Comparison 1 Once-daily long-acting beta₂-agonists/inhaled corticosteroids combined inhalers (FF/VI) versus inhaled long-acting muscarinic antagonists (TIO), Outcome 9 CAT score difference at 12 weeks.

Analysis 1.10. Comparison 1 Once-daily long-acting beta₂-agonists/inhaled corticosteroids combined inhalers (FF/VI) versus inhaled long-acting muscarinic antagonists (TIO), Outcome 10 Trough FEV1.

Comparison 2. Sensitivity analyses for rare events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality all-cause	2	880	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.14 [0.02, 0.97]
2 Pneumonia	2	880	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.56 [1.30, 43.75]

Analysis 2.1. Comparison 2 Sensitivity analyses for rare events, Outcome 1 Mortality all-cause.

Analysis 2.2. Comparison 2 Sensitivity analyses for rare events, Outcome 2 Pneumonia.

ADDITIONAL TABLES

Table 1. Other serious adverse events

Coveli 2015		
Events	FF/VI, n (%)	TIO, n (%)
Cardiac disorders		
- Cardio-respiratory arrest	0/310 (0.00)	2/313 (0.64)
- Acute myocardial infarction	0/310 (0.00)	1/313 (0.32)
- Cardiac failure	0/310 (0.00)	1/313 (0.32)
- Cardiac failure congestive	0/310 (0.00)	1/313 (0.32)
Infections and infestations		
- Urinary tract infection	2/310 (0.65)	0/313 (0.00)
- Graft infection	0/310 (0.00)	1/313 (0.32)
- Post-procedural infection	1/310 (0.32)	0/313 (0.00)
Injury, poisoning, and procedural complications		
- Alcohol poisoning	0/310 (0.00)	1/313 (0.32)
- Anaemia postoperative	1/310 (0.32)	0/313 (0.00)
- Cardiac procedure complication	0/310 (0.00)	1/313 (0.32)
- Patella fracture	1/310 (0.32)	0/313 (0.00)
Metabolism and nutrition disorders		
- Dehydration	0/310 (0.00)	1/313 (0.32)
- Hypercholesterolaemia	0/310 (0.00)	1/313 (0.32)
Neoplasms benign, malignant and unspecified (including cysts and polyps)		
- Pancreatic carcinoma	1/310 (0.32)	0/313 (0.00)
Nervous system disorders		
- Epilepsy	0/310 (0.00)	1/313 (0.32)
Psychiatric disorders		
- Alcohol abuse	0/310 (0.00)	1/313 (0.32)
- Depression	0/310 (0.00)	1/313 (0.32)
Vascular disorders		
- Blood pressure fluctuation	1/310 (0.32)	0/313 (0.00)

Table 1. Other serious adverse events (Continued)

- Leriche syndrome	0/310 (0.00)	1/313 (0.32)
- Thrombosis	1/310 (0.32)	0/313 (0.00)
Pepin 2014		
Other serious adverse events	FF/VI, n (%)	TIO, n (%)
Gastrointestinal disorders		
- Acute abdomen	1/127 (0.79)	0/130 (0.00)
- Pancreatolithiasis	1/127 (0.79)	0/130 (0.00)
General disorders		
- Pyrexia	1/127 (0.79)	0/130 (0.00)
Hepatobiliary disorders		
- Bile duct obstruction	1/127 (0.79)	0/130 (0.00)
Infections and infestations		
- Peritonsillar abscess	0/127 (0.00)	1/130 (0.77)
Injury, poisoning, and procedural complications		
- Multiple injuries	0/127 (0.00)	1/130 (0.77)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)		
- Bronchial carcinoma	1/127 (0.79)	0/130 (0.00)
Nervous system disorders		
- Altered state of consciousness	1/127 (0.79)	0/130 (0.00)
Respiratory, thoracic, and mediastinal disorders		
- Pulmonary embolism	0/127 (0.00)	1/130 (0.77)
Skin and subcutaneous tissue disorders		
- Skin ulcer	0/127 (0.00)	1/130 (0.77)

FF: fluticasone furoate; TIO: tiotropium; VI: vilanterol.

Table 2. Other adverse events

Study	Covelli 2015		Pepin 2014	
Event	FF/VI, n (%)	TIO, n (%)	FF/VI, n (%)	TIO, n (%)

Table 2. Other adverse events (Continued)

Total, other (not including serious) adverse events	31/310 (10.00)	32/313 (10.22)	8/127 (6.30)	8/130 (6.15)
Infections and infestations				
- Nasopharyngitis	16/310 (5.16)	13/313 (4.15)	5/127 (3.94)	4/130 (3.08)
Nervous system disorders				
- Headache	18/310 (5.81)	23/313 (7.35)	3/127 (2.36)	5/130 (3.85)

FF: fluticasone furoate; TIO: tiotropium; VI: vilanterol.

APPENDICES

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

Electronic searches: core databases

Database	Frequency of search
CENTRAL (the Cochrane Library)	Monthly
MEDLINE (Ovid)	Weekly
Embase (Ovid)	Weekly
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 Respiriology (APSR)	2004 onwards
British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards
European Respiratory Society (ERS)	1992, 1994, 2000 onwards

(Continued)

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 inclusion in the CAGR

COPD 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 (RCTs)

1. exp "clinical trial [publication type]"/
2. (randomized 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

To identify trials in other electronic databases we will use MEDLINE strategy and RCT filter.

Appendix 2. Search strategy to identify relevant trial reports from the 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 Adrenergic beta-2 Receptor Agonists

#8 long* NEAR beta* NEAR agonist*

#9 salmeterol*

#10 *formoterol*

#11 indacaterol*

#12 QAB149

#13 vilanterol*

#14 GW642444

#15 olodaterol*

#16 "BI 1744 CL"

#17 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16

#18 MeSH DESCRIPTOR Adrenal Cortex Hormones Explode All

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

#20 fluticasone*

#21 budesonide*

#22 beclomethasone*

#23 ciclesonide*

#24 flunisolide*

#25 mometasone*

#26 triamcinolone*

#27 #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26

#28 MeSH DESCRIPTOR Muscarinic Antagonists

#29 muscarinic* NEXT antagonist*

#30 LAMA:ti,ab

#31 tiotropium*

#32 Spiriva

#33 glycopyrronium*

#34 NVA237

#35 Seebri

#36 umeclidinium*

#37 GSK573719

#38 Incruse

#39 aclidinium*

#40 LAS34273

#41 Turdorza

#42 Eklira

#43 #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42

#44 #6 AND #17 AND #27 AND #43

(Note: in search line #4, MISC1 denotes the field in the record where the reference corresponds to condition, in this case, COPD).

CONTRIBUTIONS OF AUTHORS

Agnieszka Sliwka:

- conceived, designed, and wrote the protocol [Background](#), [Objectives](#), and [Methods](#);
- contacted the Cochrane Airways Group Information Specialist;
- co-ordinated the work of the review author team;
- performed final corrections and approved the final version of the protocol; and
- for the review, selected studies, performed full-text screening, extracted data, assessed risk of bias, performed data analysis and synthesis, and provided descriptions of results, discussion, and conclusions.

Milosz Jankowski:

- conceived, designed, and wrote the protocol [Background](#), [Objectives](#), and [Methods](#);
- performed final corrections and approved the final version of the protocol; and
- for the review, selected studies, performed full-text screening, extracted data, assessed risk of bias, and provided descriptions of results, discussion, and conclusions.

Iwona Gross-Sondej:

- conceived, designed, and wrote the protocol [Background](#), [Objectives](#), and [Methods](#);
- performed final corrections and approved the final version of the protocol; and
- for the review, selected studies, performed full-text screening, extracted data, assessed risk of bias, and provided descriptions of discussion and conclusions.

Monika Storman:

- participated in preparation of the protocol [Background](#) section;
- performed final corrections and approved the final version of the protocol; and
- for the review, selected studies, performed full-text screening, extracted data, assessed risk of bias, and provided descriptions of results and data analysis and synthesis.

Roman Nowobilski:

- performed final corrections and approved the final version of the protocol; and
- for the review, selected studies, performed full-text screening, and extracted data.

Małgorzata Bala:

- conceived, designed, and wrote the protocol [Background](#), [Objectives](#), and [Methods](#);
- performed final corrections and approved the final version of the protocol; and
- for the review, resolved disagreements in study selection, extracted data, assessed risk of bias, performed data analysis and synthesis, and provided descriptions of results, discussion, and conclusions.

DECLARATIONS OF INTEREST

AS has no known conflicts of interest.

MJ receives honoraria (as a freelancer) from the publishing company Medycyna Praktyczna, which draws its revenue from many pharmaceutical and medical companies; he is not involved in any interactions with these companies. He is unaware of any direct conflicts of interest.

IGS worked without payment as a consultant for a company that carries out trials for pharmaceutical companies (Cempra, AstraZeneca, Boehringer-Ingelheim) for unrelated indications. She is unaware of any direct conflicts of interest.

MS has no known conflicts of interest.

RN has no known conflicts of interest.

MMB receives honoraria (as a freelancer) from a systematic review company (Kleijnen Systematic Reviews Ltd.), which has also worked for pharmaceutical companies such as GlaxoSmithKline and Beecham, but was not involved in any interactions with pharmaceutical companies. She is unaware of any direct conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- Faculty of Health Science, Jagiellonian University Medical College, Krakow; II Department of Internal Medicine, Jagiellonian University Medical College, Krakow; The University Hospital in Krakow; Department of Hygiene and Dietetics; Systematic Reviews Unit - Polish Cochrane Branch, Jagiellonian University Medical College, Krakow, Poland.

The review authors wrote this protocol partially during the their working time at the above-mentioned institutions

External sources

- None, Other.

The review authors declare that no such funding was received for this systematic review

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

As only two studies were included, meta-analyses for each endpoint could not be performed and assessment of reporting biases was not possible. Paucity of data precluded also planned sensitivity and subgroup analyses. So as not to delay publication, we made only two attempts to contact trial authors to ask for additional data. Information about this is included in the results section.

Because mortality and pneumonia were rare, we conducted additional sensitivity analyses using the Peto odds ratio as appropriate in such cases.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Inhalation; Adrenal Cortex Hormones [*administration & dosage]; Adrenergic beta-2 Receptor Agonists [*administration & dosage]; Androstadienes [administration & dosage]; Benzyl Alcohols [administration & dosage]; Chlorobenzenes [administration & dosage]; Drug Administration Schedule; Forced Expiratory Volume; Muscarinic Antagonists [*administration & dosage]; Pulmonary Disease, Chronic Obstructive [drug therapy]; Quality of Life; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans