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Combined corticosteroid and long-acting beta₂-agonist in one inhaler versus placebo for chronic obstructive pulmonary disease (Review)

Nannini LJ, Poole P, Milan SJ, Holmes R, Normansell R

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[Intervention Review]

Combined corticosteroid and long-acting beta₂-agonist in one inhaler versus placebo for chronic obstructive pulmonary disease

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ABSTRACT

Background

Both long-acting beta₂-agonists (LABA) and inhaled corticosteroids (ICS) have been recommended in guidelines for the treatment of chronic obstructive pulmonary disease (COPD). Their coadministration in a combination inhaler may facilitate adherence to medication regimens and improve efficacy.

Objectives

To determine the efficacy and safety of combined ICS and LABA for stable COPD in comparison with placebo.

Search methods

We searched the Cochrane Airways Group Specialised Register of trials, reference lists of included studies and manufacturers' trial registries. The date of the most recent search was June 2013.

Selection criteria

We included randomised and double-blind studies of at least four weeks' duration. Eligible studies compared combined ICS and LABA preparations with placebo.

Data collection and analysis

Two review authors independently assessed study risk of bias and extracted data. Dichotomous data were analysed as fixed-effect odds ratios (OR) or rate ratios (RR) with 95% confidence intervals (95% CI), and continuous data as mean differences with 95% confidence intervals.

Main results

Nineteen studies met the inclusion criteria (with 10,400 participants randomly assigned, lasting between 4 and 156 weeks, mean 42 weeks). Studies used three different combined preparations (fluticasone/salmeterol, budesonide/formoterol or mometasone/formoterol). The studies were generally at low risk of bias for blinding but at unclear or high risk for attrition bias because of participant dropouts. Compared with placebo, both fluticasone/salmeterol and budesonide/formoterol reduced the rate of exacerbations. Mometasone/formoterol reduced the number of participants experiencing one or more exacerbation. Pooled analysis of the combined therapies

indicated that exacerbations were less frequent when compared with placebo (Rate Ratio 0.73; 95% CI 0.69 to 0.78, 7 studies, 7495 participants); the quality of this evidence when GRADE criteria were applied was rated as moderate. Participants included in these trials had on average one or two exacerbations per year, which means that treatment with combined therapy would lead to a reduction of one exacerbation every two to four years in these individuals. An overall reduction in mortality was seen, but this outcome was dominated by the results of one study (TORCH) of fluticasone/salmeterol. Generally, deaths in the smaller, shorter studies were too few to contribute to the overall estimate. Further longer studies on budesonide/formoterol and mometasone/formoterol are required to clarify whether this is seen more widely. When a baseline risk of death of 15.2% from the placebo arm of TORCH was used, the three-year number needed to treat for an additional beneficial outcome (NNTB) with fluticasone/salmeterol to prevent one extra death was 42 (95% CI 24 to 775). All three combined treatments led to statistically significant improvement in health status measurements, although the mean differences observed are relatively small in relation to the minimum clinically important difference. Furthermore, symptoms and lung function assessments favoured combined treatments. An increase in the risk of pneumonia was noted with combined inhalers compared with placebo treatment (OR 1.62, 95% CI 1.36 to 1.94), and the quality of this evidence was rated as moderate, but no dose effect was seen. The three-year NNTH for one extra case of pneumonia was 17, based on a 12.3% risk of pneumonia in the placebo arm of TORCH. Fewer participants withdrew from the combined treatment arms for adverse events or lack of efficacy.

Authors' conclusions

Combined inhaler therapy led to around a quarter fewer COPD exacerbations than were seen with placebo. A significant reduction in all-cause mortality was noted, but this outcome was dominated by one trial (TORCH), emphasising the need for further trials of longer duration. Furthermore, we note there has been some debate about the appropriateness of the analysis conducted in the TORCH trial (see Feedback). Increased risk of pneumonia is a concern; however, this did not translate into increased exacerbations, hospitalisations or deaths. Current evidence does not suggest any major differences between inhalers in terms of effects, but nor is the evidence strong enough to demonstrate that all are equivalent. Importantly, we cannot comment on the relative contribution of the individual components of combined therapy to the effects identified, as this review presents only the pair-wise comparison between combined therapy and placebo. To permit firmer conclusions about the effects of combined therapy, more data are needed, particularly in relation to the profile of adverse events and benefits in relation to different formulations and doses of inhaled ICS. Head-to-head comparisons are necessary to determine whether one combined inhaler is better than the others.

PLAIN LANGUAGE SUMMARY

Combined inhalers versus placebo for the treatment of chronic obstructive pulmonary disease (COPD)

Review question

We reviewed the evidence on the effects of combined inhalers in people with COPD when compared with placebo. We particularly focused on whether combined inhalers are a good but safe treatment for adults with COPD.

Background

COPD is a serious respiratory condition that affects millions of people worldwide. In most cases, it is caused by smoking. COPD is often treated by using inhalers. Currently, three types of inhalers combine a steroid and a 'long-acting beta₂-agonist' (LABA). Steroids work by reducing inflammation in the airways, and LABA work by relaxing the muscles in the airways and opening them up. Using combined inhalers is more convenient than taking the two drugs separately but is also more expensive. We looked for evidence on whether giving a combined inhaler is better or worse than giving placebo (dummy inhaler).

Study characteristics

Nineteen studies involving 10,400 people were included in this review. The studies lasted between 4 and 156 weeks. All of the people included in the studies had COPD of different severity. Both men and women were included, and most of the studies included only adults aged 45 or older.

All studies compared a combined inhaler with a placebo that was identical in appearance to the combined inhaler, so the people in the trials did not know whether they were taking the drug or the dummy inhaler. Some of the studies included two groups treated with the combined inhaler; one group was getting a higher dose and one group was getting a lower dose.

The evidence presented here is current to June 2013.

Most of the studies were sponsored by the pharmaceutical industry.

Key results

We found that people receiving a combined inhaler were less likely to have a flare-up ('exacerbation') of their COPD. The chance of having an exacerbation was reduced by about one quarter.

A small reduction in the risk of death was seen over three years, although most of the evidence about death comes from one large, long trial called TORCH. According to TORCH, approximately 42 people would need to be treated with a combined inhaler for three years to prevent one death.

We also found that people receiving combined inhalers had small improvements in quality of life, symptoms related to COPD and their breathing tests. However, these improvements may not have been very noticeable to them.

People treated with combined inhalers were more likely to have a lung infection called pneumonia. Again, most of the evidence about pneumonia comes from the TORCH trial. According to TORCH, when compared with placebo, for approximately every 17 people treated with combined inhaler, one extra person would get pneumonia.

People treated with combined inhalers were no more or less likely to experience serious unwanted events, including side effects, during treatment.

No consistent differences were found between the three different types of inhalers included in this review.

However, it is important to note that we cannot tell from this review whether it is the combination that is important or whether one of the two drugs in the combined inhaler may have had the real impact.

Quality of the evidence

The evidence presented in this review is generally considered to be of moderate quality. Most of the studies did not clearly explain how they decided which people would receive the combined inhaler and which would receive placebo, and this is an important part of a well-conducted study. Also, more people receiving placebo dropped out of the trials than those receiving a combined inhaler. This often happened because of exacerbations of COPD. This means that by the end of the trial, the groups might have been unbalanced, and this could affect the accuracy of the results.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Combined inhalers versus placebo (primary outcomes) for chronic obstructive pulmonary disease

Combined inhalers versus placebo (primary outcomes) for chronic obstructive pulmonary disease (COPD)

Patient or population: patients with COPD

Settings: community

Intervention: combined inhalers

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Combined inhalers versus placebo (primary outcomes)				
Annual exacerbation rates	1.35	0.99 (0.93 to 1.05)	Rate ratio 0.73 (0.69 to 0.78)	7473 (seven studies)	⊕⊕⊕⊖ moderate ^{1, 2}	
Participants with at least one exacerbation Duration of six months³	301 per 1000	251 per 1000 (221 to 286)	OR 0.78 (0.66 to 0.93)	3141 (eight studies)	⊕⊕⊕⊖ moderate ¹	
Mortality Duration of 18 months³	60 per 1000	50 per 1000 (41 to 59)	OR 0.82 (0.68 to 0.99)	10129 (16 studies)	⊕⊕⊕⊖ moderate ^{2, 4}	
Pneumonia Duration of 18 months³	55 per 1000	85 per 1000 (73 to 101)	OR 1.62 (1.36 to 1.94)	9620 (14 studies)	⊕⊕⊕⊖ moderate ^{1, 2}	
Hospitalisations due to COPD exacerbations Duration of 18 months³	115 per 1000	108 per 1000 (95 to 121)	OR 0.93 (0.81 to 1.06)	9492 (12 studies)	⊕⊕⊖⊖ low ^{3, 5}	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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).

CI: Confidence interval; OR: Odds ratio.

GRADE Working Group grades of evidence.

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹Downgraded because of risk of attrition bias.

²Concerns have been raised about the analysis of the largest study, TORCH. We note that the protocol was published after the trial had recruited (See [Feedback 1](#), [Feedback 2](#)).

No downgrade.

³Weighted mean duration.

⁴Downgraded because of imprecision.

⁵Downgraded because of risk of attrition bias and imprecision.

Summary of findings 2. Fluticasone/salmeterol (FPS) versus placebo for COPD

Fluticasone/salmeterol (FPS) versus placebo for COPD

Patient or population: patients with COPD

Settings: community

Intervention: fluticasone/salmeterol (FPS)

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Fluticasone/salmeterol (FPS) versus placebo (PLA)				
Adverse events—any	780 per 1000	794 per 1000 (771 to 816)	OR 1.09 (0.95 to 1.25)	5574 (nine studies)	⊕⊕⊕⊖ Low ^{2, 3}	
Duration of two years ¹						
Adverse events—'serious'	271 per 1000	287 per 1000 (261 to 314)	OR 1.08 (0.95 to 1.23)	5531 (nine studies)	⊕⊕⊕⊖ Low ^{2, 3}	
Duration of two years ¹						

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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).

CI: Confidence interval; OR: Odds ratio.

GRADE Working Group grades of evidence.

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹Weighted mean duration.

²Downgraded because of risk of attrition bias and imprecision.

³Concerns have been raised about the analysis of the largest study, TORCH. We note that the protocol was published after the trial had recruited (See [Feedback 1](#), [Feedback 2](#)).

Summary of findings 3. Budesonide/formoterol (BDF) versus placebo for COPD

Budesonide/formoterol (BDF) versus placebo for COPD

Patient or population: patients with COPD

Settings: community

Intervention: budesonide/formoterol (BDF)

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Budesonide/formoterol (BDF) versus placebo				
Adverse event—any—320/9 ⁴ Duration of nine months ³	538 per 1000	623 per 1000 (574 to 669)	OR 1.42 (1.16 to 1.74)	1552 (two studies)	⊕⊕⊕⊖ low ¹	
Adverse event—any—160/9 ⁴ Duration of nine months ³	538 per 1000	606 per 1000 (557 to 652)	OR 1.32 (1.08 to 1.61)	1556 (two studies)	⊕⊕⊕⊖ low ¹	
Adverse events—'serious'—320/9 ⁴ Duration of 10 months ³	162 per 1000	184 per 1000 (155 to 219)	OR 1.17 (0.95 to 1.45)	2476 (four studies)	⊕⊕⊕⊖ low ²	
Adverse events—'serious'—160/9 ⁴ Duration of nine months ³	113 per 1000	132 per 1000 (102 to 171)	OR 1.2 (0.89 to 1.63)	1556 (two studies)	⊕⊕⊕⊖ low ²	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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).

CI: Confidence interval; **OR:** Odds ratio.

GRADE Working Group grades of evidence.

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹Downgraded because of risk of attrition bias and imprecision and heterogeneity.

²Downgraded because of risk of attrition bias and imprecision.

³Weighted mean duration.

⁴Delivered dose.

Summary of findings 4. Mometasone/formoterol (MF/F) versus placebo for COPD

Mometasone/formoterol (MF/F) versus placebo for COPD

Patient or population: patients with chronic obstructive pulmonary disease

Settings: community

Intervention: mometasone/formoterol (MF/F)

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Mometasone/formoterol (MF/F) versus placebo				
Adverse event—any—400/10 ³ Duration of six months	362 per 1000	357 per 1000 (298 to 424)	OR 0.98 (0.75 to 1.3)	890 (two studies)	⊕⊕⊕⊖ low ¹	
Adverse event—any—200/10 ³ Duration of six months	362 per 1000	317 per 1000 (260 to 382)	OR 0.82 (0.62 to 1.09)	894 (two studies)	⊕⊕⊕⊖ low ²	
Adverse events—serious—400/10 ³ Duration of six months	74 per 1000	80 per 1000 (50 to 125)	OR 1.09 (0.66 to 1.79)	890 (two studies)	⊕⊕⊕⊖ low ²	

Adverse events—serious—200/10³	74 per 1000	53 per 1000 (32 to 89)	OR 0.71 (0.41 to 1.23)	894 (two studies)	⊕⊕○○ low ²
Duration of six months					
<p>*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (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).</p> <p>CI: Confidence interval; OR: Odds ratio.</p>					
<p>GRADE Working Group grades of evidence.</p> <p>High quality: Further research is very unlikely to change our confidence in the estimate of effect.</p> <p>Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.</p> <p>Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.</p> <p>Very low quality: We are very uncertain about the estimate.</p>					

¹Downgraded because of risk of attrition bias, imprecision and heterogeneity.

²Downgraded because of risk of attrition bias and imprecision.

³Delivered dose.

BACKGROUND

Description of the condition

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death in most industrialised countries, and it is projected to be the third leading cause of death worldwide by 2020 (GOLD 2012). The disease is predominantly caused by smoking. An estimated three million people are affected by COPD in the UK (NCGC2010). COPD is a heterogeneous syndrome that is characterised by reduced post-bronchodilator lung function (forced expiratory volume in one second/forced vital capacity (FEV₁/FVC) < 0.7 in all patients (GOLD 2012). Acute bronchodilator reversibility has traditionally been regarded as a characteristic of asthma, and only in the past few years has it been generally acknowledged that this clinical feature is also present in COPD (Hanania 2011), as it was found in the UPLIFT study (UPLIFT 2008), in which 53% of participants had an increase of at least 200 mL in FEV₁ post-salbutamol. In TORCH, an increase in predicted FEV₁ of 10% was an exclusion criterion (TORCH). Patients with COPD generally show progressive lung function loss, accompanied by worsening respiratory symptoms (e.g. dyspnoea, cough and sputum) and health status (GOLD 2012). These clinical features are a result of persisting and progressive airway inflammation (i.e. bronchial infiltration of neutrophils, macrophages, lymphocytes and mast cells) and increasing evidence of autoimmunity (Cosio 2009). Furthermore, it has been suggested that some phenotypes of COPD involve chronic systemic inflammation that has an impact on co-morbidities, such as cardiovascular disease (Garcia-Aymerich 2011).

Description of the intervention

This review focusses on combined inhalers that contain both an inhaled corticosteroid (ICS) and a long-acting beta₂-agonist (LABA).

ICS, LABA and long-acting antimuscarinic agents (LAMA) have been shown to be effective in a range of outcomes in COPD. ICS have not been shown to reduce the rate of decline in FEV₁, although short-term increases in FEV₁ and significant reductions in exacerbations have been reported (Yang 2012). LABA and LAMA reduce exacerbation frequency and symptoms and improve quality of life. On the basis of the evidence, GOLD 2012 recommends that inhaled steroids should be used in patients with an FEV₁ < 50% predicted (GOLD stages 3 and 4 or quadrant C and D in the 2012 update of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria) and a history of exacerbations (GOLD 2012). National Institute for Health and Care Excellence (NICE) guidelines recommend either a LABA with an ICS in a combined inhaler, or with a LAMA, if FEV₁ is less than 50% predicted. Furthermore, the guidelines recommended combined ICS/LABA in people with stable COPD with an FEV₁ ≥ 50% who remain breathless or have exacerbations despite maintenance therapy with a LABA (NCGC2010).

How the intervention might work

The evidence base for the addition of long-acting beta₂-agonists to inhaled steroids in asthma is well established (Ducharme 2010; Ni Chroinin 2009). In asthma, the scientific rationale for combining LABA and ICS in a single inhaler relates to synergy of action. At a molecular level, ICS up-regulate the expression of beta₂-

agonist receptors in bronchial smooth muscle. At the same time, LABA increase the genomic actions of ICS by promoting passage to the cellular nuclei. Thus, beta₂-agonists and ICS may interact in a beneficial way, with ICS preventing the loss of function of beta₂-agonists with long-term use, whereas beta₂-agonists may potentiate the local anti-inflammatory actions of ICS in people with asthma (Barnes 2002).

Some of these mechanisms may also be important in COPD. Several possible advantages associated with a combination of therapies have already been shown to improve outcomes. In particular, ICS in combination with LABA may have a greater effect than either treatment alone on the number of exacerbations, or on other outcomes such as quality of life (Nannini 2012; Nannini 2013). One clinical rationale is based on patient convenience, with the expectation that a simplified inhaler regimen may lead to greater treatment adherence (Barnes 2002).

Why it is important to do this review

This is an update of a previous review, which considered the effect of combined therapy compared with placebo, as well as both monocomponents separately, in people with COPD (Nannini 2004). The availability of several new studies has prompted us to split the review between comparisons with placebo and those with monocomponents. This review summarises the evidence from clinical trials comparing combined ICS and LABA with placebo. Reviews of the comparison between combined therapy and ICS (Nannini 2013) or long-acting beta₂-agonists (Nannini 2012) are published separately.

Concerns have been raised recently regarding the safety of LABA in asthma (Walters 2007). Moreover, questions have surrounded the validity of summary estimates from clinical trials that assessed exacerbation rates without accounting for follow-up time or adjustment for between-participant variability (Suisse 2006). Two well-known COPD guidelines (GOLD 2012; NCGC2010) had issued a strong recommendation regarding ICS/LABA combined therapy. But others are more guarded: "Recommendation 5: ACP, ACCP, ATS, and ERS suggest that clinicians may administer combination inhaled therapies (long-acting inhaled anticholinergics, long-acting inhaled beta₂-agonists, or inhaled corticosteroids) for symptomatic patients with stable COPD and FEV₁ < 60% predicted (Grade: weak recommendation, moderate-quality evidence)" (ACP 2011). Finally, the largest randomised controlled trial (RCT) of combined therapy (TORCH) demonstrated a significant reduction in mortality versus placebo (P = 0.052). We wished to see whether other combined inhalers had a similar effect.

OBJECTIVES

To determine the efficacy and safety of combined ICS and LABA for stable COPD in comparison with placebo.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised, double-blind, parallel-group clinical trials of at least four weeks' duration.

Types of participants

Adult patients (age > 40 years) with known, stable COPD fulfilling American Thoracic Society (ATS), European Respiratory Society (ERS) or Global Initiative for Chronic Obstructive Lung Disease (GOLD) diagnostic criteria. Patients were to be clinically stable with no evidence of an exacerbation for one month before study entry. Patients with significant diseases other than COPD (e.g. with a diagnosis of asthma, cystic fibrosis, bronchiectasis or other lung diseases) were excluded. However, patients with partial reversibility on pulmonary function testing were included.

Types of interventions

- Fluticasone propionate/salmeterol versus placebo (FPS).
- Budesonide/formoterol versus placebo (BDF).
- Mometasone furoate/formoterol versus placebo (MF/F).

Concomitant therapy was permitted, as long as no systematic difference was noted between treatment groups; however, trials in which participants were randomly assigned to tiotropium and combined ICS/LABA therapy versus tiotropium and placebo were excluded from the review, as this comparison is already considered in [Karner 2011](#).

Types of outcome measures

Primary outcomes

- Exacerbations, measured as rate or number of participants experiencing an exacerbation.
- All-cause mortality.
- Pneumonia.
- Hospitalisations due to COPD exacerbation (note that we accepted COPD reported as a serious adverse event as a surrogate marker for this outcome; the internationally recognised definition of a serious adverse event includes a life-threatening event or one that results in hospitalisation or prolonged hospitalisation).

Secondary outcomes

- Change in forced expiratory volume in 1 second (FEV₁) and change in forced vital capacity (FVC): trough, peak and average and other measures of pulmonary function.
- Exercise performance: six-minute walk and other measures.
- Quality of life scales: St George's Respiratory Questionnaire (SGRQ), Chronic Respiratory Disease Questionnaire (CRDQ).
- Symptoms.
- Inhaled rescue medication used during the treatment period and other concomitant medications used, including antibiotics and steroids.
- Adverse events: palpitations, tremor, hoarseness/dysphonia, oral candidiasis, cataracts, skin bruising, bone fracture, bone density, plasma cortisol level.
- Rate of withdrawal due to lack of efficacy or COPD deterioration.
- Withdrawal due to adverse events.

Search methods for identification of studies

Electronic searches

We identified trials using the Cochrane Airways Group Specialised Register of trials, which is derived from systematic searches of

bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED and PsycINFO; we also handsearched respiratory journals and meeting abstracts (see [Appendix 1](#) for more details). All records in the Specialised Register coded as 'COPD' were searched using the following terms:

((beta* and agonist*) and long*) or ((beta* and adrenergic*) and long*) and (*steroid or steroid* or corticosteroid*) or (fluticasone and salmeterol) or Seretide or Advair or (formoterol and budesonide) or Symbicort.

The most recent search was done in June 2013. We applied no restrictions on language of publication or publication type.

Searching other resources

We reviewed reference lists of all primary studies and review articles for additional references, and we contacted authors of identified randomised trials about other published and unpublished studies. In addition, we consulted the online trial registries of GlaxoSmithKline and AstraZeneca, manufacturers of FPS and BDF, respectively (www.ctr.gsk.co.uk; www.astrazenecaclinicaltrials.com).

Data collection and analysis

Selection of studies

Two review authors (LJN and PP) independently identified abstracts of trials that appeared potentially relevant. Using the full text of each study, these review authors independently selected trials for inclusion in the review. Consensus was by simple agreement, with third party adjudication used to resolve differences.

Data extraction and management

Two review authors (RN and RH) independently extracted data from included trials. RN entered the data into Review Manager, and this work was checked by RH. In some cases, we estimated information regarding outcomes from graphs. This was performed independently. Data extraction included the following items.

- **Design:** method of randomisation, presence and type of run-in period, study design (parallel, cross-over).
- **Population:** age, gender, smoking status, study setting (country, practice setting), inclusion and exclusion criteria.
- **Intervention:** dose, delivery device, duration.
- **Control:** concurrent treatments (ipratropium, beta₂-agonist, inhaled and systemic corticosteroids).
- **Outcomes:** as above.

Assessment of risk of bias in included studies

The risk of bias of included studies was assessed using The Cochrane Collaboration's risk of bias tool ([Higgins 2011](#)). Two review authors (RN and RH) assessed the risk of bias of all included studies with regard to random sequence generation, allocation concealment, blinding, incomplete outcome data and selective outcome reporting. Each item was assessed as having high, low or unclear risk of bias on the basis of relevant information reported in the randomised controlled trial.

Measures of treatment effect

For dichotomous variables, data are expressed as odds ratios (OR) with 95% confidence intervals (CI). Data for continuous variables were reported as mean differences (MD) with 95% CI.

Unit of analysis issues

The unit of analysis was the participant.

Dealing with missing data

We contacted study sponsors and primary investigators to obtain information that we could not verify by reviewing the study reports.

We used reported confidence intervals or P values to calculate standard deviations, or standard errors, when necessary.

Assessment of heterogeneity

For pooled effects, heterogeneity was assessed by using the I^2 measurement. This estimates the degree of variation between studies not attributable to the play of chance. I^2 was interpreted in relation to the following guidance (Higgins 2011).

- 0% to 40%: may not be important.
- 30% to 60%: may represent moderate heterogeneity.
- 50% to 90%: may represent substantial heterogeneity.
- 75% to 100%: may represent considerable heterogeneity (Higgins 2011).

We also considered the χ^2 test (P value < 0.10). We regarded I^2 as our primary measure of heterogeneity.

Assessment of reporting biases

We evaluated publication bias by using visual inspection of funnel plots when an adequate number of trials were aggregated in the analyses (more than ten). We recognised that an asymmetrical funnel plot can reflect heterogeneity, outcome reporting bias and small study effects and therefore is not necessarily a reflection of publication bias.

Data synthesis

For continuous variables, we used a fixed-effect mean difference (MD) for outcomes measured on the same metric. A standardised mean difference (SMD) with 95% confidence interval (95% CI) was calculated for outcomes when data were combined from studies using different metrics. All similar studies were pooled using fixed-effect MD/SMD and 95% CI.

For dichotomous variables, we calculated a fixed-effect odds ratio (OR) with 95% CI. All similar studies were pooled using a fixed-effect OR and 95% CI.

When mean treatment differences were reported, data were entered as generic inverse variance (GIV), provided a standard error for the difference could be extracted or imputed. When this method was used, the effect size was reported from the original papers, for example, as a Rate Ratio (RR). This method (GIV) was not available when the protocol was written for the review, so it was not prespecified.

We used pooled OR with 95% CI to calculate numbers needed to treat for an additional beneficial outcome (NNTB) or harm (NNTH)

using [Visual Rx](#). Control event rates were taken from the event rates in the individual trials and are reported with the corresponding duration of the trial because NNTs are time dependent (Cates 2012).

Subgroup analysis and investigation of heterogeneity

We separated the types of steroids and long-acting beta₂-agonists, and for the new studies included in this update, we also separated differing dosages of the same drug. We planned the following a priori subgroups.

- Disease severity (related to baseline FEV₁ and placebo group exacerbation rate) according to GOLD staging of IIA or IIB (moderate COPD, characterised by deteriorating lung function (IIA = FEV₁ ≤ 80% predicted; IIB = ≤ 50% predicted) with progression of symptoms) and III (severe COPD, characterised by severe airflow limitation (FEV₁ < 30% predicted) and the presence of respiratory failure or clinical signs of right heart failure (GOLD 2012).
- Prior inhaled corticosteroid plus long-acting beta₂-agonist use (dichotomised as yes/no).
- Concurrent therapy with routine beta₂-agonist (short- or long-acting), corticosteroid (systemic or inhaled) or theophylline (dichotomised as yes/no).
- Reversibility of airflow obstruction with beta₂-agonist therapy (dichotomised as partial/none). Definition: > 12% and > 200 mL from baseline FEV₁ or > 12% post-bronchodilator (metered-dose inhaler (MDI) salbutamol 200 to 400 mcg).
- Dose, duration and delivery method of therapy.

Sensitivity analysis

For pooled effects, heterogeneity was to be tested by using the I^2 measurement of the degree of variation between studies, not attributable to the play of chance. If heterogeneity was found (I^2 statistic > 30%), a random-effects model was used to determine the impact of heterogeneity on the overall pooled effect. In addition, the robustness of the results was tested using a sensitivity analysis based on the quality of the trials when possible.

RESULTS

Description of studies

Results of the search

For details of the search history, see [Table 1](#).

Included studies

Nineteen studies are included in this review. A previous ongoing study, Morgan 2004, has now been linked to the [TRISTAN](#) trial. For a full description of baseline characteristics, methods used and inclusion and exclusion entry criteria for the individual studies, see [Characteristics of included studies](#).

Design

All trials had a randomised, double-blind, parallel-group design and were of at least four weeks' duration. Methods of randomisation were described in six studies (Bourbeau 2007; Lapperre 2009; Mahler 2002; Sin 2008; Tashkin 2008; Tashkin 2012). The method of blinding was not fully described in all studies. Through correspondence from GlaxoSmithKline, trial methodology

was confirmed for [TRISTAN](#), and AstraZeneca confirmed the methodology for [Szafranski 2003](#). Study characteristics were sufficiently described in two data sets without journal publication to justify their inclusion in the review ([SFCT01](#) and [SCO104925](#)).

Participants

A total of 10,400 participants were randomly assigned to interventions within studies included in this review. Participants suffered from COPD, with variable definitions of COPD and reversibility. COPD was defined by national or international criteria as follows: ATS ([Hanania 2003](#); [Mahler 2002](#)); ERS ([TORCH](#); [TRISTAN](#)); or GOLD ([Barnes 2006](#); [Bourbeau 2007](#); [Calverley 2003](#); [Dal Negro 2003](#); [Lapperre 2009](#); [Sin 2008](#); [Szafranski 2003](#); [Zheng 2006](#)). In seven studies, definitions were not specified or were based on lung function tests and smoking history ([Doherty 2012](#); [O'Donnell 2006](#); [Rennard 2009](#); [SCO104925](#); [SFCT01](#); [Tashkin 2008](#); [Tashkin 2012](#)). Participant populations in the studies suffered from moderate to very severe COPD, with the exception of [Bourbeau 2007](#), in which participants with mild COPD were also enrolled, and [Sin 2008](#), in which enrolled participants had $FEV_1 < 80\%$ predicted. Two studies enrolled participants with reversible or non-reversible COPD ([Hanania 2003](#); [Mahler 2002](#)). In [TORCH](#), participants were not required to have had previous exacerbations requiring oral steroids or antibiotics to be included in the study. All participants were required to have a smoking history, with the exception of those enrolled in [Zheng 2006](#), which included both smokers and never smokers.

Interventions

All 19 studies compared combination therapy with placebo, but the therapies varied. Thirteen studies compared FPS with placebo, four compared BDF and two compared MF/F. In three of the FPS studies, the combination of ICS/LABA was 250 mcg/50 mcg twice daily ([Dal Negro 2003](#); [Hanania 2003](#); [O'Donnell 2006](#)). In the remainder of the FPS studies, the dose was 500 mcg/50 mcg twice daily. Previous versions of this review did not consider these dosage groups separately, and as the participant numbers are small, this has not been changed in the current update. In [Calverley 2003](#) and [Szafranski 2003](#), the combination ICS/LABA was BDF 320 mcg/9 mcg twice daily, whereas both [Rennard 2009](#) and [Tashkin 2008](#) included two combined inhaler active treatment arms: BDF 320 mcg/9 mcg twice daily and 160 mcg/9 mcg twice daily. The two studies of MF/F, [Doherty 2012](#) and [Tashkin 2012](#), also included two combined inhaler active treatment arms: 400/10 twice daily and 200/10 twice daily.

The nature of the run-in period varied between studies, but studies generally included a two- to four-week washout period from inhaled long-acting medication. In one study, all participants had a two-week run-in treatment with oral corticosteroids, inhaled

formoterol and as required a short acting beta₂-agonist (SABA) ([Calverley 2003](#)). Full details are given in the tables of included studies.

Concomitant therapy was as-needed SABA, short-acting muscarinic antagonists (SAMA) and, in some studies, tiotropium. In five studies, theophylline was also used. Eleven per cent of participants in [Hanania 2003](#) and all 18 participants in [Dal Negro 2003](#) received theophylline, in addition to the study drugs. One participant in the FPS group in [Bourbeau 2007](#) used theophylline. The exact proportion of participants in [TRISTAN](#) who were taking theophylline was not reported. In [Zheng 2006](#), 2.7% of the active treatment group used theophylline compared with 7.4% of the placebo group. Oral steroids and/or antibiotics were used in all studies in the case of exacerbations.

Duration

- 13 weeks or less: [Barnes 2006](#); [Bourbeau 2007](#); [O'Donnell 2006](#); [Sin 2008](#); [SCO104925](#).
- 24 to 26 weeks: [Doherty 2012](#); [Hanania 2003](#); [Mahler 2002](#); [Tashkin 2008](#); [Tashkin 2012](#); [Zheng 2006](#).
- 52 weeks: [Calverley 2003](#); [Dal Negro 2003](#); [SFCT01](#); [Szafranski 2003](#); [Rennard 2009](#); [TRISTAN](#).
- 130 weeks: [Lapperre 2009](#).
- 156 weeks: [TORCH](#).

Outcomes

The definition of an exacerbation varied between the included studies, and all definitions are summarised in [Appendix 2](#). [Hanania 2003](#) and [Mahler 2002](#) withdrew participants whose condition was exacerbated. Lung function, if reported, was measured as FEV_1 or peak expiratory flow (PEF). Quality of life assessment by SGRQ or CRDQ was available for [Calverley 2003](#); [Doherty 2012](#); [Hanania 2003](#); [Mahler 2002](#); [Rennard 2009](#); [SFCT01](#); [Szafranski 2003](#); [Tashkin 2008](#); [Tashkin 2012](#); [TORCH](#); [TRISTAN](#); and [Zheng 2006](#). In addition, breathlessness, cough and sputum score (BCSS) was reported by [Rennard 2009](#) and [Tashkin 2008](#). All-cause mortality was reported by [TORCH](#).

Excluded studies

Studies that did not meet the entry criteria of this review are listed in [Characteristics of excluded studies](#), together with a reason for exclusion.

Risk of bias in included studies

A summary of the risk of bias assessment for each trial is provided in [Figure 1](#).

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias): Mortality	Incomplete outcome data (attrition bias): All other outcomes	Selective reporting (reporting bias)
Barnes 2006	?	?	+	+	+	+
Bourbeau 2007	+	?	+	-	-	?
Calverley 2003	?	?	+	-	-	+
Dal Negro 2003	?	?	+	?	?	?
Doherty 2012	?	?	+	?	?	?
Hanania 2003	?	?	+	-	-	+
Lapperre 2009	+	?	+	-	-	+
Mahler 2002	?	?	+	-	-	+
O'Donnell 2006	?	?	+	+	+	?
Rennard 2009	?	?	+	-	-	?
SCO104925	?	?	+	?	?	+
SFCT01	?	?	+	-	-	+
Sin 2008	+	+	+	?	?	?
Szafranski 2003	+	+	+	-	-	+
Tashkin 2008	+	?	+	-	-	+
Tashkin 2012	+	+	+	-	-	?
TORCH	+	?	+	+	-	+
TRISTAN	+	+	+	-	-	+
Zheng 2006	?	?	+	?	?	+

Allocation

Most of our judgements on allocation procedures were unclear because of the paucity of information provided in the trial reports. We were able to ascertain a low risk of bias in four large studies (Szafranski 2003; Tashkin 2012; TORCH; TRISTAN) and in one smaller study (Sin 2008). However, as most included studies are industry-sponsored, they are extremely likely to have followed gold standards for both random sequence generation and concealment of allocation and therefore to be at low risk of bias.

Blinding

All studies were 'double-blinded', and the authors stated that identical inhaler devices were used to deliver active treatment and placebo; they therefore are likely to be at low risk of performance and detection bias. However, in all trials, further details of participant and assessor blinding were not given.

Incomplete outcome data

Most studies had high attrition rates and therefore were deemed to be at unclear or high risk of bias for all outcomes, including mortality. The TORCH trial, however, attempted to follow up all participants for their vital status and therefore was deemed to be at low risk of bias for this outcome. It should be noted that attrition rates reported in the included studies are in keeping with, if not lower than, those expected in COPD trials; therefore these studies are at low risk of bias when compared with similar trials in this field.

Selective reporting

Most included studies reported all prespecified outcomes and were deemed to be at low risk of reporting bias. However, as pointed out in feedback received, the trial protocol of the largest included study, TORCH, was submitted and published after recruitment of participants (Vestbo 2004).

Other potential sources of bias

Both SCO104925 and SFCT01 are pharmaceutical company reports that have not been published in the peer-reviewed literature.

However, the trials were sufficiently described to warrant their inclusion and are likely to be at low risk of bias.

Effects of interventions

See: [Summary of findings for the main comparison](#) Combined inhalers versus placebo (primary outcomes) for chronic obstructive pulmonary disease; [Summary of findings 2](#) Fluticasone/salmeterol (FPS) versus placebo for COPD; [Summary of findings 3](#) Budesonide/formoterol (BDF) versus placebo for COPD; [Summary of findings 4](#) Mometasone/formoterol (MF/F) versus placebo for COPD

Primary outcomes

Rate of exacerbations

Pooled results of all combined inhalers versus placebo

When data from seven trials (N = 7495) were pooled, the overall reduction in the rate of exacerbations when FPS or BDF was used was 0.73 (95% CI 0.69 to 0.78; [Analysis 1.1](#)); the quality of this evidence when GRADE criteria were used was rated as moderate ([Summary of findings for the main comparison](#)).

FPS versus placebo

A significant reduction was noted in the rate of exacerbations with combination therapy when compared with placebo (RR 0.74, 95% CI 0.69 to 0.80, three studies, 4255 participants; [Analysis 2.1](#)). This result was not altered by removing TRISTAN, a study for which the summary estimate may have been biased by inadequate adjustment for between-participant variability (Suisa 2006); see [Figure 2](#). Additional analyses were performed on exacerbations with specific definitions. Compared with placebo, FPS led to fewer exacerbations requiring oral steroids (RR 0.57, 95% CI 0.52 to 0.63, three studies), less requirement for antibiotics (RR 0.60, 95% CI 0.41 to 0.88) and fewer hospitalisations (RR 0.83, 95% CI 0.7 to 0.97, two studies).

Figure 2. Forest plot of comparison: 1 Combined inhalers versus placebo (primary outcomes), outcome: 1.1 Exacerbation rates with combined inhalers versus placebo.

BDF versus placebo

A significant effect on pooled exacerbation rates favoured BDF compared with placebo (RR 0.71, 95% CI 0.62 to 0.81); see [Figure 2](#). These results are based on data on 3240 participants from four trials ([Szafranski 2003](#); [Calverley 2003](#); [Rennard 2009](#) and [Tashkin 2008](#)).

Number of people experiencing at least one exacerbation

FPS versus placebo

No significant difference was noted between FPS and placebo in terms of the number of participants experiencing at least one exacerbation (OR 0.83, 95% CI 0.64 to 1.07, seven studies, 1817 participants; [Analysis 2.2](#))

MF/F versus placebo

The odds ratio for the numbers of participants experiencing at least one exacerbation for the 400/10 strength inhaler was 0.72 (95% CI 0.54 to 0.95, 882 participants; [Doherty 2012](#); [Tashkin 2012](#)) and 0.76 (95% CI 0.58 to 1.01) for the 200/10 strength inhaler (886 participants; [Doherty 2012](#); [Tashkin 2012](#)).

The point estimates are very similar, and the test for subgroup differences is negative. Thus it cannot be inferred from these results that one strength inhaler is significantly different from another (Chi² = 0.10, df = 1, P = 0.75, I² = 0%).

Of interest, a post hoc observation was made that the treatment effect is more pronounced when only participants with moderate or severe exacerbations are considered, that is, those requiring antibiotics and/or systemic steroids, emergency treatment or hospitalisation (OR 0.57, 95% CI 0.38 to 0.86 for 400/10; and OR 0.62, 95% CI 0.42 to 0.92 for 200/10; [Analysis 4.2](#)).

Mortality

Pooled results of all combined inhalers versus placebo

When results were pooled, the overall reduction in mortality with FPS, BDF or MF/F compared with placebo was 0.82 (95% CI 0.68 to 0.99, 16 studies, N = 10,129); the quality of this evidence was rated as moderate ([Summary of findings for the main comparison](#)). Most of the weight for mortality comes from the [TORCH](#) trial, which is the only included trial that collected mortality as a primary outcome ([Figure 3](#)).

Figure 3. Forest plot of comparison: 1 Combined inhalers versus placebo (primary outcomes), outcome: 1.2 Mortality.

Because differing length of follow-up across studies hinders the calculation of a pooled NNTB, we have tabulated this for each study individually (see [Table 2](#)). The three-year NNTB (using the baseline risk of 15.2% in the placebo arm of [TORCH](#)) to prevent one extra death is 42 (95% CI 24 to 775).

FPS versus placebo

The adjusted hazard ratio (HR) from [TORCH](#) did not identify a significant effect of FPS over placebo (HR 0.825, 95% CI 0.681 to 1.002, $P = 0.052$; [TORCH](#)). When the number of deaths in each treatment group was analysed by odds ratio and was combined with data from four other studies, a significant reduction in the odds of death favoured FPS versus placebo (OR 0.79, 95% CI 0.65 to 0.97, $N = 5543$, 10 studies; [Analysis 2.5](#)). Data were separated according to the time point and were subgrouped for data reported at three years, data at one to three years, data at one year and data at six months.

BDF versus placebo

The four studies with duration of six months to one year involving 3250 participants did not detect a significant difference in mortality between BDF and placebo (OR 1.05, 95% CI 0.57 to 1.93; [Analysis 3.3](#)).

MF/F versus placebo

Neither of two very similar studies ([Doherty 2012](#); [Tashkin 2012](#)) of 26 weeks' duration and including 1336 participants detected a significant difference between MF/F and placebo (OR 1.35, 95% CI 0.36 to 5.13; [Analysis 4.3](#)).

However, it should be noted that the confidence intervals for both MF/F and BDF are wide and overlap with those of FPS, so a decrease in mortality with MF/F or BDF cannot be excluded.

Pneumonia

Pooled results of all combined inhalers versus placebo

For combined inhalers, the pooled OR for pneumonia is 1.62 (95% CI 1.36 to 1.94, N = 9620, fixed-effect model) with a moderate level of heterogeneity ($I^2 = 32\%$); the quality of this evidence was rated as moderate ([Summary of findings for the main comparison](#)). When a random-effects model of analysis is used, the effect size is reduced

but remains significant (OR 1.57, 95% CI 1.01 to 2.42). Most of the weight for this combined result again comes from the TORCH trial, which tested the FPS inhaler.

FPS versus placebo

Pooled data from nine FPS trials (N = 5447) show a significant increase in pneumonia among participants treated with FPS in comparison with placebo (OR 1.76, 95% CI 1.46 to 2.14; [Figure 4](#)).

Figure 4. Forest plot of comparison: 1 Combined inhalers versus placebo (primary outcomes), outcome: 1.3 Pneumonia.

BDF versus placebo

Calverley 2003, Rennard 2009 and Tashkin 2008 reported data on pneumonia; no significant difference was detected between BDF and placebo (OR 0.92, 95% CI 0.57 to 1.47). The test for subgroup differences between BDF and FPS was significant ($P = 0.01$) when a fixed-effect model was used. However, when a random-effects model was applied, no significant difference between subgroups was found ($P = 0.65$).

MF/F versus placebo

Data from Doherty 2012 and Tashkin 2012 suggest no significant difference between treatments in diagnoses of pneumonia (OR 2.39, 95% CI 0.68 to 8.36, N = 1336), but the test for a subgroup

difference between MF/F and FPS was negative for both fixed-effect and random-effects models ($P = 0.64$ and 0.66 , respectively).

[Table 2](#) gives the range of numbers needed to treat for an additional harmful outcome (NNTH) across the studies for pneumonia. A pooled NNTH was not calculated because of the wide differences in duration and the likely impact this would have on the calculation of a pooled event rate. The three-year NNTH (when the baseline risk of 12.3% was used in the combination therapy arm of [TORCH](#)) for one extra participant to suffer from pneumonia was 17 (95% CI 27 to 12).

Hospitalisations due to COPD

Pooled results of combined inhalers versus placebo

No significant difference was observed between active treatment and placebo for hospitalisation (OR 0.93, 95% CI 0.81 to 1.06, N

= 9492; Figure 5); the quality of this evidence was rated as low (Summary of findings for the main comparison).

Figure 5. Forest plot of comparison: 1 Combined inhalers versus placebo (primary outcomes), outcome: 1.4 Hospitalisations due to COPD exacerbations.

Secondary outcomes

Quality of life

FPS versus placebo

Treatment with FPS improved SGRQ scores by an average of -2.9 units versus placebo (95% CI -3.61 to -2.18, four studies, N = 3346). Pooled data from Mahler 2002 and Hanania 2003 indicated a statistically significant improvement in CRDQ for those treated with FPS compared with placebo (5 units, 95% CI 2.48 to 7.52).

BDF versus placebo

A significant effect favoured BDF compared with placebo: -3.29 units on the SGRQ (95% CI -4.45 to -2.13) for the 320/9 strength inhaler, and -3.39 units (95% CI -4.70 to -2.07) for the 160/9 strength inhaler. A high level of heterogeneity was noted when these data were pooled ($I^2 = 70\%$). Random-effects modelling also generated a significant effect (MD -4.11, 95% CI -6.18 to -2.04 for 320/9;

and MD -3.39, 95% CI -4.70 to -2.07 for 160/9). The magnitude of improvement in the Szafranski 2003 BDF group was 3.9 units from baseline and was not dissimilar from the change scores from post run-in treatment in Calverley 2003 (see graphical presentation of data in the published article, page 916). However, the placebo group deteriorated more in Calverley 2003, which possibly reflects the withdrawal of active treatment, with the subsequent loss of predosing effects achieved with high-dose oral corticosteroids and LABA. In comparison, BDF may have maintained the predosing treatment effects of quality of life more successfully.

MF/F versus placebo

Treatment with MF/F resulted in a significant improvement in SGRQ scores when compared with placebo. This was true for both 400/10 (MD -3.80, 95% CI -5.75 to -1.86) and 200/10 (MD -3.91, 95% CI -6.01 to -1.81) inhalers.

Symptom score

FPS versus placebo

FPS led to improved symptom scores (transitional dyspnoea index) when compared with placebo (MD 1.04, 95% CI 0.56 to 1.53).

BDF versus placebo

Data were pooled for [Calverley 2003](#) and [Szafranski 2003](#). There was a significant effect in favour of BDF when compared with placebo (MD -0.63, 95% CI -0.90 to -0.37).

[Rennard 2009](#) and [Tashkin 2008](#) reported change from baseline in the breathlessness, cough and sputum score. Both trials described a significant improvement in average score over the treatment period for both strengths of combined inhalers (MD -0.43, 95% CI -0.59 to -0.26 for 320/9; and MD -0.44, 95% CI -0.60 to -0.28 for 160/9).

Lung function

FPS versus placebo

Pooled analysis of data was conducted without findings from the [Dal Negro 2003](#) study. Owing to the small size of this study, we were concerned that the standard deviation (SD) represented an inaccurate estimate for the SD of the population, and that the small variance increased the weight of the study out of all proportion to its size. Data pooled from seven studies revealed an MD in predose FEV₁ of 0.16 L (95% CI 0.14 to 0.19, N = 1408). Pooled data from [Zheng 2006](#) and [TORCH](#) for postdose FEV₁ indicated a significant improvement in favour of FPS over placebo of 0.09 L (95% CI 0.07 to 0.11). Results from [Rennard 2009](#) demonstrate a clear improvement in average 0- to 12-hour FEV₁ for inhalers of both strengths.

BDF versus placebo

FEV₁ data for mean percentage change from baseline were reported by two trials ([Calverley 2003](#); [Szafranski 2003](#)). There was a significant increase in FEV₁ in favour of BDF versus placebo (MD 14.40% 95% CI 11.91 to 16.90).

Predose FEV₁ and one hour postdose FEV₁ data were reported by one study, which included 858 participants ([Tashkin 2008](#)). A significant improvement was noted for both outcomes for combined inhalers of both strengths compared with placebo. [Rennard 2009](#) reported average 12-hour FEV₁ and FEV₁ at 12 hours compared with baseline. Again, a significant improvement was noted for both outcomes and for inhalers of both strengths when compared with placebo.

Both [Rennard 2009](#) and [Tashkin 2008](#) reported change from baseline morning and evening PEF, with significant benefit over placebo noted for inhalers of both strengths.

MF/F versus placebo

Both [Doherty 2012](#) and [Tashkin 2012](#) reported mean change from baseline in predose FEV₁ at 13 weeks and demonstrated a significant improvement for both 400/10 (MD 114.64, 95% CI 77.79 to 151.50) and 200/10 (MD 66.00, 95% CI 14.37 to 117.63) inhalers when compared with placebo. It should be noted that no significant difference was seen between the 400/10 and 200/10 groups (test for subgroup differences: Chi₂ = 2.77, df = 1, P = 0.10).

Mean change from baseline FEV₁ area under the curve (AUC) 0 to 12 hours is also reported by [Doherty 2012](#) and [Tashkin 2012](#) and shows significant improvement in favour of active treatment for inhalers of both strengths (MD 162.04, 95% CI 126.54 to 197.53 for 400/10; and MD 122.01, 95% CI 86.64 to 157.39 for 200/10).

Rescue medication

FPS versus placebo

Pooled data from [Mahler 2002](#) and [Hanania 2003](#) indicated a significant reduction in mean puffs per day of short-acting beta₂-agonist usage for FPS versus placebo (MD -1.19 puffs/d, 95% CI -1.83 to -0.55).

[Mahler 2002](#) reported significant increases in the percentage of nights with no awakenings requiring short-acting beta₂-agonist in favour of FPS versus placebo (5.7% vs -4.3%, respectively; P < 0.031).

[TRISTAN](#) reported a significant difference in median percentage of days without use of relief medication (FPS 14% vs placebo 0%, P < 0.001).

BDF versus placebo

BDF treatment reduced the requirement for reliever medication when compared with placebo. Combined results of [Szafranski 2003](#); [Calverley 2003](#); [Rennard 2009](#) and [Tashkin 2008](#) for the 320/9 strength inhaler show a reduction in use of rescue medication when compared with placebo (-0.98 puffs/d, 95% CI -1.18 to -0.79). Pooled results from [Rennard 2009](#) and [Tashkin 2008](#) compare the 160/9 strength inhaler with placebo and also reveal a reduction in the use of rescue medication (-1.28 puffs/d, 95% CI -1.55 to -1.00).

Safety and tolerability

FPS versus placebo

No significant difference was noted between FPS and placebo in the occurrence of overall reported adverse events (OR 1.09, 95% CI 0.95 to 1.25) or serious adverse events (OR 1.08, 95% CI 0.95 to 1.23, N = 5574, nine studies). In both cases, the quality of evidence was rated as low ([Summary of findings 2](#)).

Pneumonia, candidiasis, nasopharyngitis, hoarseness and upper respiratory tract infection (URTI) occurred more frequently among FPS-treated participants.

- Pneumonia: OR 1.80, 95% CI 1.49 to 2.18, nine studies, N = 5447.
- Candidiasis: OR 5.73, 95% CI 3.07 to 10.67, seven studies, N = 2039.
- Hoarseness: OR 8.79, 95% CI 1.11 to 69.62, two studies, N = 585.
- Nasopharyngitis: OR 1.28, 95% CI 1.05 to 1.56, two studies, N = 3535.
- URTI: OR 1.23, 95% CI 1.04 to 1.47, five studies, N = 4963.

BDF

[Rennard 2009](#) and [Tashkin 2008](#) report overall adverse event data and demonstrate a significant difference favouring placebo for inhalers of both 320/9 and 160/9 strength (OR 1.42, 95% CI 1.16 to 1.74 for 320/9; and OR 1.32, 95% CI 1.08 to 1.61 for 160/9). In both cases, the quality of this evidence was rated as low ([Summary of findings 3](#)).

When only serious adverse events were considered, the odds ratios were 1.17 (95% CI 0.95 to 1.45) for the 320/9 strength inhaler and 1.20 (95% CI 0.89 to 1.63) for the 160/9 strength inhaler; again, the quality of this evidence was rated as low ([Summary of findings 3](#)).

No difference was noted between active treatment and placebo for specific adverse events associated with ICS use, with the exception of reported episodes of candidiasis, which were noted to be significantly higher among those receiving active treatment. In addition, more cases of dysphonia were reported in the active treatment group receiving the higher-dose inhaler, but not in the lower-dose group. However, the test for subgroup differences was negative, so we cannot be certain of a dose effect.

MF/F

No significant difference in the occurrence of overall reported adverse events was reported between either strength of MF/F inhaler and placebo (OR 0.98, 95% CI 0.75 to 1.30 for 400/10; and OR 0.82, 95% CI 0.62 to 1.09 for 200/10). This finding was consistent when only serious adverse events were considered. The quality of this evidence was rated as low in both cases ([Summary of findings 4](#)).

Also, no significant differences were noted between the groups when specific adverse events associated with ICS use were considered, although the overall numbers of events were small.

Withdrawals

FPS versus placebo

Significantly fewer withdrawals from treatment were seen with FPS than with placebo (OR 0.69, 95% CI 0.62 to 0.78). Withdrawals due to adverse events and lack of efficacy also occurred less frequently on treatment with FPS than with placebo (withdrawal due to adverse event: OR 0.74, 95% CI 0.64 to 0.86, twelve studies, 5491 participants; withdrawal due to lack of efficacy: OR 0.30, 95% CI 0.22 to 0.41, eight studies, 5115 participants).

BDF versus placebo

Data were pooled from [Calverley 2003](#); [Rennard 2009](#); [Szafranski 2003](#); and [Tashkin 2008](#) for withdrawals due to adverse events, and from [Calverley 2003](#); [Rennard 2009](#) and [Szafranski 2003](#) for withdrawals due to lack of efficacy or worsening COPD.

A significant difference favoured active treatment in withdrawals due to worsening of COPD symptoms when BDF was compared with placebo (OR 0.56, 95% CI 0.43 to 0.74, three studies, 2392 participants).

No significant difference was noted between BDF and placebo in the likelihood of withdrawal due to any adverse event (OR 0.85, 95% CI 0.70 to 1.03).

MF/F versus placebo

Significantly fewer withdrawals from treatment were seen with MF/F than with placebo for inhalers of both strengths (OR 0.56, 95% CI 0.40 to 0.77 for 400/10; and OR 0.55, 95% CI 0.40 to 0.76 for 200/10).

Of note, a significant difference favoured MF/F when withdrawals due to lack of efficacy of treatment or worsening of COPD symptoms were considered. This was true for inhalers of both strengths (OR

0.24, 95% CI 0.08 to 0.74 for 400/10; and OR 0.31, 95% CI 0.11 to 0.84 for 200/10).

DISCUSSION

Summary of main results

We reviewed data from 19 randomised controlled trials (10,400 participants) assessing the efficacy and safety of combined inhaled corticosteroids and long-acting beta₂-agonists versus placebo for the treatment of COPD. Thirteen studies involved a combined inhaler of fluticasone and salmeterol, four involved budesonide and formoterol and two involved mometasone and formoterol. The findings of this review complement those of two others assessing the effects of combination inhalers with their components, that is, LABA or ICS ([Nannini 2012](#); [Nannini 2013](#)). Despite the addition of eight new studies for this update, most of the weight is still coming from the [TORCH](#) study, which is the largest trial of combined therapy (FPS) in COPD.

Primary outcomes

The main findings related to the primary outcomes of exacerbations, mortality, pneumonia and hospitalisations appear in the [Summary of findings for the main comparison](#). All eligible studies addressed at least one of the primary outcomes.

Combined therapy reduced the rate of moderate exacerbations compared with placebo by about a quarter ([Analysis 1.1](#)). But, as was found in the Cochrane reviews comparing combined inhalers with LABA alone or ICS alone ([Nannini 2013](#)), this did not translate to a statistically significant reduction in COPD hospitalisation rates. One explanation is that those receiving combined treatment who respond may have fewer and/or milder exacerbations, but equally the smaller number of hospitalisations means that less statistical power was present to show a significant difference. On the other hand, adverse effects were more common with combined treatment than with placebo, particularly the development of pneumonia. The NNTH for this outcome in studies of at least 52 weeks' duration varied from 17 to 197. Concern about pneumonia as an adverse event associated with ICS treatment has persisted ever since [TORCH](#) was published in 2006. Indeed our analysis shows that the excess of pneumonia is seen only with FPS, not with the other combined inhalers. If the [TORCH](#) study was not included, the significant OR disappeared, but heterogeneity among trials is still evident ([Analysis 1.3](#)), making it difficult to decide whether this effect is a true one. This may suggest ongoing difficulties with the accurate identification of pneumonia, or variations in participant populations, actions of medicines or the nature of lower respiratory tract infections and their treatment over the time course of a study. It is also possible that the heterogeneity in the pneumonia outcome is due to differential withdrawal rates. Withdrawal due to lack of efficacy in the FPS subgroup was greater in the placebo arm ([Analysis 2.14](#)), as was seen with BDF ([Analysis 3.18](#)) and MF/F studies ([Analysis 4.8](#)). It is interesting to note that withdrawals due to adverse events were not different between arms in BDF ([Analysis 3.17](#)), whereas for MF/F studies, withdrawals due to adverse events were greater in the placebo arm ([Analysis 4.9](#)). These findings suggest something different about the three-year [TORCH](#) study compared with the others. Whatever the case, it is reassuring that this apparent excess of pneumonia cases did not translate into greater numbers of hospitalisations or exacerbations, or greater

mortality rates. In fact, quite the opposite was noted—exacerbation rates and mortality were reduced with combined treatment.

We found that treatment with a combined inhaler led to a significant reduction in mortality compared with placebo when data from all studies were pooled. As with other outcomes, **TORCH** had a major influence on mortality; however, it should be noted that the **TORCH** investigators did not claim a significant reduction in mortality with FPS over placebo ($P = 0.052$). The difference between the study report and the OR reported in this Cochrane review may be due to variations in statistical methods. **TORCH** used a hazard ratio that was adjusted for repeated measurement. This analysis has been the subject of some debate as the study adopted a factorial design but did not report a factorial analysis (see [Feedback 1](#), [Feedback 2](#)). Furthermore, although mortality was recorded in many of the studies, it was a primary outcome in **TORCH**. In that study, cause-specific mortality was also reported, but the definition of a primary cause of death continues to pose challenges in a population of patients who may suffer from co-morbidities such as lung cancer ([McGarvey 2007](#)).

Secondary outcomes

We were unable to pool secondary outcomes and reported results for each type of combined inhaler separately. Although the only way to test whether one product is better than another is a head-to-head comparison, we found that the results for all secondary outcomes, except adverse events, were relatively similar, that is, each combined inhaler showed a small benefit over placebo in effects on health-related quality of life, symptoms, lung function, use of rescue medication and withdrawal rates. In some cases, the benefits reached accepted levels of clinical significance, but only just. Minimal clinical important differences (MCID) are sometimes used to help clinicians interpret trial findings in a meaningful way. The MCID for predose FEV₁ is thought to be approximately 100 mL ([Donohue 2005](#)). [Leidy 2003](#) suggests that changes of 1.0 in the BCSS represent substantial symptomatic improvement, changes of approximately 0.6 can be interpreted as moderate and changes of 0.3 can be considered small. A four-unit difference is the generally accepted MCID for SGRQ score ([Jones 2005](#)). Mean differences reflect an unknown range of results from individual participants, and although an MCID may be achieved on average, this neither confirms nor rules out meaningful improvement over placebo for all. Furthermore, for some of these outcomes, a high degree of heterogeneity was noted, some of which may be due to differences in study protocols.

Overall completeness and applicability of evidence

Participants and outcomes reported were typical of those described for COPD patients. The most abundant evidence comes from studies on the FPS combination, which was the only one to show a mortality benefit. Fewer data are available for the MF/F

combination, but nothing has been discovered to suggest that it behaves differently from the other inhalers.

This review addresses the efficacy and safety of combined ICS and LABA in one inhaler versus placebo as a pair-wise comparison. We did not seek to address the efficacy of the individual components (LABA and ICS) versus combined treatment, although such comparisons were included in some of studies in this review, notably the **TORCH** trial. In this large trial, it appears that the mortality benefit, while not reaching statistical significance, is driven largely by the LABA component of combined therapy. The efficacy of the individual components versus combined therapy is addressed in two linked Cochrane reviews ([Nannini 2012](#); [Nannini 2013](#)) and will be included in a forthcoming network meta-analysis ([Oba 2017](#)).

Quality of the evidence

Most trials were industry-sponsored. The risk of bias in blinding was considered low for all trials. The risk of bias from attrition was considered higher because of the number of participants withdrawn (over 20% in most trials), especially as this group may represent a more severely involved subgroup ([Kesten 2007](#)). In addition, we found significantly greater participant withdrawal in the placebo arm across all three combined inhalers ([Analysis 2.12](#), [Analysis 3.16](#) and [Analysis 4.7](#)). However, the completion rate in the included trials was generally equal to, or better than, that of other trials involving participants with COPD. Selective reporting was generally considered to be of low risk.

Intention-to-treat analyses were conducted in all studies, but for outcomes such as mean exacerbation rates, withdrawal of severe frequent exacerbators from the studies may have distorted study findings because of the lower exacerbation rates seen with active treatment. Loss of participants with more frequent exacerbations from the studies may thus limit the accuracy of mean event rates. The question of exacerbations and the appropriate statistical analysis of rate ratios cast some doubt regarding the validity of some of the findings in this review. In particular, the large long-term studies (i.e. those in excess of six months), which are adequately powered to detect statistically significant findings, may overestimate the treatment effects of this therapy ([Suissa 2006](#)). The method of weighting counts of exacerbations as described by [Suissa 2006](#) (using duration of person follow-up time as a denominator in calculating the mean group rate of exacerbations rather than an unweighted approach) was undertaken in [Calverley 2003](#); [Szafranski 2003](#); and **TORCH**. In these studies, the effects were consistent and significantly favoured combination therapy over placebo. However, the major primary outcome after mortality rate was hospitalisation due to COPD exacerbation, and this did not show any difference between treatments.

Visual inspection of a funnel plot for the mortality outcome does not suggest publication bias ([Figure 6](#)).

Figure 6. Funnel plot of comparison: 1 Combined inhalers versus placebo (primary outcomes), outcome: 1.2 Mortality.

Potential biases in the review process

The Cochrane Airways Group provided an excellent level of support in the identification of potentially relevant trials. To minimise the risk of selection and publication bias, an exhaustive search of the published literature and the unpublished literature, with no language restrictions, for potentially relevant clinical trials was underpinned by a systematic search strategy. Trial selection and data extraction followed a prespecified protocol, and the process was independently conducted by two review authors. Nevertheless, we acknowledge that additional unidentified trials may exist.

Agreements and disagreements with other studies or reviews

This Cochrane review confirms and builds upon an earlier one (Nannini 2004) and upon related reviews (Nannini 2012; Nannini 2013). For this update, we checked all previous data and added hospital admissions using COPD-related serious adverse events as a surrogate marker. To enhance clarity, several outcomes in the FPS subgroup with few contributing studies have been deleted from the current update. We have added data for MF/F versus placebo, as these studies took place after the previous review.

Our finding that combined inhaler therapy reduced death is concordant with that of another review of all inhaled medications

in COPD, which concluded that ICS/LABA was associated with the lowest risk of death among all treatments (Dong 2013).

AUTHORS' CONCLUSIONS

Implications for practice

For people with moderate or severe COPD, clinical benefit is derived when a long-acting beta₂-agonist and an inhaled corticosteroid are co-administered, compared with treatment with placebo, in terms of fewer exacerbations and possibly reduced risk of death. Furthermore, small benefits for quality of life and symptoms are noted. However, the effect of combined treatment on all-cause mortality is heavily weighted by one trial, which in itself was not reported to show a significant reduction. (This point added value to this review because the TORCH study alone did not achieve significance in mortality.) Despite positive effects on exacerbations and mortality, no effect on hospitalisation was reported. Moreover, a paradoxical finding indicates that fluticasone/salmeterol led to an increased risk of pneumonia. The NNTH to cause one additional case of pneumonia may be as low as 17, whereas the NNTB to prevent one death during the study period is 42.

Importantly, we have not commented on the relative contribution of the individual components of combined therapy to the effects identified, as this review presents only pair-wise comparisons between combined therapy and placebo. However, several

included studies comprise intervention arms in which the individual components are compared to placebo and to combined therapy, providing information about the contributions of the individual components. We also note the debate about the appropriateness of analysis conducted in the TORCH trial ([Feedback 1](#), [Feedback 2](#)). Furthermore, whether a combination is better than the two components taken separately was not addressed in this review.

Guidelines suggest that patients with symptomatic moderate to severe COPD should be given LABA or LAMA and possibly ICS; therefore it could be argued that this review is redundant. However, this review increased the level of evidence supporting the use of combined therapy (LABA/ICS) in COPD category "D" ([GOLD 2012](#)). On the other hand, this review shows that use of a combination inhaler is not associated with large benefit in terms of symptoms or quality of life over placebo. The high attrition rate presented in many studies (in TORCH, 56% completed in the placebo group) could have overshadowed the benefits of those outcomes. Our review therefore supports the current widely accepted guidance for a stepwise approach to treatment of patients with mild or moderate disease. Combined therapy seems best indicated for COPD patients with post-bronchodilator FEV₁ < 60% and frequent exacerbations and/or hospitalisations.

Implications for research

Any study should carefully document trial participants using the new GOLD COPD grading criteria. A more standardised approach to recording of serious adverse events such as pneumonia, hospitalisation, intensive care support or death would provide a more accurate picture of the benefits and harms of the long-term effects of this form of therapy.

Pharmacoeconomic analyses would be helpful to assist purchasers of health care in making decisions about the cost-effectiveness of combined inhalers. Responder analyses should be reported; this might give an idea as to which COPD phenotypes may provide the greatest benefit.

Assessment of BDF and MF/F in larger and longer trials is required to reveal whether these preparations confer benefits for mortality similar to those provided by FPS. Head-to-head trials of combined inhalers are needed if benefits are to be compared in a robust fashion. Network meta-analysis may help further elucidate the relative contribution of the individual components of combined therapy to the effects identified, in addition to the information already provided by the multi-arm trials such as [TORCH](#).

Combined therapy should be compared with separate administration of long-acting beta₂-agonist and inhaled corticosteroid at different doses in large-scale multi-centre studies using a double-dummy design, to assess whether combined therapy confers benefits over the simple addition of beta₂-agonist to different doses of inhaled steroid treatment in separate inhalers. A lower dose of ICS might still confer therapeutic benefit while reducing the incidence of pneumonia. The high attrition rate reported in many studies might be contemplated in future studies, to maintain the capacity of calculated sample size to show significant differences in outcomes such as quality of life, hospitalisation and death rates.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Barnes 2006

Methods	Parallel-group design
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Barnes 2006 (Continued)

Randomisation: not clear
Blinding: double-blind, identical inhaler devices used
Allocation concealment: unclear
Excluded: not described
Withdrawals: described
Trial duration: 13 weeks
Baseline characteristics: comparable
Intention-to-treat analysis stated

Participants	<ul style="list-style-type: none"> Setting: 18 centres in Western and Eastern Europe Participants randomly assigned: 141 (two groups: FP/SAL combination: 74; placebo: 67) Baseline characteristics: 64 years; mean FEV₁: 1.68 L; mean FEV₁: 59% predicted; mean FEV₁ reversibility: 3.9 (of predicted) Inclusion criteria: M/F 40 to 80 years of age; diagnosis of COPD (according to GOLD criteria); ≥ 2 on Medical Research Council (MRC) dyspnoea scale; poor reversibility of $< 10\%$ predicted normal Exclusion criteria: current diagnosis of asthma; recent exacerbation (within four weeks); long-term oxygen therapy (LTOT); pulmonary rehabilitation; ICS, antileukotriene or tiotropium within 14 days of visit
Interventions	<p>Run-in phase: four weeks. Treatment during this phase of the study not described</p> <ul style="list-style-type: none"> FPS 500/50 mcg twice daily Placebo <p>Inhaler device: dry powder inhaler (DPI)</p>
Outcomes	Exacerbations; withdrawals; adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised; no other information available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical inhaler devices
Incomplete outcome data (attrition bias): Mortality	Low risk	All withdrawals clearly accounted for, although slightly higher completion rate in the placebo group (95% in the placebo group, 88% in the treatment group)
Incomplete outcome data (attrition bias): All other outcomes	Low risk	All withdrawals clearly accounted for, although slightly higher completion rate in the placebo group (95% in the placebo group, 88% in the treatment group)
Selective reporting (reporting bias)	Low risk	No evidence of reporting bias

Bourbeau 2007

Methods	Randomised, double-blind, parallel-group, placebo-controlled. Duration three months
Participants	<ul style="list-style-type: none"> Setting: two respiratory centres: the Montreal Chest Institute and Hospital Laval, Canada Participants randomly assigned: 40 (FPS: 19, placebo: 21) Baseline characteristics: mean age: 64 years; mean FEV₁ % predicted: 59%; COPD severity (GOLD): mild to very severe; males: 90% Inclusion criteria: COPD (GOLD criteria), age ≥ 40 and ≤ 75 years; ≥ 10 pack-years smoking history; post-bronchodilator FEV₁ ≥ 25% of predicted; FEV₁/forced vital capacity (FVC) ≤ 0.70 Exclusion criteria: asthma or atopy; any other active lung disease, requiring home oxygen or with raised carbon dioxide tension (> 44 mm Hg); α1-antitrypsin deficiency; recent exacerbation (in the past four weeks); controlled medical condition or hypersensitivity to inhaled corticosteroids and bronchodilators
Interventions	<p>Four-week washout period from inhaled corticosteroids and long-acting beta₂-agonists</p> <ul style="list-style-type: none"> FPS 500/50 mcg twice daily Placebo twice daily <p>Additional treatment groups not covered in this review</p> <ul style="list-style-type: none"> Fluticasone 500 mcg twice daily <p>Inhaler device: DPI (Diskus)</p>
Outcomes	<ul style="list-style-type: none"> Numbers of CD8+ T lymphocytes and CD68+ macrophages, neutrophils and eosinophils Spirometric measurements (FEV₁ and FVC) CRDQ (Chronic Respiratory Disease Questionnaire) Bronchoalveolar lavage (BAL) and sputum induction (baseline, week 4 and week 12) ATS-DLD 78 questionnaire Lung volumes and carbon monoxide transfer factor (TLCO) Adverse events
Notes	Powered to detect differences in cell numbers from bronchoscopy and BAL rather than clinical outcomes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed using a central computer-generated list of random numbers, which was stratified by centre and used a block size of six set up by a data management/randomisation company
Allocation concealment (selection bias)	Unclear risk	Allocation procedure not described
Blinding (performance bias and detection bias) All outcomes	Low risk	<p>A procedure was established by GEREQ, which was in possession of the treatment code, to ensure that the treatment code would be broken only in accordance with the protocol and the criteria set up for unbinding of the study</p> <p>Observers were blinded not only to drug treatment but also to whether the biopsies were performed before or after treatment</p>
Incomplete outcome data (attrition bias): Mortality	High risk	Higher attrition rates in placebo group (71% completed in placebo group vs 100% in treatment group)

Bourbeau 2007 (Continued)

Incomplete outcome data (attrition bias): All other outcomes	High risk	Higher attrition rates in placebo group (71% completed in placebo group vs 100% in treatment group)
Selective reporting (reporting bias)	Unclear risk	"Analysis of bronchoalveolar lavage (BAL) and sputum induction results has not yet been completed and will be the subject of a future publication" Spirometric data and CRQ data not presented numerically—"No evidence of improvement in clinical outcomes was observed as measured by lung function as well as health-related quality of life questionnaires"

Calverley 2003

Methods	Parallel-group study Randomisation: unclear Blinding: double-blind (identical inhaler devices) Trial duration: 52 weeks with two-week run-in of treatment optimisation Allocation concealment: unclear Withdrawals: stated Intention-to-treat analysis: stated
Participants	<ul style="list-style-type: none"> Setting: 109 centres in 15 countries Participants randomly assigned: 510 (BDF: 254; placebo: 256). Additional treatment groups not covered in this review: budesonide: 257; formoterol: 255 Baseline characteristics: mean age: 64; mean FEV₁ L: 1; mean FEV₁ % predicted: 36; mean SGRQ: 48 Inclusion criteria: GOLD defined COPD (stages III and IV); ≥ 40 years; COPD symptoms > 2 years; smoking history ≥ 10 pack-years; FEV₁/VC ≤ 70% pre-BD; FEV₁ ≤ 50% predicted; use of SABAs as reliever medication; ≥ 1 COPD exacerbation requiring oral corticosteroids/antibiotics two to 12 months before first clinic visit Exclusion criteria: history of asthma/rhinitis before 40 years of age; any relevant cardiovascular disorders; exacerbation of COPD requiring medical intervention within four weeks of run-in/during run-in phase; non-allowed medications: oxygen therapy; ICS (aside from study medication), disodium cromoglycate, leukotriene-antagonists, 5-LO inhibitors, bronchodilators (other than study medication and prn terbutaline 0.5 mg), antihistamines, medication containing ephedrine, beta-blocking agents
Interventions	Run-in phase: All participants received 30 mg oral prednisolone twice daily and 2 × 4.5 mg formoterol twice daily (two weeks) <ul style="list-style-type: none"> BDF: 320/9 mcg twice daily Placebo (lactose monohydrate) Additional treatment groups not covered in this review <ul style="list-style-type: none"> Budesonide: 400 mcg twice daily Formoterol: 9 mcg twice daily Inhaler device: Turbuhaler
Outcomes	Time to first exacerbation; change in postmedication FEV ₁ ; number of exacerbations; time to and number of oral corticosteroid-treated episodes; am and pm PEF, slow vital capacity, health-related quality of life (HRQL); symptoms; use of reliever medication; adverse events
Notes	Classified as 'poorly reversible population' P values used to calculate pooled SEMs for the following outcomes: HRQL; FEV ₁ ; rescue medication

Calverley 2003 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised; no other information available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical inhaler devices
Incomplete outcome data (attrition bias): Mortality	High risk	High attrition rates in both groups (71% completion in the BDF group and 59% in the placebo group)
Incomplete outcome data (attrition bias): All other outcomes	High risk	High attrition rates in both groups (71% completion in the BDF group and 59% in the placebo group)
Selective reporting (reporting bias)	Low risk	No apparent indication of reporting bias

Dal Negro 2003

Methods	<p>Parallel-group study Randomisation: unclear Blinding: double-blind Method of randomisation: not reported Allocation concealment: unclear Trial duration: 52 weeks Withdrawals: stated Baseline characteristics: comparable intention-to-treat analysis: yes</p>
Participants	<ul style="list-style-type: none"> Setting: single centre in Italy Participants randomly assigned: 12 (FPS: six; placebo: six). Additional treatment groups not covered in this review: salmeterol: six Baseline characteristics: age range: 53 to 78; moderate COPD; mean FEV₁ (L): 1.46; mean FEV₁ (% predicted): 48; mean PEF (L/min): 180; mean reversibility (% baseline): 3.2 Inclusion criteria: baseline FEV₁ % predicted: ≤ 80%; FEV₁ > 800 mL; FEV₁/FVC ratio: ≤ 70% predicted; FEV₁ change ≤ 12% predicted post 400 mg salmeterol; regular treatment with oral theophylline 20 mg twice daily; SABA as required (for at least six months); current/ex-smokers with smoking history of at least 10 pack-years Exclusion criteria: current evidence of asthma or other pulmonary diseases; regular treatment with ICS; unstable respiratory disease requiring oral/parenteral corticosteroids within four weeks before the beginning of the study; changes in COPD medication in last four weeks before entering run-in; upper/lower respiratory tract infection within four weeks before last screening visit; unstable angina/unstable arrhythmias; recent myocardial infarction (MI)/heart failure; insulin-dependent diabetes mellitus; neuropsychiatric disorders; concurrent use of medications that affect COPD (e.g. beta-blockers) or interact with methylxanthine products (e.g. macrolides or fluoroquinolones); known/suspected hypersensitivity to ICS, beta₂-agonist or lactose; evidence of alcohol abuse.
Interventions	Run-in: two weeks' treatment with theophylline and as required SABA

Dal Negro 2003 (Continued)

- FPS 50/250 mcg twice daily
- Placebo

Additional treatment groups not covered in this review

- Salmeterol 50 mcg twice daily

Participants were receiving concomitant therapy: SABA as required and theophylline 400 µg/d for 12 months

Inhaler device: Diskus

Outcomes	FEV ₁ , Delta FEV ₁ , PEF am, symptom scores, rescue medication use, exacerbations (event rate and mean number per year)
Notes	<p>Classified as 'poorly reversible population'</p> <p>Mild exacerbation: requirement for increase in SABA as required by > 2 occasions/24 h on two or more consecutive days compared with baseline mean of last seven days of run-in</p> <p>Moderate exacerbation: condition requiring treatment with antibiotics and/or oral corticosteroids</p> <p>Severe exacerbation: condition requiring emergency hospital treatment and/or hospitalisation</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised; no other information available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical inhaler devices
Incomplete outcome data (attrition bias): Mortality	Unclear risk	100% completion in both groups but only 12 participants
Incomplete outcome data (attrition bias): All other outcomes	Unclear risk	100% completion in both groups but only 12 participants
Selective reporting (reporting bias)	Unclear risk	All stated outcomes reported but choice of end points used for significance calculations not always clear

Doherty 2012

Methods	Randomized, placebo-controlled, double-blind, double-dummy, parallel groups. Duration 26 weeks with a 26-week safety extension
Participants	<ul style="list-style-type: none"> • Setting: 164 centres in North, Central and South America, Europe, Africa and Asia • Participants randomly assigned: 700 (MF/F 400/10: 225, MF/F 200/10: 239, placebo: 236) • Baseline characteristics: mean age 59.3; mean FEV₁ % predicted: 38.2%; COPD severity: moderate to very severe; males 74.3%

Doherty 2012 (Continued)

- Inclusion criteria: age ≥ 40 years; $FEV_1/FVC < 0.70$, postbronchodilator FEV_1 25% to 60% predicted; symptoms of COPD (e.g. chronic cough and sputum production not attributable to another disease) for at least 24 months before enrolment; clinically acceptable laboratory tests at screening; adequate form of birth control if of child-bearing potential
- Exclusion criteria: asthma or significant reversibility; COPD exacerbation within four weeks; long-term oxygen; lung cancer; alpha-1-antitrypsin deficiency; lung surgery; cataract extractions in both eyes; glaucoma or intraocular pressure ≥ 22 mm Hg in either eye; clinically significant medical illness(es) that could interfere with the study

Interventions

Two-week washout/run-in period, in which previous long-acting COPD treatments (LABA, ICS, LABA/ICS or long-acting anticholinergic (e.g. tiotropium)) were discontinued and substituted

with a short-acting beta₂-agonist (SABA)/short-acting anticholinergic combination

- MF/F 400/10 mcg twice daily (26 weeks + 26-week safety extension)
- MF/F 200/10 mcg twice daily (26 weeks + 26-week safety extension)
- Placebo (26 weeks)

Additional treatment groups not covered in this review

- MF 400 mcg twice daily (26 weeks + 26-week safety extension)
- F 10 µg twice daily (26 weeks + 26-week safety extension)
- Inhaler device: MDI

Outcomes

- MF/F 400/10 µg compared with MF 400 µg for FEV_1 area under the curve from 0 to 12 hours postdose at 13-week end point
- MF/F 400/10 µg and MF/F 200/10 µg compared with F 10 µg for AM predose (trough) FEV_1
- Changes from baseline in FEV_1 area under the curve from 0 to 12 hours postdose day 1; weeks 1, 13, 26; and the 26-week end point
- Changes from baseline in trough FEV_1 each visit and at the 26-week end point
- Serial spirometry tests
- Respiratory health status (SGRQ)
- COPD symptom-free nights
- Partly stable COPD
- Time to first COPD exacerbation
- Adverse events

Notes

Post hoc in a subgroup of participants with baseline $FEV_1 < 50\%$ predicted (severe or very severe COPD) for coprimary end points

COPD exacerbations were categorised as mild, moderate or severe

A mild exacerbation was defined as a clinically judged deterioration of COPD symptoms (managed with increased short-acting bronchodilator use: ≥ 12 inhalations/d of

SABA/short-acting anticholinergic, or $\geq$ two nebulized treatments/d of 2.5 mg SABA/short-acting anticholinergic) on any two consecutive days

A moderate exacerbation was defined as a clinically judged deterioration of COPD with an acute change in symptoms that required antibiotic and/or oral steroid treatment for lower airway disease

A severe exacerbation was defined as a deterioration of COPD that resulted in emergency treatment or hospitalisation due to COPD

Risk of bias

Bias

Authors' judgement

Support for judgement

Doherty 2012 (Continued)

Random sequence generation (selection bias)	Unclear risk	"At baseline, subjects were randomised in a 1:1:1:1:1 ratio"—no further details, but likely to be low risk
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Placebo-controlled, double-blind, double-dummy
Incomplete outcome data (attrition bias): Mortality	Unclear risk	Moderate attrition rate across all treatment groups (84% completion in higher-dose treatment group, 85% in the lower-dose treatment group, 80% in the placebo group)
Incomplete outcome data (attrition bias): All other outcomes	Unclear risk	Moderate attrition rate across all treatment groups (84% completion in higher-dose treatment group, 85% in the lower-dose treatment group, 80% in the placebo group)
Selective reporting (reporting bias)	Unclear risk	Not all outcomes are supported with data

Hanania 2003

Methods	Parallel-group study Randomisation: method unclear Blinding: double-blind Allocation concealment: unclear Excluded: described Withdrawals: described Trial duration: 24 weeks with 2-week run-in period Baseline characteristics: comparable Intention-to-treat analysis: not stated
Participants	<ul style="list-style-type: none"> Setting: USA, multi-centre (76 hospitals) Participants randomly assigned: 368 (FPS: 183; placebo: 185). Additional treatment groups not covered in this review: salmeterol: 177; fluticasone: 183 Baseline characteristics: mean age: 64; mean FEV₁: 1.27 L (42% predicted) Inclusion criteria: stable COPD; FEV₁ 40% to 65% predicted; FEV₁/FVC < 70% predicted; symptoms of chronic bronchitis and moderate dyspnoea Exclusion criteria: current diagnosis of asthma, use of oral steroids in past six weeks, abnormal electrocardiogram (ECG), LTOT, moderate to severe exacerbation in run-in. Other significant medical disorder
Interventions	Run-in: two weeks' treatment with placebo inhaler and as required SABA <ul style="list-style-type: none"> FPS 50/250 mcg twice daily Placebo Additional treatment groups not covered in this review <ul style="list-style-type: none"> Salmeterol 50 mcg twice daily Fluticasone 250 mcg twice daily Inhaler device: Diskus

Hanania 2003 (Continued)

Outcomes	Lung function: change in FEV ₁ from baseline to end of study (M); PEF data not stratified by reversibility; quality of life: CRDQ, chronic bronchitis symptoms questionnaire (CBSQ) not stratified by reversibility; Dyspnoea and symptoms: transitional dyspnoea index (TDI); baseline dyspnoea index not stratified by reversibility; exacerbations; rescue salbutamol use
Notes	FEV ₁ reversibility < 12% or 200 mL (of baseline FEV ₁). Reversibility stratified data. Mean percentage increase in non-reversible participants = 8.8

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised; no other information available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical inhaler devices
Incomplete outcome data (attrition bias): Mortality	High risk	High attrition rates in both groups (70% completion in treatment group, 68% in placebo group)
Incomplete outcome data (attrition bias): All other outcomes	High risk	High attrition rates in both groups (70% completion in treatment group, 68% in placebo group)
Selective reporting (reporting bias)	Low risk	No apparent indication of reporting bias

Lapperre 2009

Methods	Ramdomised, placebo-controlled, parallel-group study. Duration 30 months
Participants	<ul style="list-style-type: none"> Setting: two university medical centres in The Netherlands Participants randomly assigned: 57 (FPS: 28, placebo: 29) Baseline characteristics: mean age: 60.5; mean percentage predicted FEV₁: 61%; COPD severity: moderate to severe (GOLD); males: 85.5% Inclusion criteria: age: 45 to 75 years; ≥ 10 pack-years smoking history; lung function GOLD stages II and III Exclusion criteria: asthma, ICS within six months
Interventions	<p>No run-in</p> <ul style="list-style-type: none"> FPS 500/50 mcg twice daily for 30 months Placebo twice daily for 30 months <p>Additional treatment groups not covered in this review</p> <ul style="list-style-type: none"> Fluticasone 500 mcg twice daily for the first six months, followed by placebo, twice daily, for 24 months Fluticasone 500 mcg twice daily for 30 months <p>Inhaler device: DPI (Diskus)</p>

Lapperre 2009 (Continued)

Outcomes	• Inflammatory cell counts in bronchial biopsies and induced sputum • Postbronchodilator spirometry rate of FEV₁ decline • Hyperresponsiveness to methacholine PC20 assessed by standardised procedures • Dyspnoea score by modified Medical Research Council (MRC) dyspnoea scale • Health status by St George's Respiratory Questionnaire (SGRQ) • Clinical COPD Questionnaire (CCQ)

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	At entry, an independent randomisation centre provided participant and medication numbers by using a minimisation procedure that balanced treatment groups
Allocation concealment (selection bias)	Unclear risk	No details given of allocation procedure
Blinding (performance bias and detection bias) All outcomes	Low risk	Study medications were individually numbered, with 60 doses per inhaler; all active treatment medications and placebo were identical in appearance
Incomplete outcome data (attrition bias): Mortality	High risk	High attrition rates in both groups (75% completion in treatment group, 69% in placebo group)
Incomplete outcome data (attrition bias): All other outcomes	High risk	High attrition rates in both groups (75% completion in treatment group, 69% in placebo group)
Selective reporting (reporting bias)	Low risk	All outcome measures described are reported

Mahler 2002

Methods	Parallel-group study Randomisation: stratified by reversibility and investigative site Blinding: double-blind Allocation concealment: unclear Excluded: described. Withdrawals: described. Trial duration: 24 weeks Baseline characteristics: comparable Intention-to-treat analysis: stated
Participants	<ul style="list-style-type: none"> • Setting: multi-centre study (65 centres) • Participants randomly assigned: 346 (FPS: 165; placebo: 181); additional treatment groups not covered in this review: salmeterol: 160; fluticasone: 168 • Baseline characteristics: mean age: 63; FEV₁: 1.2 to 3 L • Inclusion criteria: participants with COPD according to ATS guidelines; baseline prebronchodilation FEV₁ < 65% predicted and > 0.70 L; baseline prebronchodilation FEV₁/FVC < 70% predicted; age > 40 years; 20 pack-years history smoking; day or night symptoms present on four of last seven days during run-in period

Mahler 2002 (Continued)

- Exclusion criteria: history of asthma; corticosteroid use in last six weeks; abnormal ECG; oxygen therapy; moderate or severe exacerbation during run-in; significant concurrent disease

Interventions	<p>Run-in: two weeks' treatment with placebo inhaler and as required SABA</p> <ul style="list-style-type: none"> • FPS 500/50 mcg twice daily • Placebo <p>Additional treatment groups not covered in this review</p> <ul style="list-style-type: none"> • Salmeterol 50 mcg twice daily • Fluticasone 500 mcg twice daily <p>Inhaler device: Diskus</p>
Outcomes	Lung function: change in FEV ₁ from baseline to end of study (M); quality of life: CRDQ, CBSQ not stratified by reversibility; dyspnoea and symptoms: end of study dyspnoea (TDI) Exacerbations. Rescue salbutamol use
Notes	COPD participants reversible and non-reversible; < 15% (baseline) improvement in FEV ₁ to salbutamol; reversibility stratified data; mean FEV ₁ reversibility 11.0%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised; stratified by reversibility and investigative site
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical inhaler devices
Incomplete outcome data (attrition bias): Mortality	High risk	High attrition rates in both groups (68% completion in treatment group, 62% in placebo group)
Incomplete outcome data (attrition bias): All other outcomes	High risk	High attrition rates in both groups (68% completion in treatment group, 62% in placebo group)
Selective reporting (reporting bias)	Low risk	No apparent indication of reporting bias

O'Donnell 2006

Methods	<p>Parallel-group design Randomisation: not clear Blinding: double-blind Allocation concealment: unclear Excluded: not described Withdrawals: described Trial duration: 8 weeks Baseline characteristics: comparable</p>
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O'Donnell 2006 (Continued)

Intention-to-treat analysis stated

Participants	<ul style="list-style-type: none"> Setting: 22 centres in North America Participants randomly assigned: 126 (FPS: 62; placebo: 64) <p>Additional treatment groups not covered in this review</p> <ul style="list-style-type: none"> Salmeterol: 59 <p>Baseline characteristics: 65 years; FEV₁: 1.12 L Inclusion criteria: M/F ≥ 40 years of age; diagnosis of COPD; ≥ 10 pack-years; baseline Borg dyspnoea index < 7; FEV₁ < 70% predicted; functional residual capacity (FRC) ≥ 120% predicted Exclusion criteria: current diagnosis of asthma; use of xanthines/LABA/oral corticosteroids/ICS</p>
Interventions	<p>Run-in: two weeks; single-blind placebo</p> <ul style="list-style-type: none"> FPS 500/50 mcg twice daily Placebo <p>Additional treatment groups not covered in this review</p> <ul style="list-style-type: none"> Salmeterol 50 mcg twice daily <p>Inhaler device: DPI</p>
Outcomes	Withdrawals; exercise time; FEV ₁ ; adverse events
Notes	Study downloaded from ctr.gsk.co.uk

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised; no other information available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical inhaler devices
Incomplete outcome data (attrition bias): Mortality	Low risk	Low attrition rates in both groups (95% completion in treatment group, 92% in placebo group)
Incomplete outcome data (attrition bias): All other outcomes	Low risk	Low attrition rates in both groups (95% completion in treatment group, 92% in placebo group)
Selective reporting (reporting bias)	Unclear risk	Does not contribute data to the analysis of exacerbations as rate ratios, mortality or hospitalisations

Rennard 2009

Methods	Randomized, double-blind, double-dummy, parallel-group, active- and placebo-controlled. Duration 12 months
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Rennard 2009 (Continued)

Participants	<ul style="list-style-type: none"> Setting: 237 centres in US, Europe and Mexico Participants randomly assigned: 1469 (BDF 320/9: 494, BDF 160/9: 494, placebo 481) Baseline characteristics: mean age: 62.3; mean % predicted FEV₁: 39.7%; COPD severity: moderate to very severe; males: 63.5% Inclusion criteria: age ≥ 40 years; COPD for > 2 years; ≥ 10 pack-years smoking history; pre-bronchodilator (FEV₁) ≤ 50% predicted; pre-bronchodilator FEV₁/forced vital capacity (FVC) < 70%; modified Medical Research Council dyspnoea scale score ≥ 2; COPD exacerbation within one to 12 months (see Tashkin 2008) Exclusion criteria: asthma or allergic rhinitis before 40 years of age; oral steroid use; any significant disease or disorder that may jeopardise the safety of the participant (see Tashkin 2008)
Interventions	<p>Two-week run-in period, during which participants received ICS monotherapy if previously stable on ICS (alone or in combination) and ipratropium bromide at a fixed dose if previously receiving anti-cholinergics. Albuterol (salbutamol) was permitted for rescue use throughout the study</p> <ul style="list-style-type: none"> BDF 320/9 mcg twice daily BDF 160/9 mg twice daily Placebo twice daily <p>Additional treatment groups not covered in this review</p> <ul style="list-style-type: none"> Formoterol 9 mg twice daily <p>Inhaler device: pMDI/DPI</p>
Outcomes	<ul style="list-style-type: none"> Predose and one hour postdose FEV₁ over the 12-month treatment period Participant-reported outcome variables regarding disease status (including PEF), collected via questionnaires and diaries Health care utilisation Safety variables, including adverse events, vital signs, ECG, physical examination, haematology and clinical chemistry
Notes	<p>Subgroup performed serial spirometry assessment</p> <p>COPD exacerbation was defined as worsening of COPD requiring an oral corticosteroid or hospitalisation</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, but no details given of sequence generation
Allocation concealment (selection bias)	Unclear risk	No details of allocation procedure given
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, double-dummy; blinding maintained until end of 12-month study period
Incomplete outcome data (attrition bias): Mortality	High risk	High attrition rate across all treatment groups (73% completion in higher-dose treatment group, 71% in lower-dose treatment group, 64% in placebo group)

Rennard 2009 (Continued)

Incomplete outcome data (attrition bias): All other outcomes	High risk	High attrition rate across all treatment groups (73% completion in higher-dose treatment group, 71% in lower-dose treatment group, 64% in placebo group)
Selective reporting (reporting bias)	Unclear risk	All primary and secondary outcomes reported, although numerical data not available for all outcomes Average FEV ₁ was listed as a coprimary outcome in the methods section but as a secondary outcome in the results section

SC0104925

Methods	Randomized, double-blind, placebo-controlled, parallel-group. Duration 12 weeks	
Participants	<ul style="list-style-type: none"> Setting: 11 centres: four centres in the Russian Federation, four centres in the United States, two centres in Chile and one centre in Estonia Participants randomly assigned: 81 (FPS: 39, placebo: 42) Baseline characteristics: mean age: 64.4; mean FEV₁ 5 predicted: not given; COPD severity: moderate to severe; males: 79% Inclusion criteria: ≥ 40 years of age; clinical history of COPD with evidence of bronchitis; ≥ 10 pack-years smoking history; FEV₁/FVC ≤ 70% and measured postalbuterol FEV₁ ≥ 30% and ≤ 70% of predicted normal Exclusion criteria: child-bearing potential 	
Interventions	No run-in described <ul style="list-style-type: none"> FPS 500/50 mcg Placebo Additional treatment groups not covered in this review <ul style="list-style-type: none"> Fluticasone 500 mcg Salmeterol 50 mcg 	
Outcomes	<ul style="list-style-type: none"> Predose resistance difference between 5 Hz and 15 Hz (R5 to R15) as measured by IOS Predose and two hours postdose low-frequency reactance area (AX); two hours postdose R5 to R15; postalbuterol computed tomography (CT) parameters of area of airway wall (Aaw) and area of airway lumen (Ai) Adverse events 	
Notes	Trial designed to assess novel outcome measures, clinical efficacy. No relevant outcomes for meta-analysis apart from adverse events	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised but no details of sequence generation
Allocation concealment (selection bias)	Unclear risk	No details of allocation procedure
Blinding (performance bias and detection bias)	Low risk	"Double-blind, placebo-controlled"

SC0104925 (Continued)

All outcomes

Incomplete outcome data (attrition bias): Mortality	Unclear risk	Moderate attrition rates in both groups (90% completion in treatment group, 90% in placebo group)
Incomplete outcome data (attrition bias): All other outcomes	Unclear risk	Moderate attrition rates in both groups (90% completion in treatment group, 90% in placebo group)
Selective reporting (reporting bias)	Low risk	All outcome measures reported

SFCT01

Methods	Parallel-group design Randomisation: not clear Blinding: double-blind Allocation concealment: unclear Excluded: not described Withdrawals: described Trial duration: 52 weeks Baseline characteristics: comparable Intention-to-treat analysis stated
Participants	<ul style="list-style-type: none">Setting: 49 centres in Italy, 7 in PolandParticipants randomly assigned: 256 (FPS: 131; placebo: 125) Additional treatment groups not covered in this review <ul style="list-style-type: none">Fluticasone: 131 Baseline characteristics: 65 years; FEV ₁ : not reported Inclusion criteria: M/F ≥ 40 years of age; diagnosis of COPD; ≥ 10 pack-years; FEV ₁ < 70% predicted and > 800 mL; reversibility < 10% predicted normal (and < 200 mL) Exclusion criteria: not described
Interventions	Run-in: two weeks. All maintenance LABA and ICS treatment ceased <ul style="list-style-type: none">FPS 500/50 mcg twice dailyPlacebo Additional treatment groups not covered in this review <ul style="list-style-type: none">Fluticasone 500 mcg twice daily Inhaler device: MDI
Outcomes	Withdrawals; exacerbations; FEV ₁ ; adverse events
Notes	Unpublished study downloaded from ctr.gsk.co.uk
Risk of bias	
Bias	Authors' judgement Support for judgement

SFCT01 (Continued)

Random sequence generation (selection bias)	Unclear risk	Described as randomised; no other information available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical inhaler devices
Incomplete outcome data (attrition bias): Mortality	High risk	High attrition rates in both groups (66% completion in treatment group, 68% in placebo group)
Incomplete outcome data (attrition bias): All other outcomes	High risk	High attrition rates in both groups (66% completion in treatment group, 68% in placebo group)
Selective reporting (reporting bias)	Low risk	No apparent indication of reporting bias

Sin 2008

Methods	Double-blind, randomised, placebo-controlled, parallel-group. Duration four weeks
Participants	<ul style="list-style-type: none"> Setting: 11 centres, Western Canada Participants randomly assigned: 137 (FPS: 92, placebo: 45) Baseline characteristics: mean age: 68.4; mean FEV₁ % predicted: 46.4%; COPD severity: moderate to very severe; males: 62.7% Inclusion criteria: age ≥ 40 years; clinical diagnosis of COPD (GOLD); FEV₁ < 80% predicted; FEV₁/FVC < 0.70; ≥ 10 pack-years smoking history Exclusion criteria: exacerbations in last four weeks; known chronic systemic infections or inflammatory conditions; solid organ transplantation; myocardial infarction or cerebrovascular accident within the past three months; child-bearing potential; participation in a drug trial within the past four weeks; unlikely to survive longer than six months; URTI in last four weeks; unable to follow instructions; long-term oral theophylline use and unable or unwilling to stop Use of oral corticosteroids or long-term immunosuppressive agents
Interventions	<p>Run-in phase during which participants received fluticasone (500 mcg twice daily) for four weeks (short-acting beta₂-agonists (e.g. salbutamol) and/or anticholinergic (ipratropium) were allowed as rescue medication) followed by a medication withdrawal phase, wherein inhaled corticosteroids, LABA and theophylline products were withdrawn for four weeks (SABA (e.g. salbutamol) and/or anticholinergic (ipratropium) inhalers allowed as rescue medications)</p> <ul style="list-style-type: none"> FPS 500/50 mcg twice daily Placebo twice daily <p>Additional treatment groups not covered in this review</p> <ul style="list-style-type: none"> Fluticasone 500 mcg twice daily <p>Inhaler device: DPI (Diskus)</p>
Outcomes	<ul style="list-style-type: none"> Serum C-reactive protein (CRP), interleukin-6 (IL-6) and surfactant protein D (SPD) Health status (SGRQ) FEV₁ and FVC

Sin 2008 (Continued)

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was carried out centrally according to a computer-generated sequence stratified according to current smoking status with allocation concealment in a 1 (placebo arm) to 2 (fluticasone four arms) to 2 (fluticasone/salmeterol) distribution ratio
Allocation concealment (selection bias)	Low risk	"With allocation concealment"; however, further details not given
Blinding (performance bias and detection bias) All outcomes	Low risk	During this phase (RCT), all participants and study personnel will be blinded to the treatment assignment. (For safety reasons, during severe exacerbations (i.e. those requiring hospitalisation or emergency visit for COPD), the treating physician can break the "code" and place study participants on medications needed to treat the exacerbation)
Incomplete outcome data (attrition bias): Mortality	Unclear risk	Higher attrition in placebo group (96% completion in treatment group, 87% in placebo group)
Incomplete outcome data (attrition bias): All other outcomes	Unclear risk	Higher attrition in placebo group (96% completion in treatment group, 87% in placebo group)
Selective reporting (reporting bias)	Unclear risk	All outcome measures stated in protocol have been reported, with exception of "Other secondary molecules such as IL-8, tumour necrosis factor-alpha, monocyte chemoattractant protein and other molecules will be measured at a later date as part of a post hoc exploratory work". Also SPD levels reported extensively but did not feature in the protocol

Szafranski 2003

Methods	<p>Parallel-group study</p> <p>Randomisation: randomised, double-blind, placebo-controlled parallel-group trial</p> <p>Duration: 52 weeks</p> <p>Methods of randomisation: computer-generated scheme at AstraZeneca, Lund, Sweden. At each centre, eligible participants received an enrolment code, and then after run-in, participants were allocated the next consecutive participant number.</p> <p>Allocation concealment: adequate</p> <p>Blinding: All Turbuhaler inhalers were identical to ensure that the participant, the pharmacist and the investigator were blinded to the allocated treatment</p> <p>Excluded: not stated</p> <p>Withdrawals: stated</p> <p>Intention-to treat-analysis: stated</p>
Participants	<ul style="list-style-type: none"> Setting: 89 centres in Central and South America, Europe and South Africa Participants: 413 (BDF: 208; placebo: 205) <p>Additional treatment groups not covered in this review</p> <ul style="list-style-type: none"> Formoterol: 201; budesonide: 198 <p>Baseline characteristics: mean age: 64 years; mean FEV₁ % predicted: 36%; mean reversibility: 6% predicted normal</p>

Szafranski 2003 (Continued)

Inclusion criteria: age ≥ 40 years; COPD for ≥ 2 years; smoking history ≥ 10 pack-years; FEV₁ $\leq 50\%$ predicted; FEV₁/FVC $\leq 70\%$; symptom score ≥ 2 during at least seven days of run-in; use of bronchodilators for reliever medication; ≥ 1 severe COPD exacerbation within two to 12 months before study entry
Exclusion criteria: history of asthma/rhinitis before age 40; using beta-blockers; current respiratory tract disease other than COPD

Interventions	Run-in: two weeks. Treatment with prn SABA only <ul style="list-style-type: none"> BDF 320/9 mcg twice daily Placebo Additional treatment groups not covered in this review <ul style="list-style-type: none"> Budesonide 400 µg twice daily Formoterol 9 µg twice daily Inhaler device: Turbuhaler
Outcomes	Symptoms, adverse events, exacerbations, lung function
Notes	Classified as 'poorly reversible' subgroup; exacerbation defined as requirement of oral steroids and/or antibiotics and/or hospitalisation for respiratory symptoms; mild exacerbation defined as requirement of ≥ 4 inhalations per day P values used to calculate pooled standard errors of the mean (SEMs) for following outcomes: symptoms; rescue medication usage

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated scheme
Allocation concealment (selection bias)	Low risk	At each centre, eligible participants received an enrolment code, and then after run-in, participants were allocated to the next consecutive participant number
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical inhaler devices
Incomplete outcome data (attrition bias): Mortality	High risk	High attrition rates in both groups (72% completion in treatment group, 56% in placebo group)
Incomplete outcome data (attrition bias): All other outcomes	High risk	High attrition rates in both groups (72% completion in treatment group, 56% in placebo group)
Selective reporting (reporting bias)	Low risk	No apparent indication of reporting bias

Tashkin 2008

Methods	Randomised, double-blind, double-dummy, placebo-controlled, parallel-group. Duration six months
Participants	<ul style="list-style-type: none"> Setting: 194 centres in the US, Czech Republic, the Netherlands, Poland and South Africa

Tashkin 2008 (Continued)

- Participants randomly assigned: 858 (BDF 320/9: 277, BDF 160/9: 281, placebo 300)
- Baseline characteristics: mean age: 63.3; mean FEV₁ % predicted: 40.1%; COPD severity: moderate to very severe; males: 67.1%
- Inclusion criteria: ≥ 40 years, pre-bronchodilator FEV₁ $\leq 50\%$ predicted, pre-bronchodilator FEV₁/forced vital capacity $< 70\%$; symptoms for $\geq$ two years; ≥ 10 pack-years smoking history; $\geq$ one COPD exacerbation within one to 12 months; ≥ 2 Modified Medical Research Council dyspnoea scale score; ≥ 2 BCS score for at least half of the two-week run-in period
- Exclusion criteria: asthma or allergic rhinitis before 40 years of age; significant/unstable cardiovascular disorder; clinically significant respiratory tract disorder other than COPD; alpha-1 antitrypsin deficiency; oral steroid use; any other significant disease or disorder that may jeopardise the safety of the participant; oral or ophthalmic non-cardioselective beta-adrenoceptor antagonist use; pregnancy and breast-feeding

Interventions

Two-week run-in period; participants continued ICS monotherapy if they had previously been receiving ICS alone or in combination with LABA, and participants who had previously been receiving anticholinergic therapies were placed on stable doses of ipratropium bromide. A short-acting beta₂-agonist was allowed for rescue use

- BDF 320/9 twice daily
- BDF 160/9 twice daily
- Placebo twice daily

Additional treatment groups not covered in this review

- Budesonide 320 mcg twice daily + formoterol 9 mcg twice daily
- Budesonide 320 mcg twice daily
- Formoterol 9 mcg twice daily

Inhaler device: MDI and Turbohaler (double-dummy)

Outcomes

- Predose and one hour postdose FEV₁ over the six-month treatment period
- Participant-reported outcome variables regarding disease status (including PEF), collected via questionnaires and diaries
- Health care utilisation
- Safety variables, including adverse events, vital signs, ECG, physical examination, hematology and clinical chemistry
- Serial spirometry
- Pharmacokinetics

Notes
Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly assigned in balanced blocks according to computer-generated randomisation to one of the treatments administered twice daily
Allocation concealment (selection bias)	Unclear risk	No details of allocation procedure
Blinding (performance bias and detection bias) All outcomes	Low risk	Randomised, double-blind, double-dummy
Incomplete outcome data (attrition bias): Mortality	High risk	High attrition rates in both groups (86% completion in both treatment groups, 74% completion in placebo group)

Tashkin 2008 (Continued)

Incomplete outcome data (attrition bias): All other outcomes	High risk	High attrition rates in both groups (86% completion in both treatment groups, 74% completion in placebo group)
Selective reporting (reporting bias)	Low risk	All outcomes reported, no evidence of reporting bias

Tashkin 2012

Methods	Randomized, placebo-controlled, double-blind, double-dummy, parallel groups. Duration 26 weeks with 26-week safety extension
Participants	<ul style="list-style-type: none"> Setting: 131 centres located in South America, Asia, Africa, Europe and North America Participants randomly assigned: 636 (MF/F 400/10: 217, MF/F 200/10: 207, placebo 212) Baseline characteristics: mean age: 59.8; mean FEV₁ % predicted: not stated; COPD severity: moderate to very severe; males: 79% Inclusion criteria: ≥ 40 years; current or ex-smokers with ≥ 10 pack-years history; moderate to very severe COPD (pre-bronchodilator FEV₁/forced vital capacity (FVC) ratio ≤ 0.70), symptoms of COPD (chronic cough and sputum production not attributable to another disease process) for at least 24 months; postbronchodilator FEV₁ ≤ 60% predicted normal and ≥ 25% predicted normal at screening; medically acceptable form of birth control Exclusion criteria: significant reversibility (> 400 mL postalbuterol/salbutamol); long-term oxygen; exacerbation of COPD requiring medical intervention within four weeks before randomisation; beta-blocking agents; or treatment with additional excluded medication (other than SABA short-acting anticholinergic to be used as rescue medication); history of significant medical illness or a disorder that might interfere with the study; pregnancy or breast-feeding; asthma; lung cancer; alpha-1-antitrypsin deficiency; lobectomy; pneumonectomy; lung volume reduction surgery; cataract extractions in both eyes; or other significant ocular problems (glaucoma, trauma, opacification)
Interventions	<p>Two-week open-label wash out/run-in period in which long-acting bronchodilators and corticosteroids were discontinued and substituted with a short-acting beta₂-agonist-anticholinergic fixed-dose combination</p> <ul style="list-style-type: none"> MF/F 400/10 mcg twice daily MF/F 200/10 mcg twice daily Placebo <p>Additional treatment groups not covered in this review</p> <ul style="list-style-type: none"> MF 400 mcg twice daily Formoterol 10 mcg twice daily <p>Inhaler device: MDI</p>
Outcomes	<ul style="list-style-type: none"> Mean change from baseline in FEV₁ area under the curve (AUC) from 0 to 12 hours postdose (AUC 0 to 12 hours) at the week 13 end point Mean change from baseline in morning predose FEV₁ at the week 13 end point Change in health status as assessed according to total scores on St George's Respiratory Questionnaire (SGRQ) Change in symptom-free nights Time to first mild, moderate or severe COPD exacerbation Proportion of participants with partly stable COPD Adverse events

Tashkin 2012 (Continued)

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The sponsor's statistician produced a computer-generated randomisation schedule with treatment codes in blocks using SAS. Randomization was stratified according to the participant's smoking status at the time of randomisation
Allocation concealment (selection bias)	Low risk	Randomised treatment assignment was provided to the investigative site by means of an interactive voice response system at the time participants were randomly assigned
Blinding (performance bias and detection bias) All outcomes	Low risk	Placebo-controlled, double-blind, double-dummy study NB: Sponsor's statistician was used
Incomplete outcome data (attrition bias): Mortality	High risk	High attrition rates in all groups (81% completion in higher-dose treatment group and 82% in lower-dose treatment group, 75% in placebo group)
Incomplete outcome data (attrition bias): All other outcomes	High risk	High attrition rates in all groups (81% completion in higher-dose treatment group and 82% in lower-dose treatment group, 75% in placebo group)
Selective reporting (reporting bias)	Unclear risk	Numerical data for multiple outcomes not presented, as failed to reach significance

TORCH

Methods	Parallel-group design Randomisation: permuted block randomisation with stratification for smoking status and country Blinding: double-blind (identical inhaler devices) Allocation concealment: adequate Excluded: described Withdrawals: described Trial duration: 156 weeks Baseline characteristics: comparable Intention-to-treat analysis: stated
Participants	<ul style="list-style-type: none"> Setting: 444 centres in North America, Central America and Asia Pacific Participants randomly assigned: 3091 (FPS: 1546; placebo: 1545) Additional treatment groups not covered in this review <ul style="list-style-type: none"> Salmeterol: 1542; fluticasone: 1551 Baseline characteristics: 65 years; male: 76% Inclusion criteria: M/F 40 to 80 years of age; diagnosis of COPD (ERS); < 10% reversibility of predicted FEV ₁ ; FEV ₁ /FVC ratio < 70%; FEV ₁ < 60% predicted; ≥ 10 pack-year smoking history Exclusion criteria: asthma or respiratory diseases other than COPD; lung volume reduction surgery (LVRS)/lung transplant; requirement for > 12 hours/d LTOT; long-term oral corticosteroid therapy; serious uncontrolled disease likely to interfere with medication/cause death in next three years
Interventions	Run-in: two weeks. All maintenance treatment with ICS and LABA ceased

TORCH (Continued)

- FPS combination 500/50 mcg twice daily
- Placebo

Additional treatment groups not covered in this review

- Fluticasone 500 mcg twice daily
- Salmeterol 50 mcg twice daily

Inhaler device: DPI

Outcomes	All-cause mortality; change in SGRQ; exacerbations (requiring antibiotics, steroids, hospitalisation or combination of these); lung function; withdrawals; adverse events
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Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated scheme. Permuted block randomisation with stratification for smoking status and country
Allocation concealment (selection bias)	Unclear risk	Centralised randomisation schedule but no details of allocation procedures
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical inhaler devices
Incomplete outcome data (attrition bias): Mortality	Low risk	Mortality was the primary outcome, and vital status was checked in those who withdrew
Incomplete outcome data (attrition bias): All other outcomes	High risk	High attrition rates for other outcomes in both groups (66% completion in treatment group, 56% completion in placebo group)
Selective reporting (reporting bias)	Low risk	No apparent indication of reporting bias, but as highlighted in feedback received, the trial protocol was submitted for publication in October 2003 after recruitment of participants (2000 to 2002) (Feedback 1 ; Feedback 2)

TRISTAN

Methods	<p>Parallel-group design</p> <p>Randomisation: computer-generated; numbers were generated off-site; once a treatment number had been assigned to a participant, it could not be assigned to any other participant</p> <p>Blinding: double-blind; participants received identically packaged and presented placebos</p> <p>Excluded: described</p> <p>Withdrawals: described</p> <p>Trial duration: two-week run-in period; 52 weeks treatment; 2-week follow-up</p> <p>Baseline characteristics: comparable intention-to-treat analysis: stated</p>
Participants	<ul style="list-style-type: none"> • Setting: 196 centres in Europe, South Africa and Australia • Participants randomly assigned: 719 (FPS: 358; placebo: 361) <p>Additional treatment groups not covered in this review</p> <ul style="list-style-type: none"> • Salmeterol: 372; fluticasone: 375

TRISTAN (Continued)

Baseline characteristics: mean age 63 years; mean FEV₁ 1.26 L (44% predicted)
Inclusion criteria: baseline FEV₁ 25% to 75% predicted; FEV₁/FVC ratio ≤ 70%; poor reversibility: < 10% increase in predicted FEV₁ 30 minutes after inhalation of 400 mcg salbutamol; at least 10 pack-years smoking history; history of exacerbations (at least one in the last year) requiring OCS and/or antibiotics; at least one episode of acute COPD per year in the previous three years
Exclusion criteria: respiratory disorders other than COPD; oxygen treatment; systemic corticosteroids, high doses of inhaled corticosteroids (> 1000 mcg daily beclomethasone dipropionate, budesonide or flunisolide or > 500 mcg daily fluticasone) or antibiotics in the four weeks before the two-week run-in period

Interventions	<p>Run-in: two weeks. All maintenance treatment with ICS and LABA ceased</p> <ul style="list-style-type: none"> FPS 50 mcg/500 mcg twice daily Placebo <p>Additional treatment groups not covered in this review</p> <ul style="list-style-type: none"> Salmeterol 50 mcg twice daily Fluticasone 500 mcg twice daily <p>Inhaler device: DPI</p>
Outcomes	FEV ₁ ; PEF; exercise tolerance; quality of life: SGRQ; dyspnoea and symptoms (symptom score for shortness of breath, cough and sputum production); exacerbations (defined as requirement for antibiotics, oral steroids or both); rescue salbutamol use
Notes	FEV ₁ reversibility (% predicted normal); mean reversibility (% predicted) 3.8

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation schedule
Allocation concealment (selection bias)	Low risk	Numbers were generated off-site. Once a treatment number had been assigned to a participant, it could not be assigned to any other participant. Participants who satisfied the eligibility criteria were assigned the next sequential treatment number from the list
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical inhaler device
Incomplete outcome data (attrition bias): Mortality	High risk	High attrition rates in both groups (75% completion in treatment group and 61% in placebo group)
Incomplete outcome data (attrition bias): All other outcomes	High risk	High attrition rates in both groups (75% completion in treatment group and 61% in placebo group)
Selective reporting (reporting bias)	Low risk	No apparent indication of reporting bias

Zheng 2006

Methods	Randomised, double-blind, placebo-controlled, parallel-group. Duration 24 weeks
Participants	<ul style="list-style-type: none"> Setting: 12 hospitals in China Participants randomly assigned: 445 (FPS: 297, placebo: 148) Baseline characteristics: mean age: 66.32; mean FEV₁ % predicted: 47%; COPD severity: moderate to very severe; males: 88.5% Inclusion criteria: 40 to 79 years; COPD as per GOLD criteria; poor reversibility of airflow obstruction (increase of < 10%); FEV₁/FVC ratio (postbronchodilator) < 70% Exclusion criteria: asthma, lung cancer, sarcoidosis, active tuberculosis, lung fibrosis, bronchiectasis, serious uncontrolled other system disorders; long-term oxygen therapy (LTOT); had received inhaled corticosteroids at a dose of > 1000 µg/d (beclomethasone or budesonide) or > 500 µg/d (fluticasone) or had received systemic corticosteroids in the last four weeks before entry to the run-in period
Interventions	Two-week run-in period during which participants stopped taking ICSs and LABAs <ul style="list-style-type: none"> FPS 500/50 twice daily Placebo Inhaler device: DPI (Diskus)
Outcomes	<ul style="list-style-type: none"> Prebronchodilator FEV₁ St George's Respiratory Questionnaire (SGRQ) Use of relief bronchodilator and nighttime awakenings from Daily Record Cards Postbronchodilator FEV₁ COPD exacerbations Adverse events
Notes	Trial included non-smokers (11% from FPS arm and 14% from placebo arm)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomization was stratified at week 0 by smoking status"—sequence generation not described but likely to be low risk
Allocation concealment (selection bias)	Unclear risk	Allocation procedure not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind. FPS combination product 50/500 µg twice daily or matched placebo twice daily for 24 weeks of treatment
Incomplete outcome data (attrition bias): Mortality	Unclear risk	Moderate attrition rates in both groups (88% completion in treatment group and 89% in placebo group)
Incomplete outcome data (attrition bias): All other outcomes	Unclear risk	Moderate attrition rates in both groups (88% completion in treatment group and 89% in placebo group)
Selective reporting (reporting bias)	Low risk	All stated outcomes reported

AUC: Area under the curve; BCSS: Breathless, Cough and Sputum Score; BDF: Budesonide/formoterol combination; CBSQ: Chronic Bronchitis Symptom Questionnaire; COPD: chronic obstructive pulmonary disease; CRDQ: Chronic Respiratory Disease Questionnaire;

DPI: Dry powder inhaler; ERS: European Respiratory Society; FEV₁: Forced expiratory volume in one second; FPS: Fluticasone/salmeterol combination; FVC: Forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; ICS: inhaled corticosteroid; LABA: long-acting beta₂-agonists; LAMA: long-acting muscarinic antagonist; LTOT: Long-term oxygen therapy; MDI: Metered-dose inhaler; MMRC: Modified Medical Research Council; PEF: Peak expiratory flow; SABA: short-acting beta-agonist; SAMA: Short-acting muscarinic antagonist; SD: Standard deviation; SGRQ: St George's Respiratory Questionnaire.

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

Study	Reason for exclusion
Aaron 2004	Irrelevant comparison
Aaron 2007	Patients were randomised to tiotropium+combined ICS/LABA therapy versus tiotropium+placebo
Bathoorn 2008	Trial focuses on treatment of COPD exacerbations
Bleecker 2011	Assessment of effects of Gly16Arg genotype in response to budesonide/ formoterol in two clinical trials
Borgstrom 2003	Healthy volunteers
Cazzola 2000	Single-blind assessment of additive benefit of inhaled fluticasone to salmeterol. Although dosage was identical to Seretide/Advair (i.e. FP 500ug; SAL 50mcg), treatment was administered through separate inhalers
Cazzola 2002a	Single-blind randomised crossover study comparing combination salmeterol and fluticasone with formoterol and budesonide - excluded as duration of study was too short (12 hours)
Cazzola 2003	Acute phase COPD
Cazzola 2004	Randomised trial comparing combination salmeterol/fluticasone with separately administered fluticasone and theophylline for 4 months. Excluded as the comparison was not within the scope of the review
Cazzola 2004b	The duration of this study was too short (<1 week)
Chapman 2002	Review article
Cukier 2007	Crossover trial investigating use of nebulised saline versus nebulised salbutamol
De Backer 2011	Assessment of the acute effect of budesonide/formoterol
Donohue 2004	Irrelevant comparison
Ferguson 2006	Trial did not compare combined ICS/LABA therapy versus placebo
GlaxoSmithKline 2004	Trial includes patients with asthma
GlaxoSmithKline 2004a	Trial includes patients with asthma
Golabi 2006	Crossover trial comparing tiotropium versus salmeterol/fluticasone
Haque 2006	Focus on macrophages and glucoreceptor proteins
INSPIRE	Trial compared tiotropium versus seretide
Jiang 2011	Study not blinded

Study	Reason for exclusion
Jung 2012	Patients were randomised to tiotropium+combined ICS/LABA therapy versus tiotropium+placebo
Kardos 2007	Comparison of combination therapy long-acting beta-agonist
Lindberg 2007	Crossover study examining effect of only a single dose (two inhalations) of budesonide/formoterol , salmeterol/fluticasone, salbutamol or placebo
Lindenberg 2006	Crossover study examining effect of only a single dose (two inhalations) of budesonide/formoterol, salmeterol/fluticasone, salbutamol or placebo
Mittmann 2010	Patients were randomised to tiotropium+combined ICS/LABA therapy versus tiotropium+placebo
Mittmann 2011	Patients were randomised to tiotropium+combined ICS/LABA therapy versus tiotropium+placebo
NCT00144911	Combined ICS/LABA not compared to placebo
NCT00269126	Crossover study examining effect of adding fluticasone to salmeterol
NCT00476099	Combined ICS/LABA not compared to placebo
Noschese 2003	Non-randomised study.
Sagcan 2007	Focus of study is on sleep quality of COPD patients
SAM40116	Within study treatment group imbalances in dosage of steroids/combination therapy based upon historical steroid dose
Schermer 2007	Combined ICS/LABA not compared to placebo
SCO100250	Trial compared fluticasone/salmeterol versus salmeterol
SCO100470	Comparison of combination therapy long-acting beta-agonist
SCO40034	Comparison of tiotropium and combination therapy
SCO40043	Trial compared fluticasone/salmeterol versus salmeterol
Sethi 2006	Trial focuses on bacterial colonisation of sputum
Shaker 2009	Trial compared budesonide versus placebo
Sharafkhaneh 2011	Combined ICS/LABA not compared to placebo
Soriano 2002	Non-randomised retrospective survival analysis
Southard 2011	Combined ICS/LABA not compared to placebo
Stallberg 2008	Trial focuses on treatment of COPD exacerbations
Sun 2004	Irrelevant comparison
Sutherland 2006	Trial focuses on Seretide compared to salmeterol
Trofimenko 2006	Study not blinded and no placebo arm

Study	Reason for exclusion
Vestbo 2004	Review article.
Welte 2009	Trial focuses on budesonide/formoterol added to tiotropium
Welte 2009a	Trial focuses on budesonide/formoterol added to tiotropium
Welte 2009b	Trial focuses on budesonide/formoterol added to tiotropium
Welte 2009c	Trial focuses on budesonide/formoterol added to tiotropium
Welte 2009d	Trial focuses on budesonide/formoterol added to tiotropium
Wilson 2007	Study compares patients' preferences of 4 dry powder inhalers
Worth 2009	Study duration less than minimum of four weeks
Worth 2009a	Study duration less than minimum of four weeks
Worth 2010	Study duration less than minimum of four weeks
Wouters 2005	Study excluded as it assessed the withdrawal of FP from combination therapy
Zhong 2011	Combined ICS/LABA not compared to placebo
Zhong 2012	Combined ICS/LABA not compared to placebo

DATA AND ANALYSES

Comparison 1. Combined inhalers versus placebo (primary outcomes)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Exacerbation rates with combined inhalers versus placebo	7		Rate Ratio (Fixed, 95% CI)	0.73 [0.69, 0.78]
1.1 Fluticasone/salmeterol	3		Rate Ratio (Fixed, 95% CI)	0.74 [0.69, 0.80]
1.2 Budesonide/formoterol	4		Rate Ratio (Fixed, 95% CI)	0.71 [0.62, 0.81]
2 Mortality	16	10129	Odds Ratio (M-H, Fixed, 95% CI)	0.82 [0.68, 0.99]
2.1 Fluticasone/salmeterol	10	5543	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.65, 0.97]
2.2 Budesonide/formoterol	4	3250	Odds Ratio (M-H, Fixed, 95% CI)	1.05 [0.57, 1.93]
2.3 Mometasone/formoterol	2	1336	Odds Ratio (M-H, Fixed, 95% CI)	1.35 [0.36, 5.13]
3 Pneumonia	14	9620	Odds Ratio (M-H, Fixed, 95% CI)	1.62 [1.36, 1.94]
3.1 Fluticasone/salmeterol	9	5447	Odds Ratio (M-H, Fixed, 95% CI)	1.76 [1.46, 2.14]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.2 Budesonide/formoterol	3	2837	Odds Ratio (M-H, Fixed, 95% CI)	0.92 [0.57, 1.47]
3.3 Mometasone/formoterol	2	1336	Odds Ratio (M-H, Fixed, 95% CI)	2.39 [0.68, 8.36]
4 Hospitalisations due to COPD exacerbations	12	9492	Odds Ratio (M-H, Random, 95% CI)	0.92 [0.80, 1.06]
4.1 Fluticasone/salmeterol	7	5309	Odds Ratio (M-H, Random, 95% CI)	0.89 [0.75, 1.04]
4.2 Budesonide/formoterol	3	2847	Odds Ratio (M-H, Random, 95% CI)	1.17 [0.87, 1.58]
4.3 Mometasone/formoterol	2	1336	Odds Ratio (M-H, Random, 95% CI)	0.57 [0.31, 1.07]
5 Number of participants with at least one exacerbation	9	3141	Odds Ratio (M-H, Fixed, 95% CI)	0.78 [0.66, 0.93]
5.1 Fluticasone/salmeterol	7	1817	Odds Ratio (M-H, Fixed, 95% CI)	0.83 [0.64, 1.07]
5.2 Mometasone/formoterol	2	1324	Odds Ratio (M-H, Fixed, 95% CI)	0.74 [0.58, 0.94]

Analysis 1.1. Comparison 1 Combined inhalers versus placebo (primary outcomes), Outcome 1 Exacerbation rates with combined inhalers versus placebo.

Analysis 1.2. Comparison 1 Combined inhalers versus placebo (primary outcomes), Outcome 2 Mortality.

Analysis 1.3. Comparison 1 Combined inhalers versus placebo (primary outcomes), Outcome 3 Pneumonia.

Analysis 1.4. Comparison 1 Combined inhalers versus placebo (primary outcomes), Outcome 4 Hospitalisations due to COPD exacerbations.

Analysis 1.5. Comparison 1 Combined inhalers versus placebo (primary outcomes), Outcome 5 Number of participants with at least one exacerbation.

Comparison 2. Fluticasone/salmeterol (FPS) versus placebo (PLA)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Exacerbations	3	3777	Rate ratio (Fixed, 95% CI)	0.74 [0.69, 0.80]
1.1 Poorly reversible population	3	3777	Rate ratio (Fixed, 95% CI)	0.74 [0.69, 0.80]
2 Number of participants with at least one exacerbation	7	1817	Odds Ratio (M-H, Fixed, 95% CI)	0.83 [0.64, 1.07]
2.1 Reversible population	1	126	Odds Ratio (M-H, Fixed, 95% CI)	0.32 [0.06, 1.66]
2.2 Partially reversible population (mixed population)	2	713	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.69, 1.44]
2.3 Poorly reversible population	3	841	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.54, 1.15]
2.4 Unclear reversibility	1	137	Odds Ratio (M-H, Fixed, 95% CI)	0.31 [0.09, 1.05]
3 Participants with at least one exacerbation by type	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Requirement for oral steroids	2	417	Odds Ratio (M-H, Fixed, 95% CI)	1.01 [0.61, 1.68]
3.2 Requirement for antibiotic treatment	1	140	Odds Ratio (M-H, Fixed, 95% CI)	0.80 [0.26, 2.44]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.3 Requirement for oral steroid or antibiotic treatment	1	140	Odds Ratio (M-H, Fixed, 95% CI)	3.32 [0.13, 82.80]
3.4 Hospitalisation	1	140	Odds Ratio (M-H, Fixed, 95% CI)	3.32 [0.13, 82.80]
4 Exacerbations by type	3		Rate ratio (Fixed, 95% CI)	Subtotals only
4.1 Requirement for oral steroids	3		Rate ratio (Fixed, 95% CI)	0.57 [0.52, 0.63]
4.2 Requirement for antibiotic treatment	1		Rate ratio (Fixed, 95% CI)	0.60 [0.41, 0.88]
4.3 Hospitalisation	2		Rate ratio (Fixed, 95% CI)	0.83 [0.70, 0.97]
5 Mortality	10	5543	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.65, 0.97]
5.1 Mortality: three-year data	1	3057	Odds Ratio (M-H, Fixed, 95% CI)	0.81 [0.66, 0.99]
5.2 Mortality: one-year data	3	987	Odds Ratio (M-H, Fixed, 95% CI)	0.46 [0.13, 1.65]
5.3 Mortality: six-month data	3	1154	Odds Ratio (M-H, Fixed, 95% CI)	0.54 [0.11, 2.75]
5.4 Mortality: three-month data	3	345	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Change from baseline in St George's Respiratory Questionnaire (total score)	4		Mean Difference (Fixed, 95% CI)	-2.90 [-3.61, -2.18]
6.1 Poorly reversible population	4		Mean Difference (Fixed, 95% CI)	-2.90 [-3.61, -2.18]
7 Change from baseline in Chronic Respiratory Disease Questionnaire scores	2	712	Mean Difference (IV, Fixed, 95% CI)	5.0 [2.48, 7.52]
7.1 Partially reversible population (mixed population)	2	712	Mean Difference (IV, Fixed, 95% CI)	5.0 [2.48, 7.52]
8 Change from baseline in Transitional Dyspnoea Index (TDI) scores	2	707	Mean Difference (IV, Fixed, 95% CI)	1.04 [0.56, 1.53]
8.1 Partially reversible population (mixed population)	2	707	Mean Difference (IV, Fixed, 95% CI)	1.04 [0.56, 1.53]
9 Change from baseline in predose FEV₁	5		Mean Difference (Fixed, 95% CI)	0.16 [0.14, 0.19]
9.1 Reversible population	3		Mean Difference (Fixed, 95% CI)	0.19 [0.15, 0.24]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.2 Poorly reversible population	4		Mean Difference (Fixed, 95% CI)	0.15 [0.11, 0.18]
10 Change from baseline in postdose FEV ₁	2		Mean Difference (Fixed, 95% CI)	0.09 [0.07, 0.11]
10.1 Poorly reversible population	2		Mean Difference (Fixed, 95% CI)	0.09 [0.07, 0.11]
11 Change from baseline in rescue medication usage (puffs/d)	2	703	Mean Difference (IV, Fixed, 95% CI)	-1.19 [-1.83, -0.55]
11.1 Partially reversible population (mixed population)	2	703	Mean Difference (IV, Fixed, 95% CI)	-1.19 [-1.83, -0.55]
12 Withdrawals—total	13	5769	Odds Ratio (M-H, Fixed, 95% CI)	0.69 [0.62, 0.78]
12.1 Reversible population	1	121	Odds Ratio (M-H, Fixed, 95% CI)	2.95 [0.30, 29.18]
12.2 Partially reversible population (mixed population)	2	709	Odds Ratio (M-H, Fixed, 95% CI)	0.82 [0.60, 1.13]
12.3 Poorly reversible population	6	4632	Odds Ratio (M-H, Fixed, 95% CI)	0.68 [0.60, 0.76]
12.4 Unclear reversibility	4	307	Odds Ratio (M-H, Fixed, 95% CI)	0.55 [0.25, 1.17]
13 Withdrawals due to adverse events	11	5491	Odds Ratio (M-H, Fixed, 95% CI)	0.74 [0.64, 0.86]
13.1 Reversible population	1	123	Odds Ratio (M-H, Fixed, 95% CI)	0.36 [0.01, 8.90]
13.2 Partially reversible population (mixed population)	1	354	Odds Ratio (M-H, Fixed, 95% CI)	0.69 [0.31, 1.51]
13.3 Poorly reversible population	6	4630	Odds Ratio (M-H, Fixed, 95% CI)	0.76 [0.65, 0.89]
13.4 Unclear reversibility	4	384	Odds Ratio (M-H, Fixed, 95% CI)	0.31 [0.11, 0.93]
14 Withdrawals due to lack of efficacy	8	5115	Odds Ratio (M-H, Fixed, 95% CI)	0.30 [0.22, 0.41]
14.1 Partially reversible population (mixed population)	1	346	Odds Ratio (M-H, Fixed, 95% CI)	0.29 [0.08, 1.04]
14.2 Poorly reversible population	6	4632	Odds Ratio (M-H, Fixed, 95% CI)	0.30 [0.21, 0.42]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.3 Unclear reversibility	1	137	Odds Ratio (M-H, Fixed, 95% CI)	0.30 [0.08, 1.11]
15 Adverse events—any	9	5574	Odds Ratio (M-H, Fixed, 95% CI)	1.09 [0.95, 1.25]
15.1 Reversible population	1	126	Odds Ratio (M-H, Fixed, 95% CI)	1.20 [0.59, 2.46]
15.2 Partially reversible population (mixed population)	2	717	Odds Ratio (M-H, Fixed, 95% CI)	1.42 [1.03, 1.96]
15.3 Poorly reversible population	5	4650	Odds Ratio (M-H, Fixed, 95% CI)	1.03 [0.88, 1.21]
15.4 Unclear reversibility	1	81	Odds Ratio (M-H, Fixed, 95% CI)	0.58 [0.19, 1.79]
16 Adverse events—'serious'	9	5531	Odds Ratio (M-H, Fixed, 95% CI)	1.08 [0.95, 1.23]
16.1 Reversible population	1	123	Odds Ratio (M-H, Fixed, 95% CI)	0.53 [0.05, 6.05]
16.2 Partially reversible population	2	709	Odds Ratio (M-H, Fixed, 95% CI)	0.71 [0.38, 1.35]
16.3 Poorly reversible population	6	4699	Odds Ratio (M-H, Fixed, 95% CI)	1.10 [0.97, 1.26]
17 Adverse events—pneumonia	9	5447	Odds Ratio (M-H, Fixed, 95% CI)	1.80 [1.49, 2.18]
17.1 Reversible population	1	126	Odds Ratio (M-H, Fixed, 95% CI)	0.34 [0.01, 8.47]
17.2 Partially reversible population (mixed population)	2	709	Odds Ratio (M-H, Fixed, 95% CI)	5.55 [0.26, 116.46]
17.3 Poorly reversible population	4	4394	Odds Ratio (M-H, Fixed, 95% CI)	1.80 [1.48, 2.18]
17.4 Unclear reversibility	2	218	Odds Ratio (M-H, Fixed, 95% CI)	3.31 [0.13, 83.73]
18 Adverse events—candidiasis	7	2039	Odds Ratio (M-H, Fixed, 95% CI)	5.73 [3.07, 10.67]
18.1 Reversible population	1	126	Odds Ratio (M-H, Fixed, 95% CI)	1.03 [0.06, 16.88]
18.2 Partially reversible population (mixed population)	2	717	Odds Ratio (M-H, Fixed, 95% CI)	11.13 [3.36, 36.90]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
18.3 Poorly reversible population	3	1115	Odds Ratio (M-H, Fixed, 95% CI)	4.40 [2.01, 9.62]
18.4 Unclear reversibility	1	81	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
19 Adverse events—hoarseness	2	585	Odds Ratio (M-H, Fixed, 95% CI)	1.61 [0.61, 4.26]
19.1 Poorly reversible population	2	585	Odds Ratio (M-H, Fixed, 95% CI)	1.61 [0.61, 4.26]
20 Adverse events—palpitations	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
20.1 Poorly reversible population	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
21 Adverse events—blood glucose increased	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
21.1 Poorly reversible population	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
22 Adverse event—skin bruising	1	445	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
22.1 Poorly reversible population	1	445	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
23 Adverse events—bronchitis	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
23.1 Poorly reversible population	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
24 Adverse events—upper respiratory tract infection	5	4963	Odds Ratio (M-H, Fixed, 95% CI)	1.23 [1.04, 1.47]
24.1 Partially reversible population (mixed population)	2	709	Odds Ratio (M-H, Fixed, 95% CI)	1.25 [0.81, 1.92]
24.2 Poorly reversible population	3	4254	Odds Ratio (M-H, Fixed, 95% CI)	1.23 [1.02, 1.48]
25 Adverse events—nasopharyngitis	2	3535	Odds Ratio (M-H, Fixed, 95% CI)	1.28 [1.05, 1.56]
25.1 Poorly reversible population	2	3535	Odds Ratio (M-H, Fixed, 95% CI)	1.28 [1.05, 1.56]
26 Adverse events—cough	3	612	Odds Ratio (M-H, Fixed, 95% CI)	0.55 [0.23, 1.27]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
26.1 Reversible population	1	126	Odds Ratio (M-H, Fixed, 95% CI)	3.15 [0.13, 78.72]
26.2 Partially reversible population (mixed population)	1	346	Odds Ratio (M-H, Fixed, 95% CI)	0.49 [0.18, 1.31]
26.3 Poorly reversible population	1	140	Odds Ratio (M-H, Fixed, 95% CI)	0.35 [0.04, 3.48]
27 Adverse events—headache	4	3922	Odds Ratio (M-H, Fixed, 95% CI)	1.05 [0.84, 1.31]
27.1 Reversible population	1	123	Odds Ratio (M-H, Fixed, 95% CI)	0.22 [0.02, 2.01]
27.2 Partially reversible population (mixed population)	2	709	Odds Ratio (M-H, Fixed, 95% CI)	1.38 [0.91, 2.10]
27.3 Poorly reversible population	1	3090	Odds Ratio (M-H, Fixed, 95% CI)	0.96 [0.73, 1.26]

Analysis 2.1. Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 1 Exacerbations.

Analysis 2.2. Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 2 Number of participants with at least one exacerbation.

Analysis 2.3. Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 3 Participants with at least one exacerbation by type.

Analysis 2.4. Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 4 Exacerbations by type.

Analysis 2.5. Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 5 Mortality.

Analysis 2.6. Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 6 Change from baseline in St George's Respiratory Questionnaire (total score).

Analysis 2.7. Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 7 Change from baseline in Chronic Respiratory Disease Questionnaire scores.

Analysis 2.8. Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 8 Change from baseline in Transitional Dyspnoea Index (TDI) scores.

Analysis 2.9. Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 9 Change from baseline in predose FEV₁.

Analysis 2.10. Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 10 Change from baseline in postdose FEV₁.

Analysis 2.11. Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 11 Change from baseline in rescue medication usage (puffs/d).

Analysis 2.12. Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 12 Withdrawals—total.

Analysis 2.13. Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 13 Withdrawals due to adverse events.

Analysis 2.14. Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 14 Withdrawals due to lack of efficacy.

Analysis 2.15. Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 15 Adverse events—any.

Analysis 2.16. Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 16 Adverse events—'serious'.

Analysis 2.17. Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 17 Adverse events—pneumonia.

Analysis 2.18. Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 18 Adverse events—candidiasis.

Analysis 2.19. Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 19 Adverse events—hoarseness.

Analysis 2.20. Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 20 Adverse events—palpitations.

Analysis 2.21. Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 21 Adverse events—blood glucose increased.

Analysis 2.22. Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 22 Adverse event—skin bruising.

**Analysis 2.23. Comparison 2 Fluticasone/salmeterol (FPS)
versus placebo (PLA), Outcome 23 Adverse events—bronchitis.**

Study or subgroup	FPS n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
2.23.1 Poorly reversible population				
TORCH	121/1546	91/1544		1.36[1.02,1.8]
Favours FPS 0.1 0.2 0.5 1 2 5 10 Favours placebo				

**Analysis 2.24. Comparison 2 Fluticasone/salmeterol (FPS) versus placebo
(PLA), Outcome 24 Adverse events—upper respiratory tract infection.**

Study or subgroup	FPS n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
2.24.1 Partially reversible population (mixed population)					
Hanania 2003	22/178	26/185		9.41%	0.86[0.47,1.59]
Mahler 2002	28/165	18/181		6%	1.85[0.98,3.49]
Subtotal (95% CI)	343	366		15.41%	1.25[0.81,1.92]
Total events: 50 (FPS), 44 (Placebo)					
Heterogeneity: Tau ² =0; Chi ² =2.9, df=1(P=0.09); I ² =65.48%					
Test for overall effect: Z=1(P=0.32)					
2.24.2 Poorly reversible population					
TORCH	213/1546	170/1544		61.76%	1.29[1.04,1.6]
TRISTAN	44/358	43/361		15.81%	1.04[0.66,1.62]
Zheng 2006	32/297	14/148		7.02%	1.16[0.62,2.24]
Subtotal (95% CI)	2201	2053		84.59%	1.23[1.02,1.48]
Total events: 289 (FPS), 227 (Placebo)					
Heterogeneity: Tau ² =0; Chi ² =0.79, df=2(P=0.67); I ² =0%					
Test for overall effect: Z=2.2(P=0.03)					
Total (95% CI)	2544	2419		100%	1.23[1.04,1.47]
Total events: 339 (FPS), 271 (Placebo)					
Heterogeneity: Tau ² =0; Chi ² =3.69, df=4(P=0.45); I ² =0%					
Test for overall effect: Z=2.42(P=0.02)					
Test for subgroup differences: Chi ² =0, df=1 (P=0.96), I ² =0%					
Favours FPS 0.1 0.2 0.5 1 2 5 10 Favours placebo					

**Analysis 2.25. Comparison 2 Fluticasone/salmeterol (FPS) versus
placebo (PLA), Outcome 25 Adverse events—nasopharyngitis.**

Study or subgroup	FPS n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
2.25.1 Poorly reversible population					
TORCH	215/1546	165/1544		82.24%	1.35[1.09,1.68]
Zheng 2006	53/297	28/148		17.76%	0.93[0.56,1.55]
Subtotal (95% CI)	1843	1692		100%	1.28[1.05,1.56]
Total events: 268 (FPS), 193 (Placebo)					
Heterogeneity: Tau ² =0; Chi ² =1.74, df=1(P=0.19); I ² =42.68%					
Favours FPS 0.1 0.2 0.5 1 2 5 10 Favours placebo

Analysis 2.26. Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 26 Adverse events—cough.

Analysis 2.27. Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 27 Adverse events—headache.

Comparison 3. Budesonide/formoterol (BDF) versus placebo (PLA)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Severe exacerbations	2		Rate ratio (Fixed, 95% CI)	0.74 [0.62, 0.88]
1.1 Poorly reversible	2		Rate ratio (Fixed, 95% CI)	0.74 [0.62, 0.88]
2 Mean severe exacerbation rates per participant per year	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 Poorly reversible population	2		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Mortality	4	3250	Odds Ratio (M-H, Fixed, 95% CI)	1.05 [0.57, 1.93]
4 Change from baseline in St George's Respiratory Questionnaire (total score)	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 320/9 mcg	4	2350	Mean Difference (IV, Fixed, 95% CI)	-3.73 [-4.83, -2.63]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.2 160/9 mcg	2	1442	Mean Difference (IV, Fixed, 95% CI)	-3.39 [-4.70, -2.07]
5 Quality of life—change scores	2		SGRQ (Fixed, 95% CI)	-6.06 [-7.90, -4.22]
5.1 Poorly reversible	2		SGRQ (Fixed, 95% CI)	-6.06 [-7.90, -4.22]
6 Symptoms (change scores)	2		Symptom scale (Fixed, 95% CI)	-0.63 [-0.90, -0.37]
6.1 Poorly reversible	2		Symptom scale (Fixed, 95% CI)	-0.63 [-0.90, -0.37]
7 Breathlessness, cough and sputum score (BCSS) change from baseline—average over treatment period	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7.1 320/9 mcg	2	1533	Mean Difference (IV, Fixed, 95% CI)	-0.43 [-0.59, -0.26]
7.2 160/9 mcg	2	1536	Mean Difference (IV, Fixed, 95% CI)	-0.44 [-0.60, -0.28]
8 Rescue medication usage	4		Mean Difference (Fixed, 95% CI)	Subtotals only
8.1 320/9 mcg	4		Mean Difference (Fixed, 95% CI)	-0.98 [-1.18, -0.79]
8.2 160/9 mcg	2		Mean Difference (Fixed, 95% CI)	-1.28 [-1.55, -1.00]
9 Mean FEV ₁ (% change from baseline)	2		Mean Difference (Fixed, 95% CI)	14.40 [11.91, 16.90]
9.1 Poorly reversible	2		Mean Difference (Fixed, 95% CI)	14.40 [11.91, 16.90]
10 Average 12-hour FEV ₁ change from baseline—end of treatment (L)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
10.1 320/9 mcg	1	246	Mean Difference (IV, Fixed, 95% CI)	0.19 [0.12, 0.26]
10.2 160/9 mcg	1	245	Mean Difference (IV, Fixed, 95% CI)	0.16 [0.10, 0.22]
11 Predose FEV ₁ [L] change from baseline to the average over the randomised treatment period	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
11.1 320/9 mcg	1	577	Mean Difference (IV, Fixed, 95% CI)	0.08 [0.04, 0.12]
11.2 160/9 mcg	1	581	Mean Difference (IV, Fixed, 95% CI)	0.06 [0.03, 0.09]
12 1 Hour postdose FEV ₁ [L] change from baseline to the average over the randomised treatment period	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
12.1 320/9 mcg	1	577	Mean Difference (IV, Fixed, 95% CI)	0.17 [0.14, 0.20]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.2 160/9 mcg	1	581	Mean Difference (IV, Fixed, 95% CI)	0.16 [0.13, 0.19]
13 FEV ₁ at 12-hour change from baseline—end of treatment (L)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
13.1 320/9 mcg	1	246	Mean Difference (IV, Fixed, 95% CI)	0.1 [0.03, 0.17]
13.2 160/9 mcg	1	245	Mean Difference (IV, Fixed, 95% CI)	0.07 [0.00, 0.14]
14 Morning PEFr change from baseline, average over treatment period (L/min)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
14.1 320/9 mcg	2	1530	Mean Difference (IV, Fixed, 95% CI)	19.12 [15.69, 22.55]
14.2 160/9 mcg	2	1535	Mean Difference (IV, Fixed, 95% CI)	14.63 [11.47, 17.80]
15 Evening PEFr mean change from baseline, average over treatment period (L/min)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
15.1 320/9 mcg	2	1529	Mean Difference (IV, Fixed, 95% CI)	16.09 [12.61, 19.57]
15.2 160/9 mcg	2	1531	Mean Difference (IV, Fixed, 95% CI)	12.74 [9.56, 15.91]
16 Withdrawals—total	4		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1 320/9 mcg	4	2475	Odds Ratio (M-H, Fixed, 95% CI)	0.57 [0.48, 0.68]
16.2 160/9 mcg	2	1556	Odds Ratio (M-H, Fixed, 95% CI)	0.62 [0.50, 0.78]
17 Withdrawals due to adverse events	4		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
17.1 320/9 mcg	4	2475	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.61, 1.01]
17.2 160/9 mcg	2	1556	Odds Ratio (M-H, Fixed, 95% CI)	0.95 [0.70, 1.30]
18 Withdrawals due to lack of efficacy	3		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
18.1 320/9 mcg	3	1898	Odds Ratio (M-H, Fixed, 95% CI)	0.46 [0.34, 0.63]
18.2 160/9 mcg	1	975	Odds Ratio (M-H, Fixed, 95% CI)	1.01 [0.60, 1.71]
19 Adverse event—any	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
19.1 320/9 mcg	2	1552	Odds Ratio (M-H, Fixed, 95% CI)	1.42 [1.16, 1.74]
19.2 160/9 mcg	2	1556	Odds Ratio (M-H, Fixed, 95% CI)	1.32 [1.08, 1.61]
20 Adverse events—'serious'	4		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
20.1 320/9 mcg	4	2476	Odds Ratio (M-H, Fixed, 95% CI)	1.17 [0.95, 1.45]
20.2 160/9 mcg	2	1556	Odds Ratio (M-H, Fixed, 95% CI)	1.20 [0.89, 1.63]
21 Adverse events—pneumonia	3		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
21.1 320/9 mcg	3	2062	Odds Ratio (M-H, Fixed, 95% CI)	0.89 [0.52, 1.52]
21.2 160/9 mcg	2	1556	Odds Ratio (M-H, Fixed, 95% CI)	0.80 [0.45, 1.42]
22 Adverse events—candidiasis	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
22.1 320/9 mcg	2	1552	Odds Ratio (M-H, Fixed, 95% CI)	3.45 [1.88, 6.34]
22.2 160/9 mcg	2	1556	Odds Ratio (M-H, Fixed, 95% CI)	2.05 [1.07, 3.92]
23 Adverse events—dysphonia	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
23.1 320/9 mcg	2	1552	Odds Ratio (M-H, Fixed, 95% CI)	4.07 [1.52, 10.90]
23.2 160/9 mcg	2	1556	Odds Ratio (M-H, Fixed, 95% CI)	1.17 [0.37, 3.67]
24 Adverse events—cataracts	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
24.1 320/9 mcg	1	975	Odds Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 7.97]
24.2 160/9 mcg	1	975	Odds Ratio (M-H, Fixed, 95% CI)	1.95 [0.18, 21.59]
25 Adverse events—COPD	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
25.1 320/9 mcg	2	1552	Odds Ratio (M-H, Fixed, 95% CI)	0.92 [0.69, 1.22]
25.2 160/9 mcg	2	1556	Odds Ratio (M-H, Fixed, 95% CI)	1.16 [0.88, 1.53]
26 Adverse events—tremor	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
26.1 320/9 mcg	1	577	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
26.2 160/9 mcg	1	581	Odds Ratio (M-H, Fixed, 95% CI)	7.55 [0.39, 146.88]
27 Adverse events—palpitations	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
27.1 320/9 mcg	1	577	Odds Ratio (M-H, Fixed, 95% CI)	3.26 [0.13, 80.37]
27.2 160/9 mcg	1	581	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
28 Adverse events—lumbar spine bone density change from baseline (g/cm²)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
28.1 320/9 mcg	1	149	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.03, -0.01]
28.2 160/9 mcg	1	149	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.01, 0.01]
29 Adverse events—hip bone density change from baseline (g/cm ²)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
29.1 320/9 mcg	1	149	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.01, 0.01]
29.2 160/9 mcg	1	147	Mean Difference (IV, Fixed, 95% CI)	0.01 [0.00, 0.02]

Analysis 3.1. Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 1 Severe exacerbations.

Analysis 3.2. Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 2 Mean severe exacerbation rates per participant per year.

Analysis 3.3. Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 3 Mortality.

Analysis 3.4. Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 4 Change from baseline in St George's Respiratory Questionnaire (total score).

Analysis 3.5. Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 5 Quality of life—change scores.

Analysis 3.6. Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 6 Symptoms (change scores). **Analysis 3.7. Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 7 Breathlessness, cough and sputum score (BCSS) change from baseline—average over treatment period.** **Analysis 3.8. Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 8 Rescue medication usage.**

Analysis 3.9. Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 9 Mean FEV₁ (% change from baseline).

Analysis 3.10. Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 10 Average 12-hour FEV₁ change from baseline—end of treatment (L).

Analysis 3.11. Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 11 Predose FEV₁ [L] change from baseline to the average over the randomised treatment period.

Analysis 3.12. Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 12 1 Hour postdose FEV₁ [L] change from baseline to the average over the randomised treatment period.

Analysis 3.13. Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 13 FEV₁ at 12-hour change from baseline—end of treatment (L).

Analysis 3.14. Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 14 Morning PEFR change from baseline, average over treatment period (L/min).

Analysis 3.15. Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 15 Evening PEFR mean change from baseline, average over treatment period (L/min).

Analysis 3.16. Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 16 Withdrawals—total.

Analysis 3.17. Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 17 Withdrawals due to adverse events.

Analysis 3.18. Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 18 Withdrawals due to lack of efficacy.

Analysis 3.19. Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 19 Adverse event—any.

Analysis 3.20. Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 20 Adverse events—'serious'.

Analysis 3.21. Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 21 Adverse events—pneumonia.

Analysis 3.22. Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 22 Adverse events—candidiasis.

Analysis 3.23. Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 23 Adverse events—dysphonia.

Analysis 3.24. Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 24 Adverse events—cataracts.

Analysis 3.25. Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 25 Adverse events—COPD.

Analysis 3.26. Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 26 Adverse events—tremor.

Analysis 3.27. Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 27 Adverse events—palpitations.

Study or subgroup	BDF n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Test for overall effect: Not applicable					
Test for subgroup differences: Not applicable					
Favours BDF 0.01 0.1 1 10 100 Favours placebo					

Analysis 3.28. Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 28 Adverse events—lumbar spine bone density change from baseline (g/cm²).

Study or subgroup	N	BDF Mean(SD)	N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
3.28.1 320/9 mcg							
Rennard 2009	83	-0 (0)	66	0 (0)		100%	-0.02[-0.03,-0.01]
Subtotal ***	83		66			100%	-0.02[-0.03,-0.01]
Heterogeneity: Not applicable							
Test for overall effect: Z=3.03(P=0)							
3.28.2 160/9 mcg							
Rennard 2009	83	0 (0)	66	0 (0)		100%	0[-0.01,0.01]
Subtotal ***	83		66			100%	0[-0.01,0.01]
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Chi ² =4.6, df=1 (P=0.03), I ² =78.24%							
Favours placebo -0.05 -0.025 0 0.025 0.05 Favours BDF							

Analysis 3.29. Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 29 Adverse events—hip bone density change from baseline (g/cm²).

Study or subgroup	N	BDF Mean(SD)	N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
3.29.1 320/9 mcg							
Rennard 2009	84	-0 (0)	65	-0 (0)		100%	0[-0.01,0.01]
Subtotal ***	84		65			100%	0[-0.01,0.01]
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
3.29.2 160/9 mcg							
Rennard 2009	82	0 (0)	65	-0 (0)		100%	0.01[0,0.02]
Subtotal ***	82		65			100%	0.01[0,0.02]
Heterogeneity: Not applicable							
Test for overall effect: Z=3.01(P=0)							
Test for subgroup differences: Chi ² =4.56, df=1 (P=0.03), I ² =78.05%							
Favours placebo -0.05 -0.025 0 0.025 0.05 Favours BDF							

Comparison 4. Mometasone/formoterol (MF/F) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants with at least one exacerbation	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 400/10 mcg	2	882	Odds Ratio (M-H, Fixed, 95% CI)	0.72 [0.54, 0.95]
1.2 200/10 mcg	2	886	Odds Ratio (M-H, Fixed, 95% CI)	0.76 [0.58, 1.01]
2 Number of participants having at least one moderate or severe exacerbation	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 400/10 mcg	2	882	Odds Ratio (M-H, Fixed, 95% CI)	0.57 [0.38, 0.86]
2.2 200/10 mcg	2	886	Odds Ratio (M-H, Fixed, 95% CI)	0.62 [0.42, 0.92]
3 Mortality	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 400/10 mcg	2	890	Odds Ratio (M-H, Fixed, 95% CI)	1.72 [0.41, 7.25]
3.2 200/10 mcg	2	894	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.20, 4.98]
4 Change from baseline in St George's Respiratory Questionnaire (total score)	2		Mean Difference (Fixed, 95% CI)	Subtotals only
4.1 400/10 mcg	2	866	Mean Difference (Fixed, 95% CI)	-3.80 [-5.75, -1.86]
4.2 200/10 mcg	2	869	Mean Difference (Fixed, 95% CI)	-3.91 [-6.01, -1.81]
5 Change from baseline in FEV₁ AUC₀₋₁₂ hours (mL)—week 13	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 400/10 mcg	2	862	Mean Difference (IV, Fixed, 95% CI)	162.04 [126.54, 197.53]
5.2 200/10 mcg	2	869	Mean Difference (IV, Fixed, 95% CI)	122.01 [86.64, 157.39]
6 Mean change from baseline AM predose FEV₁ at 13 weeks (mL)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 400/10 mcg	2	856	Mean Difference (IV, Fixed, 95% CI)	114.64 [77.79, 151.50]
6.2 200/10 mcg	2	859	Mean Difference (IV, Fixed, 95% CI)	70.43 [33.63, 107.23]
7 Withdrawals—total	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 400/10 mcg	2	890	Odds Ratio (M-H, Fixed, 95% CI)	0.56 [0.40, 0.77]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.2 200/10 mcg	2	894	Odds Ratio (M-H, Fixed, 95% CI)	0.55 [0.40, 0.76]
8 Withdrawals due to lack of efficacy	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 400/10 mcg	2	890	Odds Ratio (M-H, Fixed, 95% CI)	0.24 [0.08, 0.74]
8.2 200/10 mcg	2	894	Odds Ratio (M-H, Fixed, 95% CI)	0.31 [0.11, 0.84]
9 Withdrawals due to adverse events	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 400/10 mcg	2	890	Odds Ratio (M-H, Fixed, 95% CI)	1.07 [0.58, 1.98]
9.2 200/10 mcg	2	894	Odds Ratio (M-H, Fixed, 95% CI)	0.37 [0.16, 0.84]
10 Adverse events—any	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 400/10 mcg	2	890	Odds Ratio (M-H, Fixed, 95% CI)	0.98 [0.75, 1.30]
10.2 200/10 mcg	2	894	Odds Ratio (M-H, Fixed, 95% CI)	0.82 [0.62, 1.09]
11 Adverse events—serious	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 400/10 mcg	2	890	Odds Ratio (M-H, Fixed, 95% CI)	1.09 [0.66, 1.79]
11.2 200/10 mcg	2	894	Odds Ratio (M-H, Fixed, 95% CI)	0.71 [0.41, 1.23]
12 Adverse events—pneumonia	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 400/10 mcg	2	890	Odds Ratio (M-H, Fixed, 95% CI)	3.14 [0.84, 11.65]
12.2 200/10 mcg	2	894	Odds Ratio (M-H, Fixed, 95% CI)	1.67 [0.40, 7.04]
13 Adverse events—candidiasis	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.1 400/10 mcg	2	890	Odds Ratio (M-H, Fixed, 95% CI)	2.22 [0.50, 9.91]
13.2 200/10 mcg	2	894	Odds Ratio (M-H, Fixed, 95% CI)	1.01 [0.17, 5.87]
14 Adverse events—dysphonia	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
14.1 400/10 mcg	1	461	Odds Ratio (M-H, Fixed, 95% CI)	2.11 [0.19, 23.41]
14.2 200/10 mcg	1	475	Odds Ratio (M-H, Fixed, 95% CI)	1.98 [0.18, 22.02]
15 Adverse events—cataract	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
15.1 400/10 mcg	1	429	Odds Ratio (M-H, Fixed, 95% CI)	0.98 [0.06, 15.72]
15.2 200/10 mcg	1	419	Odds Ratio (M-H, Fixed, 95% CI)	1.02 [0.06, 16.48]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16 Adverse events—COPD requiring hospitalisation	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1 400/10 mcg	2	890	Odds Ratio (M-H, Fixed, 95% CI)	0.80 [0.40, 1.60]
16.2 200/10 mcg	2	894	Odds Ratio (M-H, Fixed, 95% CI)	0.36 [0.15, 0.86]

Analysis 4.1. Comparison 4 Mometasone/formoterol (MF/F) versus placebo, Outcome 1 Number of participants with at least one exacerbation.

Analysis 4.2. Comparison 4 Mometasone/formoterol (MF/F) versus placebo, Outcome 2 Number of participants having at least one moderate or severe exacerbation.

Analysis 4.3. Comparison 4 Mometasone/formoterol (MF/F) versus placebo, Outcome 3 Mortality.

Analysis 4.4. Comparison 4 Mometasone/formoterol (MF/F) versus placebo, Outcome 4 Change from baseline in St George's Respiratory Questionnaire (total score).

Analysis 4.5. Comparison 4 Mometasone/formoterol (MF/F) versus placebo, Outcome 5 Change from baseline in FEV₁ AUC_{0–12} hours (mL)—week 13.

Analysis 4.6. Comparison 4 Mometasone/formoterol (MF/F) versus placebo, Outcome 6 Mean change from baseline AM predose FEV₁ at 13 weeks (mL).

Analysis 4.7. Comparison 4 Mometasone/formoterol (MF/F) versus placebo, Outcome 7 Withdrawals—total.

Analysis 4.8. Comparison 4 Mometasone/formoterol (MF/F) versus placebo, Outcome 8 Withdrawals due to lack of efficacy.

Analysis 4.9. Comparison 4 Mometasone/formoterol (MF/F) versus placebo, Outcome 9 Withdrawals due to adverse events.

Analysis 4.10. Comparison 4 Mometasone/formoterol (MF/F) versus placebo, Outcome 10 Adverse events—any.

Analysis 4.11. Comparison 4 Mometasone/formoterol (MF/F) versus placebo, Outcome 11 Adverse events—serious.

Analysis 4.12. Comparison 4 Mometasone/formoterol (MF/F) versus placebo, Outcome 12 Adverse events—pneumonia.

Analysis 4.13. Comparison 4 Mometasone/formoterol (MF/F) versus placebo, Outcome 13 Adverse events—candidiasis.

Analysis 4.14. Comparison 4 Mometasone/formoterol (MF/F) versus placebo, Outcome 14 Adverse events—dysphonia.

Analysis 4.15. Comparison 4 Mometasone/formoterol (MF/F) versus placebo, Outcome 15 Adverse events—cataract.

Analysis 4.16. Comparison 4 Mometasone/formoterol (MF/F) versus placebo, Outcome 16 Adverse events—COPD requiring hospitalisation.

ADDITIONAL TABLES

Table 1. Search history

Version	Detail
First published version—Issue 4, 2003 (all years to April 2002)	References identified: 34 References retrieved: seven Studies excluded: three (Cazzola 2000; Chapman 2002; Soriano 2002) Studies identified from supplementary searching: four (Dal Negro 2003; Hanania 2003—both included; Cazzola 2002a; Cazzola 2004—both excluded).

Table 1. Search history (Continued)

Studies included: four	
Second published version—Issue 3, 2004 (April 2003 to April 2004)	References identified: 12 References retrieved: three (two papers full publications of previously included or cited studies (Dal Negro 2003; Hanania 2003). Handsearching identified two further references to the COSMIC 2003 study Studies identified from supplementary searching: one (TRISTAN 2003) New studies included: two Total studies included: six
Third published version—Issue 3, 2005 (April 2004 to April 2005)	References identified: 52 References retrieved: 46 (references to studies already included/excluded/ongoing: 24) New unique studies identified: 10 (ongoing studies: two) New studies included: zero Total studies included: six
Fourth published version (April 2005 to April 2007)	References identified: 66 References retrieved: 27 (references to studies already included/excluded/ongoing) New unique studies identified: five (ongoing studies: zero) New studies included: five Total studies included: 11
Fifth published version (April 2007 to June 2013)	References identified: 129 New unique studies identified: eight (ongoing studies: zero) New studies included: eight Total studies included: 19

Table 2. Rates and NNTB of mortality and NNTH of pneumonia

Study ID	Study duration	Placebo rate (%)	NNTB for mortality	Placebo rate (%)	NNTH for pneumonia
		mortality		pneumonia	
TORCH	156 weeks	15.2	42 (24 to 775)	12.3	17 (27 to 12)
TRISTAN	52 weeks	1.94	292 (164 to 5256)	0.83	197 (339 to 131)
Calverley 2003	52 weeks	1.95	249 (149 to 1307)	3.6	48 (82 to 32)
Szafranski 2003	52 weeks	4.5	110 (66 to 581)	0	N/A
Rennard 2009	52 weeks	0.83	674 (379 to 12,149)	4.78	37 (63 to 25)
Tashkin 2008	26 weeks	0.33	1689 (950 to 30,403)	1	164 (282 to 109)
Doherty 2012	26 weeks	0.85	659 (370 to 11,865)	0.85	193 (331 to 128)
Tashkin 2012	26 weeks	0.47	1187 (668 to 21,377)	0.47	346 (595 to 229)
Mahler 2002	24 weeks	1.66	340 (191 to 6125)	0	N/A
O'Donnell 2006	8 weeks	0	N/A	1.56	107 (182 to 71)

APPENDICES

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

Electronic searches: core databases

Database	Frequency of search
CENTRAL (<i>The Cochrane Library</i>)	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
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards

MEDLINE search strategy used to identify trials for the CAGR

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 RCTs

1. exp "clinical trial (publication type)"/
2. (randomised or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. Animals/
10. Humans/
11. 9 not (9 and 10)
12. 8 not 11

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

Appendix 2. Definitions of exacerbations

Study ID	Definition of exacerbation
Barnes 2006	No definition found
Bourbeau 2007	No definition found
Calverley 2003	<p>Mild exacerbations = number of days with intake of four or more puffs of rescue medication</p> <p>Severe exacerbation = intake of a course of oral steroids and/or antibiotics and/or hospitalisation due to respiratory symptoms</p>
Dal Negro 2003	<p>Mild exacerbation = requiring increased use of salbutamol prn by > 2 occasions/24 hour period on two or more consecutive days compared with the baseline mean of last seven days of run-in period</p> <p>Moderate exacerbation = requiring treatment with antibiotics and/or oral corticosteroids</p> <p>Severe exacerbation = requiring emergency hospital treatment and/or hospitalisation</p>

(Continued)

Doherty 2012	<p>Mild exacerbation = clinically judged deterioration of COPD symptoms (managed with increased short-acting bronchodilator use: ≥ 12 inhalations/d of SABA/short-acting anticholinergic, or ≥ 2 nebulized treatments/d of 2.5 mg SABA/short-acting anticholinergic) on any two consecutive days</p> <p>Moderate exacerbation = clinically judged deterioration of COPD with an acute change in symptoms that required antibiotic and/or oral steroid treatment for lower airway disease</p> <p>Severe exacerbation = deterioration of COPD that resulted in emergency treatment or hospitalisation due to COPD</p>
Hanania 2003	<p>Moderate exacerbation = requiring treatment with antibiotics and/or corticosteroids</p> <p>Severe exacerbation = requiring hospitalisation</p>
Lapperre 2009	No definition found
Mahler 2002	“exacerbations defined by treatment”—no further details
O'Donnell 2006	No definition found
Rennard 2009	“a course of oral steroids and/or hospitalisation due to a worsening of COPD”
SCO104925	No definition found
SFCT01	No definition found
Sin 2008	“Exacerbations were defined as worsening of COPD symptoms leading to hospitalisation, a visit to the emergency room, or use of an antimicrobial agent and/or systemic corticosteroids as an outpatient”
Szafranski 2003	<p>Mild exacerbations = a day with ≥ 4 inhalations of reliever medication above the mean run-in use</p> <p>Severe exacerbation = use of oral steroids and/or antibiotics and/or hospitalisation due to respiratory symptoms</p>
Tashkin 2008	“Worsening of COPD symptoms that required treatment with oral corticosteroids and/or hospitalisation”
Tashkin 2012	<p>Mild exacerbation = clinically judged deterioration of COPD symptoms (managed with increased short-acting bronchodilator use: ≥ 12 inhalations/d of SABA/short-acting anticholinergic, or ≥ 2 nebulized treatments/d of 2.5 mg SABA/short-acting anticholinergic) on any two consecutive days</p> <p>Moderate exacerbation = clinically judged deterioration of COPD with an acute change in symptoms that required antibiotic and/or oral steroid treatment for lower airway disease</p> <p>Severe exacerbation = deterioration of COPD that resulted in emergency treatment or hospitalisation due to COPD</p>
TORCH	“A symptomatic deterioration requiring treatment with antibiotic agents, systemic corticosteroids, hospitalisation, or a combination of these”
TRISTAN	“Exacerbations were defined a priori as a worsening of COPD symptoms that required treatment with antibiotics, oral corticosteroids, or both. Episodes that required corticosteroid treatment or hospital admission were noted separately”
Zheng 2006	“A worsening of symptoms that required treatment with antibiotics or oral corticosteroids and/or hospitalisation” (analysed separately as those requiring antibiotics, those requiring corticosteroids, those requiring hospitalisation)

Appendix 3. Definitions of pneumonia

Study ID	Definition of pneumonia
Barnes 2006	No definition found
Bourbeau 2007	No definition found
Calverley 2003	No definition found
Dal Negro 2003	No definition found
Doherty 2012	“Including the AE terms of pneumonia, pneumonia viral, pneumonia aspiration, and lobar pneumonia”
Hanania 2003	No definition found
Lapperre 2009	No definition found
Mahler 2002	No definition found
O'Donnell 2006	No definition found
Rennard 2009	“Pneumonia events were reported by physicians based on the Medical Dictionary for Regulatory Activities (version 10.0) pneumonia-related preferred terms (pneumonia, bronchopneumonia, lobar pneumonia or pneumonia staphylococcal)”
SCO104925	No definition found
SFCT01	No definition found
Sin 2008	No definition found
Szafranski 2003	No definition found
Tashkin 2008	“Diagnosis of pneumonia was generally based on clinical judgment, without radiological confirmation in all cases”
Tashkin 2012	“Including the AE terms of pneumonia, pneumonia viral, pneumonia aspiration, and lobar pneumonia”
TORCH	“Since the finding was unexpected, there was no prospective definition of pneumonia in the study protocol (e.g. confirmation on chest radiography)”
TRISTAN	No definition found
Zheng 2006	No definition found

FEEDBACK

Comment on analysis choice in TORCH trial and presentation in Cochrane review, 24 August 2017

Summary

The authors compared inhalers with combination drugs (a steroid plus a long-acting beta-2 agonist), with placebo and write in their abstract that the number needed to treat to prevent one death with fluticasone/salmeterol was 42 (1). They explain, just before Objectives, that the largest randomised trial of combination therapy (TORCH) demonstrated a significant reduction in mortality versus placebo ($P = 0.052$) and that they wished to see whether other combined inhalers had a similar effect. Just above “Implications for research,” we are told that “whether a combination is better than the two components taken separately was not addressed in this review,” and under “Authors’ Conclusions” the authors advocate that the combination should be compared with its two components.

I find this information misleading. Firstly, the review authors overlook that the TORCH trial (and several other trials) was designed to answer what they call for in future research, namely whether the combination was better than any of its components.

Secondly, the authors give readers the impression that the combination reduces mortality. However, the fact is that the steroid contributes absolutely nothing to the mortality benefit. The primary outcome in the TORCH trial was total mortality (2). GlaxoSmithKline randomised 6184 patients to four groups: placebo; salmeterol; fluticasone; and both drugs together. By definition, this design is factorial. It is powerful, as it allows the investigators to study three research questions with a sample size that would usually only allow one question to be answered. Such a trial can tell us whether the two drugs are effective, and whether the combination is better than any of its components. However, the analysis in the TORCH trial included only half of the patients, thereby spoiling the advantage of the factorial design, although the published trial protocol stated that a factorial analysis was to be performed (3).

Nowhere in the 15-page trial report is the factorial analysis to be found, and the abstract of the TORCH trial gives readers the impression that the combination was better than any of its components, which is the result the authors of the Cochrane review quote.

The authors of a letter to the editor used a factorial analysis and showed that the effect of the combination was entirely due to salmeterol (4); the hazard ratio for fluticasone was 1.00 (0.87 to 1.15), $p = 0.99$. In other similar trials, both GlaxoSmithKline and AstraZeneca did not perform a factorial analysis (5).

Peter C Gøtzsche, pcg@cochrane.dk, Director of the Nordic Cochrane Centre

References

1. Nannini LJ, Poole P, Milan SJ, et al. Combined corticosteroid and long-acting beta2-agonist in one inhaler versus placebo for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2013;11:CD003794.
2. Calverley PM, Anderson JA, Celli B, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007;356:775–89.
3. Gøtzsche PC. Questionable research and marketing of a combination drug for smoker’s lungs. *J R Soc Med* 2014;107:256–7.
4. La Vecchia C and Fabbri LM. Prevention of death in COPD. *N Engl J Med* 2007;356:2211–2.
5. Suissa S, Ernst P, Vandemheen KL, et al. Methodological issues in therapeutic trials of COPD. *Eur Respir J* 2008;31:927–33.

Reply

We thank Professor Gøtzsche for his interest in our Cochrane Review and thought-provoking feedback.

This review addressed the efficacy and safety of combined inhaled corticosteroid (ICS) and long acting beta-agonist (LABA) in one inhaler versus placebo as a pair-wise comparison. We did not seek to address the efficacy of the individual components (LABA and ICS) versus combined treatment; this was addressed in other Cochrane reviews (1, 2) and will be included in a forthcoming network meta-analysis (3).

We note from the correspondence cited that the appropriateness of factorial analysis of the TORCH trial is the subject of debate (4). We have now highlighted this debate in the discussion and referenced this feedback in the review.

Nannini LJ, Poole P, Milan SJ, Holmes R, Normansell R. RN prepared the response and all authors agreed to its publication.

1. Nannini LJ, Poole P, Milan SJ, Kesterton A. Combined corticosteroid and long-acting beta2-agonist in one inhaler versus inhaled corticosteroids alone for chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2013, Issue 8. Art. No.: CD006826. DOI: 10.1002/14651858.CD006826.pub2.
2. Nannini LJ, Lasserson TJ, Poole P. Combined corticosteroid and long-acting beta2-agonist in one inhaler versus long-acting beta2-agonists for chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2012, Issue 9. Art. No.: CD006829. DOI: 10.1002/14651858.CD006829.pub2.

3. Oba Y, Fadila M, Keeney E, Dias S. Fixed-dose combination inhalers compared to long-acting bronchodilators for COPD: a network meta-analysis (Protocol). Cochrane Database of Systematic Reviews 2017, Issue 3. Art. No.: CD012620. DOI: 10.1002/14651858.CD012620.

4. Calverley PM, Anderson JA and Celli B. Prevention of Death in COPD. N Engl J Med 2007; 356:2213-2214. DOI: 10.1056/NEJMc070783

Contributors

Peter C Gøtzsche, pcg@cochrane.dk, Director of the Nordic Cochrane Centre

My concerns about the analysis of TORCH remain, 27 October 2017

Summary

The authors of the Cochrane review have changed their review because of my comment. However, the only thing they changed was that they added this sentence about the TORCH trial in the discussion section: "This analysis has been the subject of some debate as the study adopted a factorial design but reported [sic] did not use factorial analysis (see Feedback 1)."

It is misleading to say that the analysis of the TORCH trial "has been the subject of some debate." As I explained in my comment, the analysis of the TORCH trial is wrong and in violation of the published trial protocol, which stated that a factorial analysis was to be performed. The correct factorial analysis showed that the effect of the combination on mortality was entirely due to salmeterol; the hazard ratio for fluticasone was 1.00 (0.87 to 1.15), $p = 0.99$.

Since the steroid contributed absolutely nothing to the mortality reduction, the Cochrane review is misleading because it gives readers the impression that the reduction in mortality was due to the combination. Nowhere in the Cochrane review is it mentioned that the analysis of the TORCH trial was seriously misleading; in fact, its reported result is believed.

In the abstract and in the plain language summary, the Cochrane authors still mention that a reduction in mortality was seen without explaining that the steroid did not contribute to this. In their background section, they mention that combined therapy in the TORCH trial reduced mortality versus placebo, and under results (FPS versus placebo) they mention again this mortality benefit without any reservations that it was only one of the drugs in the combination that caused this.

The Cochrane review needs to be amended to reflect the above.

Peter C Gøtzsche, pcg@cochrane.dk, Director of the Nordic Cochrane Centre

Reply

Reply from the authors 22 November 2017

We thank Professor Gøtzsche for his continued interest in our review. We would like to re-emphasise this review did not set out to elucidate the relative contribution of long-acting beta₂-agonist (LABA) and inhaled corticosteroids (ICS) to the benefits or harms associated with combination therapy. A separate Cochrane Review, comparing combined therapy with LABA alone, goes some way to addressing this issue; it shows no significant difference between treatments for mortality, but the confidence interval is too wide to support an assertion of no difference. ("There was no significant difference in mortality between people on combined inhalers and those on LABA, from 10 studies on 10,680 participants (OR 0.92; 95% CI 0.76 to 1.11, downgraded to moderate quality evidence due to statistical imprecision"¹)

Furthermore, we disagree that the post-hoc factorial analysis of TORCH proves that fluticasone contributes "absolutely nothing" to the mortality benefit as the confidence interval (0.87 to 1.15) is again not sufficiently narrow to rule out possible benefit or harm.

Indeed, the authors of the article cited by Professor Gøtzsche acknowledge there is uncertainty about the impact of ICS, rather than completely ruling out a benefit: "in conclusion, after proper consideration of the various methodological shortcomings in the design and analysis of randomised trials, the effectiveness of inhaled corticosteroids in treating chronic obstructive pulmonary disease remains doubtful, while the benefit observed with combination therapy may be due exclusively to the beneficial effects of the long-acting bronchodilator alone."²

We note from previous correspondence published in the New England Journal Medicine that there is some uncertainty about whether ICS and LABA may have some synergistic effect, and therefore factorial analysis would be less appropriate. In a response in 2007 the authors of the TORCH trial state: "factorial analysis assumes that each treatment has the same additive effect in the absence and presence of the other treatment. This was not the case for the TORCH trial. Our data show the clear clinical superiority of combination treatment with salmeterol and fluticasone, including fewer exacerbations and better health status."³

It is a Cochrane standard that conclusions are based solely on the evidence presented in the review. However, we have made some minor adjustments to the abstract, plain language summary and conclusions to highlight that we cannot comment on the relative contribution of the different components of combined therapy and it may not be the combination, per se, which is beneficial.

Nannini LJ, Poole P, Milan SJ, Holmes R, Normansell R. RN prepared the response and all authors agreed to its publication.

1. Nannini LJ, Lasserson TJ, Poole P. Combined corticosteroid and long-acting beta2-agonist in one inhaler versus long-acting beta2-agonists for chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 2012, Issue 9. Art. No.: CD006829. DOI: 10.1002/14651858.CD006829.pub2.
2. Suissa S, Ernst P, Vandemheen KL, et al. Methodological issues in therapeutic trials of COPD. Eur Respir J 2008;31:927–33
3. Calverley PM, Anderson JA and Celli B. Prevention of Death in COPD. N Engl J Med 2007; 356:2213–2214. DOI: 10.1056/NEJMc070783

Independent methodological assessment, 27/02/2018

Following a further comment from Professor Gøtzsche over the authors response to his concerns, the Cochrane Editorial Unit arranged for an independent review of the Cochrane review and the evidence about the TORCH trial. Here is the review by Professor Julian Higgins:

The review addresses combination therapy versus placebo. The TORCH trial has a primary analysis that addresses this comparison, and all indications from the protocol documents are that this was planned as the primary analysis ("The primary objective of this study is to determine whether there is a significant reduction in all-cause mortality in COPD patients treated with SFC compared with placebo", from Vestbo et al, Eur Respir J 2004). Representation of the trial in the body of the review therefore looks entirely appropriate to me.

The question of whether the finding for combined therapy vs placebo is driven by one or other of the components does not seem relevant to the selection of the result or its inclusion in the Cochrane review, or indeed in conclusions drawn about the effect of combined therapy. I assume here that the objectives of the Cochrane review were not driven by observed findings of the TORCH trial, and in any case, I welcome the plans to perform a network meta-analysis to cover single and combined therapies.

I do not find any evidence in the 2004 protocol or the supplement to the 2007 paper (a more detailed protocol) that a factorial-style analysis was planned. I therefore do not concur with Peter Gøtzsche's apparent belief that the following text implies a factorial approach: "The other objectives of the study include comparisons of mortality in the SFC group with that seen in the salmeterol and FP groups, and in the salmeterol and FP groups compared with the placebo group." To me, these imply pair-wise comparisons of specific treatment groups, and not a plan to compare salmeterol vs no salmeterol and FP vs no FP, and similarly do not indicate a plan to investigate interaction between the two components (furthermore, the results of these particular analyses are clearly to be seen in Table 2 of the NEJM paper). Although I would consider the approach to analysing the trial to be surprising (NB not 'wrong'), given its factorial design, the analyses performed do seem to concur with the documents described as protocols. It is a concern, however, that the initial published protocol was submitted in October 2003, while within it, the protocol clearly indicates that it is retrospectively written: "The first patient was recruited in September 2000 and the last in November 2002."

I believe that remarks in the Authors' Conclusions sections of the Cochrane review would benefit from some clarifications. There is a claim that "Network meta-analysis may help elucidate the relative contribution of the individual components of combined therapy to the effects identified". Quite a lot of information about this is provided by the results of the TORCH trial for the particular components it evaluated, and it seems a little remiss to fail to comment on this. For issues around single vs combined therapy, the indication from the TORCH trial that salmeterol was driving the main result appears very relevant, and might be commented upon before calling for network meta-analyses to address the same question.

A subsequent comment is as follows: "Combined therapy should be compared with separate administration of long-acting beta₂-agonist and inhaled corticosteroid at different doses in large-scale multi-centre studies using a double dummy design". Again, it looks as if the TORCH trial does this to some extent, so the call for new trials without recognizing this might be misplaced.

Contributors

Feedback contributor: Peter C Gøtzsche, pcg@cochrane.dk, Director of the Nordic Cochrane Centre

Author response: Nannini LJ, Poole P, Milan SJ, Holmes R, Normansell R.

Independent review: Julian Higgins, Population Health Sciences, Bristol Medical School, University of Bristol

WHAT'S NEW

Date	Event	Description
14 March 2018	Amended	The Cochrane Editorial Unit (CEU) conducted an independent review following on from two pieces of feedback received about the analysis of the TORCH trial. The results of the independent review have been added to Feedback 2 and some changes have been made within the review to note to the possible issues in the TORCH trial.

HISTORY

Protocol first published: Issue 3, 2002

Review first published: Issue 4, 2003

Date	Event	Description
20 November 2017	Feedback has been incorporated	Feedback incorporated to review - see Feedback .
23 October 2017	Amended	Feedback and author response to feedback attributed to the respective author(s).
9 October 2017	Feedback has been incorporated	Feedback added to the review together with a response from the author team and an additional sentence to highlight this debate in the discussion section.
26 June 2013	New citation required and conclusions have changed	Inclusion of a new combination inhaler (Mometasone furoate/formoterol (MF/F)). Eight new studies included (Bourbeau 2007 ; Doherty 2012 ; Lapperre 2009 ; Rennard 2009 ; SCO104925 ; Sin 2008 ; Tashkin 2008 ; Tashkin 2012). Background was rewritten, outcomes were redefined, withdrawals were included as an outcome, and methods now reflect the latest version of the <i>Cochrane Handbook for Systematic Reviews of Interventions</i> . We presented data in subgroups according to different doses of the same drug for this update. Conclusions are strengthened by the addition of eight new studies.
26 June 2013	New search has been performed	New literature search run.
11 November 2009	Amended	Spelling corrections and minor reformatting
8 April 2008	Amended	Converted to new review format.
26 February 2008	Amended	Summary of findings table now added to review prepared centrally in GRADEpro by the Summary of Findings table working party (Nancy Santesso)
2 August 2007	New citation required and conclusions have changed	<p>Seven new studies met the entry criteria of the review (Barnes 2006; Kardos 2007; TORCH; SCO100470; SCO40030; SFCT01; SCO10054). New unpublished data have been incorporated for three studies previously included (Hanania 2003; Mahler 2002; TRISTAN).</p> <p>What was known before: Statistically significant findings in favour of combination treatment over placebo. Conflicting findings when combination treatment compared with monocomponent therapies.</p> <p>What new data contribute to the review: Data on all primary and secondary endpoints. Combined estimates now indicate that combination fluticasone and salmeterol is significantly more effective than fluticasone alone in reducing the rate of exacerbations.</p>
30 April 2004	New citation required and conclusions have changed	Two new studies are included in this update (Calverly 2003; Hanania 2003). One study previously reported in abstract form has now been published and baseline and outcome data incorporated in this version of the review (Dal Negro 2003).

Date	Event	Description
		<p>Data on lung function have been pooled on a WMD rather than a SMD. Pooled SEMs have been calculated from the published p values, and have been used to calculate some exacerbation outcomes, as well as symptoms, quality of life and lung function for some of the comparators.</p> <p>The Discussion and Conclusion reflect the incorporation of the new data, and the data calculated from previously published and included studies.</p>

CONTRIBUTIONS OF AUTHORS

In the 2013 update, LJN and PP updated the background section with input from SJM; SJM and RN updated the methods section. Studies were selected and appraised by LJN and PP, and data were extracted by RN and RH and then were entered by RN and checked by RH. RN and RH conducted the analysis with input from RH, LJN and PP. The results section was written by RN with input from RH, LJN and PP. The discussion, conclusion and abstract were written by LJN and PP with input from RN and RH.

LJN and PP developed the protocol. In previous versions of the review, studies were assessed by LJN and Toby Lasserson (TJL). TJL and LJN checked data and entered them into [RevMan 2011](#). TJL and LJN conducted the analysis. TJL and LJN developed the discussion with input from PP. Chris Cates (CJC) participated in the 2004 and 2007 updates of the review and offered statistical advice and input in calculating SEM and SD for the included studies when appropriate.

DECLARATIONS OF INTEREST

None known.

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Internal sources

- Hamamelis Trust, UK.
- St George's, University of London, UK.

External sources

- NIHR, UK.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have provided estimates of mortality from all included studies.

Since the protocol of this Cochrane review was published, several different aspects of review methodology have changed in light of more recent recommendations regarding the methodology of Cochrane reviews.

- Risk of bias assessment (*Cochrane Handbook for Systematic Reviews of Interventions*, Chapter 8): This has now displaced the Jadad scores used to determine study quality in previous versions of the review.
- Generic inverse variance (*Cochrane Handbook for Systematic Reviews of Interventions*, Chapters 7 and 9): This method of meta-analysing adjusted effect estimates from clinical trials has enabled us to measure exacerbation outcomes as rate ratios.
- Summary of findings tables: We have adopted the GRADE methodology for assessing the strength of evidence and determining effect size in absolute terms for key outcomes in this review ([GRADE working group](#)).
- In 2012, the inclusion criteria were clarified as *randomised, double-blind, parallel-group clinical trials of at least 4 weeks' duration*. This was done to bring consistency to the inclusion criteria of the three Cochrane reviews considering combined corticosteroid and long-acting beta₂-agonist in a single inhaler for chronic obstructive pulmonary disease.
- In 2012, we added the comparison of mometasone furoate/formoterol versus placebo.
- In 2012 we presented data subgrouped according to dose.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenergic beta-2 Receptor Agonists [*therapeutic use]; Bronchodilator Agents [*therapeutic use]; Drug Combinations; Nebulizers and Vaporizers; Pulmonary Disease, Chronic Obstructive [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Humans