Inhaled corticosteroids versus long-acting beta$_2$-agonists for chronic obstructive pulmonary disease (Review)

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[Intervention Review]

Inhaled corticosteroids versus long-acting beta$_2$-agonists for chronic obstructive pulmonary disease

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ABSTRACT

Background

Long-acting beta$_2$-agonists and inhaled corticosteroids can be used as maintenance therapy by patients with moderate to severe chronic obstructive pulmonary disease. These interventions are often taken together in a combination inhaler. However, the relative added value of the two individual components is unclear.

Objectives

To determine the relative effects of inhaled corticosteroids (ICS) compared to long-acting beta$_2$-agonists (LABA) on clinical outcomes in patients with stable chronic obstructive pulmonary disease.

Search strategy

We searched the Cochrane Airways Group Specialised Register of trials (latest search August 2011) and reference lists of articles.

Selection criteria

We included randomised controlled trials comparing inhaled corticosteroids and long-acting beta$_2$-agonists in the treatment of patients with stable chronic obstructive pulmonary disease.

Data collection and analysis

Three authors independently assessed trials for inclusion and then extracted data on trial quality, study outcomes and adverse events. We also contacted study authors for additional information.

Main results

We identified seven randomised trials (5997 participants) of good quality with a duration of six months to three years. All of the trials compared ICS/LABA combination inhalers with LABA and ICS as individual components. Four of these trials included fluticasone and salmeterol monocomponents and the remaining three included budesonide and formoterol monocomponents. There was no statistically significant difference in our primary outcome, the number of patients experiencing exacerbations (odds ratio (OR) 1.22; 95% CI 0.89 to 1.67), or the rate of exacerbations per patient year (rate ratio (RR) 0.96; 95% CI 0.89 to 1.02) between inhaled corticosteroids and

long-acting beta$_2$-agonists. The incidence of pneumonia, our co-primary outcome, was significantly higher among patients on inhaled corticosteroids than on long-acting beta$_2$-agonists whether classified as an adverse event (OR 1.38; 95% CI 1.10 to 1.73) or serious adverse event (Peto OR 1.48; 95% CI 1.13 to 1.93). Results of the secondary outcomes analysis were as follows. Mortality was higher in patients on inhaled corticosteroids compared to patients on long-acting beta$_2$-agonists (Peto OR 1.17; 95% CI 0.97 to 1.42), although the difference was not statistically significant. Patients treated with beta$_2$-agonists showed greater improvements in pre-bronchodilator FEV_1 compared to those treated with inhaled corticosteroids (mean difference (MD) 18.99 mL; 95% CI 0.52 to 37.46), whilst greater improvements in health-related quality of life were observed in patients receiving inhaled corticosteroids compared to those receiving long-acting beta$_2$-agonists (St George's Respiratory Questionnaire (SGRQ) MD -0.74; 95% CI -1.42 to -0.06). In both cases the differences were statistically significant but rather small in magnitude. There were no statistically significant differences between ICS and LABA in the number of hospitalisations due to exacerbations, number of mild exacerbations, peak expiratory flow, dyspnoea, symptoms scores, use of rescue medication, adverse events, all cause hospitalisations, or withdrawals from studies.

Authors' conclusions

Placebo-controlled trials have established the benefits of both long-acting beta-agonist and inhaled corticosteroid therapy for COPD patients as individual therapies. This review, which included trials allowing comparisons between LABA and ICS, has shown that the two therapies confer similar benefits across the majority of outcomes, including the frequency of exacerbations and mortality. Use of long-acting beta-agonists appears to confer a small additional benefit in terms of improvements in lung function compared to inhaled corticosteroids. On the other hand, inhaled corticosteroid therapy shows a small advantage over long-acting beta-agonist therapy in terms of health-related quality of life, but inhaled corticosteroids also increase the risk of pneumonia. This review supports current guidelines advocating long-acting beta-agonists as frontline therapy for COPD, with regular inhaled corticosteroid therapy as an adjunct in patients experiencing frequent exacerbations.

PLAIN LANGUAGE SUMMARY

Comparing inhaled corticosteroids with long-acting beta$_2$-agonists in treating chronic obstructive pulmonary disease (COPD)

Inhalers containing corticosteroids, long-acting beta$_2$-agonists or both can be used to treat severe chronic obstructive pulmonary disease (COPD). However, the benefits and harms of the two individual treatments are unclear when comparing one treatment with the other.

We looked at clinical trials that compared the two kinds of inhalers to find the effects of each on health and well-being in patients with COPD. We found seven studies (involving 5997 participants) comparing the long-term benefits and side effects of inhaled corticosteroids and long-acting beta$_2$-agonists for treating COPD. Overall, we found no significant difference between the two drugs in the number of people having an exacerbation (worsening of COPD symptoms). More people taking inhaled corticosteroids suffered episodes of pneumonia compared to people using long-acting beta$_2$-agonists, although pneumonia was extremely rare in both groups. Inhaled corticosteroids do not improve lung function as much as long-acting beta$_2$-agonists but did improve patients' quality of life more than long-acting beta$_2$-agonists. The differences in lung function and quality of life were rather small.

BACKGROUND

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines for the treatment of patients with chronic obstructive pulmonary disease (COPD) state that beta$_2$-agonists are a central therapy for the alleviation of symptoms (GOLD 2010). Inhaled long-acting beta$_2$-agonists (LABAs) improve lung function (Boyd 1997) and health-related quality of life (Jones 1997) and are recommended by current National Institute for Health and Clinical Excellence (NICE) guidelines in the treatment of COPD (NICE 2010). A Cochrane review of the efficacy of LABA in people with stable COPD reported significant benefits on a range of outcomes including improved lung function, improved health-related quality of life and fewer exacerbations of COPD, confirming LABA as an effective therapy in COPD (Appleton 2006).

Long-term treatment with inhaled corticosteroids (ICS) has not been found to modify the rate of decline in forced expiratory volume in one second (FEV_1) (Pauwels 1999; Vestbo 1999; Burge

2000; Lung Health 2000) but, in moderate or severe COPD, ICS has been shown to reduce the frequency and severity of exacerbations (Burge 2000). Both the GOLD and NICE guidelines recommend the addition of regular treatment with inhaled corticosteroids to bronchodilator treatment for patients with an FEV_1 < 50% predicted who are symptomatic or suffer repeated exacerbations of COPD (GOLD 2010; NICE 2010). Treatment with inhaled corticosteroids has also been shown to reduce the rate of deterioration in health-related quality of life (Spencer 2001) through a reduction in exacerbation frequency (Spencer 2003). A Cochrane review of ICS for stable COPD reported a range of therapeutic benefits including improved lung function, improved health-related quality of life and fewer exacerbations of COPD, with no associated impact on mortality rates compared to placebo (Yang 2007).

This evidence for the effectiveness of LABA and ICS for COPD has led to the development of combination therapies that contain both an inhaled corticosteroid and a long-acting $beta_2$-agonist (Calverley 2003 a). However, the relative benefits of LABA and ICS in the treatment of COPD has not been fully explored. Recent findings from clinical trials suggest that the impact of combination therapies on a range of outcomes may not be a simple additive effect, for example in the comparisons of combination versus monocomponents (ICS or LABA) for exacerbation rates (Calverley 2003 a; Calverley 2007). This makes an investigation of the relative added value of LABAs compared to ICS even more important. Of particular concern is the relative impact of the treatments on adverse outcomes such as mortality.

The aim of this review is to evaluate the relative added value of inhaled corticosteroids compared to long-acting $beta_2$-agonists on clinical endpoints.

OBJECTIVES

To determine the relative effects of inhaled corticosteroids and long-acting $beta_2$-agonists on clinical endpoints in patients with stable COPD.

METHODS

Criteria for considering studies for this review

Types of studies

We included published and unpublished randomised trials (RCTs) that included comparisons between inhaled corticosteroids and long-acting $beta_2$-agonists in the treatment of patients with stable COPD.

Types of participants

We included patients with a clinical diagnosis of COPD, and not asthma, that fulfilled any of the following internationally recognised diagnostic guidelines: American Thoracic Society (ATS), European Respiratory Society (ERS) and Global Initiative for Chronic Obstructive Lung Disease (GOLD). We only included studies with patients who were clinically stable at study entry, as defined by an exacerbation-free study run-in period, and that had excluded patients with significant comorbidity.

Types of interventions

We included regular inhaled corticosteroids compared with regular inhaled long-acting $beta_2$-agonists administered by any inhalation device. We included the following inhaled corticosteroid versus inhaled long-acting $beta_2$-agonist comparisons.

1.1. Formoterol versus beclomethasone
1.2. Formoterol versus budesonide
1.3. Formoterol versus ciclesonide
1.4. Formoterol versus fluticasone
1.5. Formoterol versus mometasone
1.6. Formoterol versus triamcinolone
2.1. Salmeterol versus beclomethasone
2.2. Salmeterol versus budesonide
2.3. Salmeterol versus ciclesonide
2.4. Salmeterol versus fluticasone
2.5. Salmeterol versus mometasone
2.6. Salmeterol versus triamcinolone

We allowed long-acting anticholinergics, for example tiotropium, as co-interventions.

Types of outcome measures

Primary outcomes

1. Moderate or severe exacerbations: defined as those requiring treatment with antibiotics or oral corticosteroids, or both, expressed as the total number of exacerbations
2. Hospitalisations due to exacerbations
3. Pneumonia

Secondary outcomes

1. All cause mortality
2. Mild exacerbations: defined as a worsening of symptoms not necessitating treatment with antibiotics or oral corticosteroids, expressed as the total number of exacerbations
3. Change in forced expiratory volume in 1 second (FEV_1) and other measures of pulmonary function
4. Quality of life scales
5. Symptom scores of breathlessness and other symptom scores

6. Inhaled rescue medication use during the treatment period
7. Adverse events
8. All cause hospitalisations
9. Withdrawal from study

Search methods for identification of studies

Electronic searches

We searched the Cochrane Airways Group Specialised Register for randomised controlled trials. The Register is derived from systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*), MEDLINE, EMBASE and CINAHL, and handsearching of respiratory journals and meeting abstracts (please see the Airways Group search methods for further details). All records in the Register coded as 'COPD' were searched using the following strategy:
((bronchodilator* AND long*) OR ((beta* AND agonist*) AND long-acting OR "long acting") OR ((beta* AND adrenergic*) AND long-acting OR "long acting") OR salmeterol OR Serevent OR formoterol OR Foradil OR Oxis OR eformoterol OR fenoterol OR bambuterol OR Bambec) AND ((*steroid OR steroid* OR corticosteroid* OR corticoid* OR glucocorticoid* OR "adrenal cortex hormones") OR (fluticasone OR Flixotide OR beclomethasone OR beclometasone OR QVAR OR budesonide OR Pulmicort OR mometasone OR Asmanex OR triamcinolone OR Kenalog OR ciclesonide OR Alvesco OR CIC OR flunisolide OR Aerobid)).

Searching other resources

We checked the reference lists of all included randomised controlled trials and review articles for additional references. We contacted authors of identified randomised trials about other published and unpublished studies.

Data collection and analysis

Selection of studies

Two of us (SS and DJE) independently assessed the titles and abstracts of all retrieved trials. Using the full text of each study, we independently selected trials for inclusion in the review. We resolved disagreements about relevance by consensus.

Data extraction and management

Three of us (SS, DJE and CK) independently extracted data from the included studies and the data were then aggregated. We sought data missing from the publications through correspondence with the study authors. We extracted variance data from all arms of the included studies to enable calculation of the variance of the ICS versus LABA difference, where this was not reported. We combined data from all trials using RevMan 5.

Assessment of risk of bias in included studies

We assessed the risk of bias for all included studies according to recommendations outlined in the *Cochrane Handbook of Systematic Reviews of Interventions* (Higgins 2008) for the following items.

1. Allocation sequence generation.
2. Concealment of allocation.
3. Blinding of participants and investigators.
4. Incomplete outcome data.
5. Selective outcome reporting.

We graded each potential source of bias as either low, high or unclear. We noted other sources of bias.

Measures of treatment effect

We summarised proportional outcomes, such as the proportion who improved, using an odds ratio (OR) with a fixed-effect Mantel-Haenszel model, unless zero cells were present in which case we used Peto odds ratios. We analysed continuous data as weighted mean difference (MD) with a fixed-effect model. In trials where individual group data were not reported and treatment effects were only given as differences between treatment groups, we analysed data using the generic inverse variance (GIV) function with a fixed-effect model. A number of trials reported the difference between ICS and LABA arms but did not report the appropriate variance around this difference. In this case, we calculated the variance of the difference between ICS and LABA using the variances of all the trial arms, see Appendix 1. We did not impute variances from other studies in any of the analyses in this review.

Dealing with missing data

We contacted investigators and manufacturers of the preparations for missing data, where necessary.

Assessment of heterogeneity

We performed tests for heterogeneity using the I^2 statistic in RevMan 5. Where I^2 was greater than 20% we also conducted a sensitivity analysis by pooling data with a random-effects model and comparing this to the results of the fixed-effect model.

Assessment of reporting biases

We planned to inspect funnel plots for signs of publication bias.

Subgroup analysis and investigation of heterogeneity

We pooled the analysis across studies but performed subgroup analyses for each corticosteroid versus beta$_2$-agonist comparison. The treatment periods were stratified into less than one year, and more than one year. We pooled studies with different doses of the same inhaled corticosteroid and planned to carry out subgroup testing to compare different doses, when the data allowed this.

Sensitivity analysis

We planned to carry out sensitivity analysis based on study quality.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

The electronic search returned 431 references. From these, we identified 115 as potentially relevant. After further assessment we found that 99 references belonging to seven studies were eligible and 16 references were excluded with reasons given. The latest search was run in August 2011.

Included studies

Full details of all included studies can be found in the Characteristics of included studies table.

Study design

All the included studies were multi-centre, randomised, double-blind, placebo-controlled with a parallel-group design. TORCH 2007 was the longest trial with a treatment duration of three years. Calverley 2003, Szafranski 2003 and TRISTAN 2003 were one-year studies, and Hanania 2003, Mahler 2002 and Tashkin 2008 had a duration of six months.

Sample size

The studies included 5997 participants of which 2991 were randomised to LABA treatment and 3006 to ICS treatment. TORCH 2007 was the largest study with 3093 participants. The other studies had between 300 to 800 participants each.

Participants

The mean age of participants was 64 years. The average gender distribution varied from 62% males in Hanania 2003 to 78% in Szafranski 2003. All participants were diagnosed with COPD according to GOLD 2010, ATS or ERS classifications. Disease severity in the included studies ranged from moderate to very severe COPD. The average baseline lung function varied from 1.0 to 1.3 L for FEV_1, and from 36% to 45% for FEV_1 predicted, across the studies.

Interventions

In Calverley 2003, Szafranski 2003, and Tashkin 2008 the LABA used was formoterol at 4.5 µg, two inhalations twice daily; and the ICS was budesonide, two inhalations twice daily at 200, 200 and 160 µg, respectively. Hanania 2003, Mahler 2002, TORCH 2007 and TRISTAN 2003 looked at the LABA salmeterol and the ICS fluticasone. Salmeterol was used at a dose of 50 µg twice daily and the ICS fluticasone at 500 µg twice daily. The exception was Hanania 2003, which used fluticasone at a dose of 250 µg twice daily.

Permitted co-treatment

All included studies allowed reliever medication, such as terbutaline or salbutamol, when necessary to relieve symptoms. In the majority of studies tiotropium was not a permitted co-treatment. Calverley 2003 also allowed courses of oral corticosteroids (maximum three weeks per course) and antibiotics in the event of exacerbations, and parenteral steroids or nebulised treatment (single injections or inhalations), or both, at emergency visits. Tashkin 2008 allowed oral and parenteral corticosteroids (not depot formulations), acute use of xanthines, increased use of inhaled beta-adrenoceptor agonists and ipratropium bromide, nebulized beta-adrenoceptor agonists and ipratropium bromide. TORCH 2007 allowed patients to continue any medication for COPD other than corticosteroids and inhaled long-acting bronchodilators. TRISTAN 2003 allowed regular treatment with anticholinergics, mucolytics and theophylline. All non-COPD medications could be continued if the dose remained constant, whenever possible, and if their use would not be expected to affect lung function.

Outcomes

All the included studies looked at COPD exacerbations, FEV_1, health-related quality of life and adverse events. Most of the studies

also recorded symptoms, use of reliever medication, dyspnoea and peak expiratory flow (PEF).

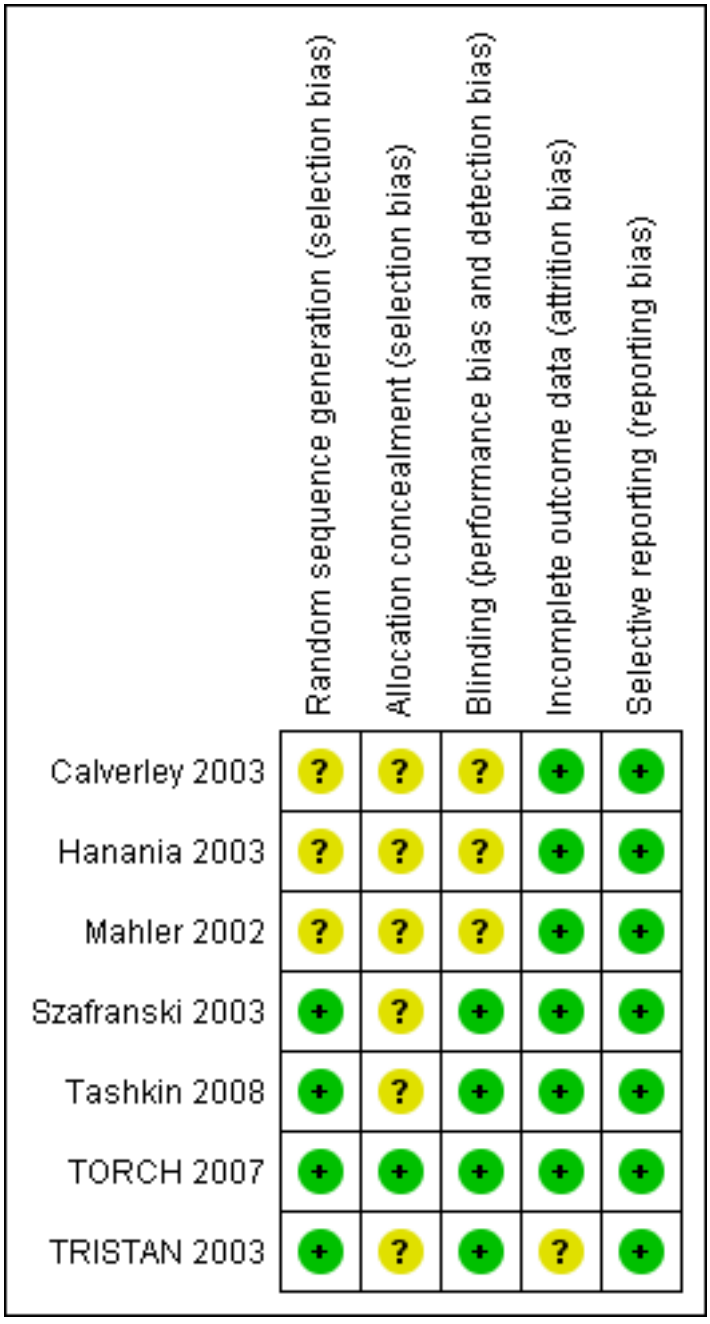
Excluded studies

Fourteen references from 11 studies were excluded as they failed to meet the eligibility criteria for the review (see Characteristics of excluded studies). Nine of these did not include trial arms of monotreatment with inhaled corticosteroid and long-acting beta$_2$-agonist (Della Cioppa 2001; Cazzola 2003; Barnes 2005; Gosman 2006; Jiang 2009; Nungtjik 2009; Worth 2009; Mittmann 2010). The remaining two references were reviews (Lyseng-Williamson 2002; Reynolds 2004).

Risk of bias in included studies

An assessment of the risk of bias for each study is presented in the Characteristics of included studies, and an overview of the findings is shown in Figure 1.

Figure 1. Risk of bias summary: review authors' judgements about each 'Risk of bias' item for each included study.



Allocation

Szafranski 2003, Tashkin 2008, TORCH 2007 and TRISTAN 2003 reported using computer-generated randomisation schedules for list generation and were therefore judged to be at low risk of bias. Patients who met the inclusion criteria were assigned the next consecutive treatment number from the generated list. Information regarding sequence generation for the other included studies, and details of allocation concealment procedures for all included studies (except TORCH 2007), were not reported and these were judged to be at unclear risk of bias. In TORCH 2007 the principal investigators were provided with the participant's treatment number as well as a treatment pack number through an automated 24-hour telephone number. For all other studies there were insufficient descriptions of allocation concealment methods to allow judgement of anything other than unclear risk of bias against this criterion.

Blinding

All the included studies were double-blind, though only Szafranski 2003, Tashkin 2008, TORCH 2007 and TRISTAN 2003 gave details of the blinding of participants and clinicians, permitting a judgement of low risk of bias. In Szafranski 2003 all the inhalers were identical to ensure that the patients, pharmacists and the investigators were blinded to the allocated treatment. In Tashkin 2008 patients received both a pressurized metered-dose inhaler and a dry powder inhaler containing either active treatment or placebo, or combinations of active treatment and placebo, as appropriate. In TORCH 2007 and TRISTAN 2003 study drugs were packaged in identical inhaler devices to ensure that both the patients and investigators were unaware of treatment allocation.

Incomplete outcome data

All included studies had substantial withdrawal rates (20% to 40%). However, the rates were broadly comparable in the ICS and LABA treatment groups with the exception of Mahler 2002, where there was a notable difference between ICS (40%) and LABA (28%) dropout rates. Most of the studies, including Mahler 2002, described intention-to-treat data analyses, though TRISTAN 2003 did not state whether follow-up data were collected for discontinued patients.

Selective reporting

All included trials adequately reported the outcome data specified in the published methods and were therefore judged to be at low risk of bias for this criterion.

Effects of interventions

Please note that a number of trials reported the difference between ICS and LABA arms but did not report the appropriate variance around this difference. In these cases we calculated the variance of the difference between ICS and LABA using the variances of all the trial arms, see Appendix 1. Variances were not imputed from other studies in any of the analyses in this review.

Inhaled corticosteroid versus long-acting beta$_2$-agonist

Primary outcome: exacerbations

Four studies (4750 participants) reported exacerbation rate ratios between ICS or LABA and placebo or a ICS/LABA combination (Calverley 2003; Szafranski 2003; TRISTAN 2003; TORCH 2007). Analysis of the rate ratio (RR) between ICS and LABA was not statistically significant (RR 0.96; 95% confidence interval (CI) 0.89 to 1.02) (Analysis 1.1), and the CI was narrow enough to exclude large differences between the two treatments, see Figure 2. There was no evidence of a class effect when comparing the fluticasone/salmeterol trials to the budesonide/formoterol trials in a subgroup analysis (Chi^2 = 1.57, df = 1, P = 0.21). There was no statistically significant difference in exacerbation RR between studies of $\leq$ 1 year and > 1 year of treatment (Chi^2 = 0.11, df = 1, P = 0.75), see Figure 3. Tashkin 2008 was excluded from the analysis because CIs, P values or standard deviations were not reported for any of the rate ratio comparisons. Two studies comparing fluticasone versus salmeterol reported the number of patients experiencing exacerbations requiring either treatment with antibiotics or corticosteroids, or both, or hospitalisation during the treatment period (Mahler 2002; Hanania 2003) (688 participants, Analysis 1.2). In these studies, although more patients on ICS (136/351) suffered exacerbations than on LABA (115/337), the CIs were wide and there was no statistically significant difference between the groups (OR 1.22; 95% CI 0.89 to 1.67).

Figure 2. Forest plot of comparison: 1 Inhaled corticosteroids versus long-acting beta$_2$-agonists by ICS and LABA, outcome: 1.1 Exacerbation rate ratios.

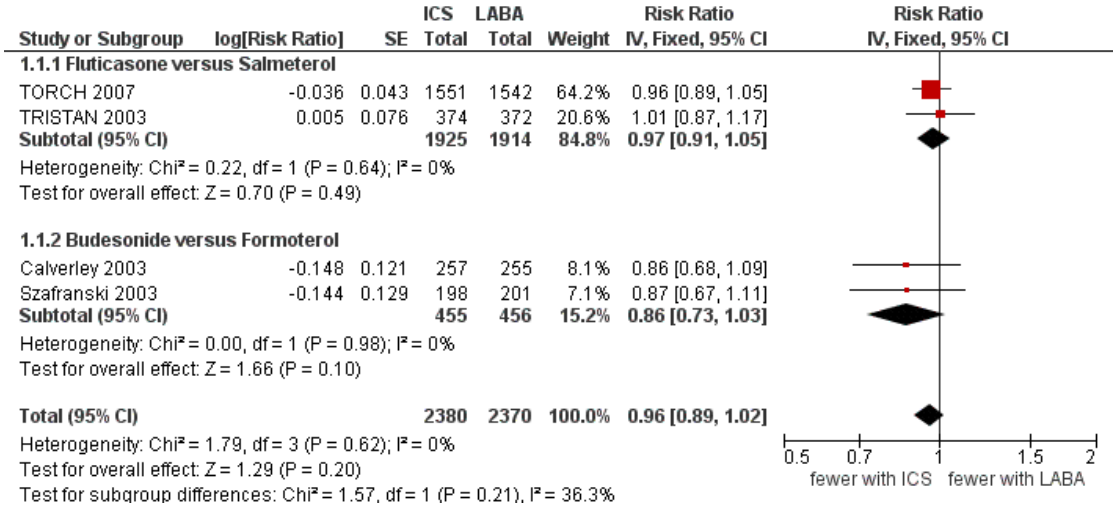
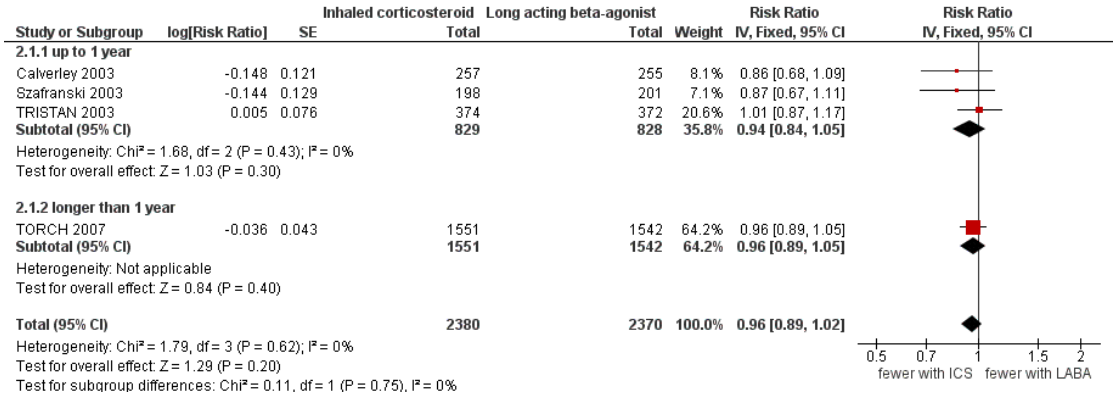


Figure 3. Forest plot of comparison: 2 Inhaled corticosteroids versus long-acting beta$_2$-agonists by length of study, outcome: 2.1 Exacerbation rate ratios.



Primary outcome: hospitalisations due to exacerbations

Exacerbations leading to hospitalisations were only reported in a single trial (TORCH 2007) with 3093 participants. A comparison of rate ratios showed there was no significant difference in the risk of hospitalisation due to exacerbation between fluticasone and salmeterol (RR 1.07; 95% CI 0.91 to 1.26) (Analysis 1.3).

Primary outcome: pneumonia

Three studies (4164 participants) reported the number of patients suffering from episodes of pneumonia as adverse events (Calverley 2003; TORCH 2007; Tashkin 2008). The three-year study, TORCH 2007 (3093 participants), showed a significantly higher incidence of pneumonia in patients on fluticasone compared to patients on salmeterol (OR 1.43; 95% CI 1.13 to 1.81). The other two shorter studies (Tashkin 2008: six months, Calverley 2003: 1 year), comparing budesonide/formoterol, had few events and wide CIs and showed no statistically significant

difference between the treatment groups (OR 0.84; 95% CI 0.36 to 1.96), see Figure 4. There was no significant difference between the results of TORCH 2007 and the other two studies (Chi^2 = 1.43, df = 1, P = 0.23). Overall there was an increased risk of pneumonia on ICS compared to LABA (OR 1.38; 95% CI 1.10 to 1.73) as shown in Figure 4. This result is also shown as a Cates plot in Figure 5, which demonstrates that for every 100 people treated over 2.4 years, there would be seven pneumonia cases if they were all given LABA and nine pneumonia cases if they were all given ICS. These calculations are based on the assumption that, in such a hypothetical situation, the patients were not also receiving the other treatment.

Figure 4. Forest plot of comparison: 1 Inhaled corticosteroids versus long-acting beta$_2$-agonists by ICS and LABA, outcome: 1.4 Pneumonia adverse event.

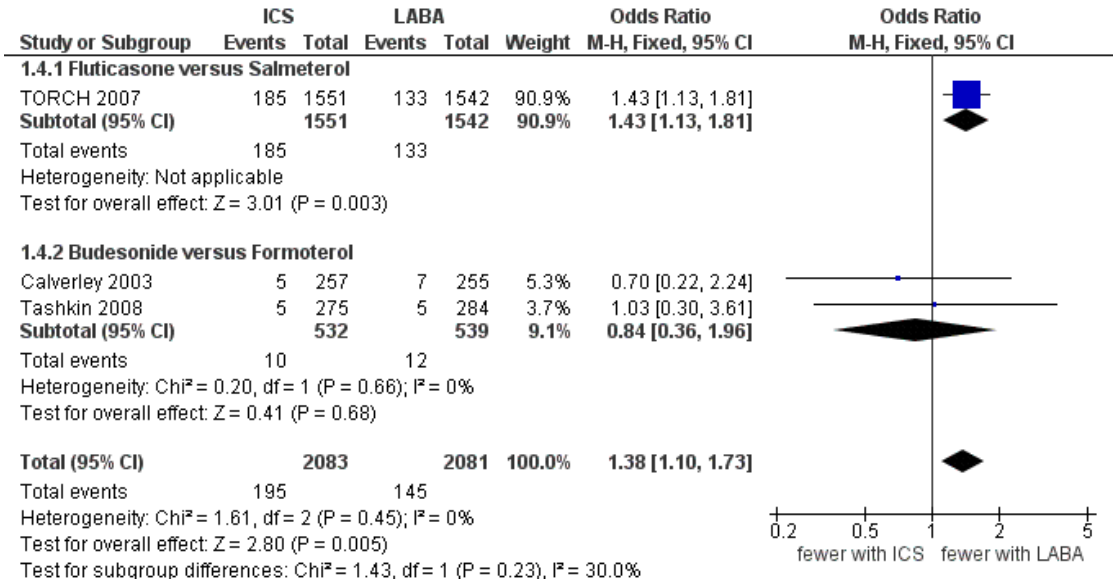
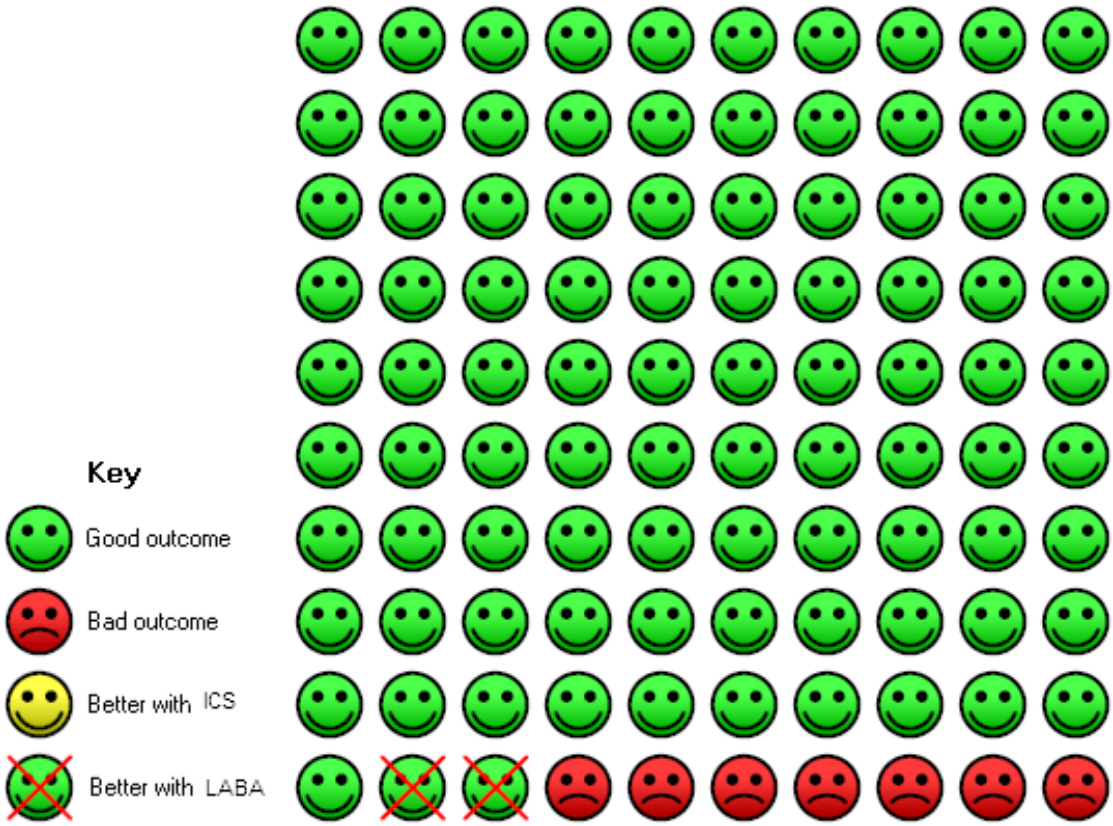
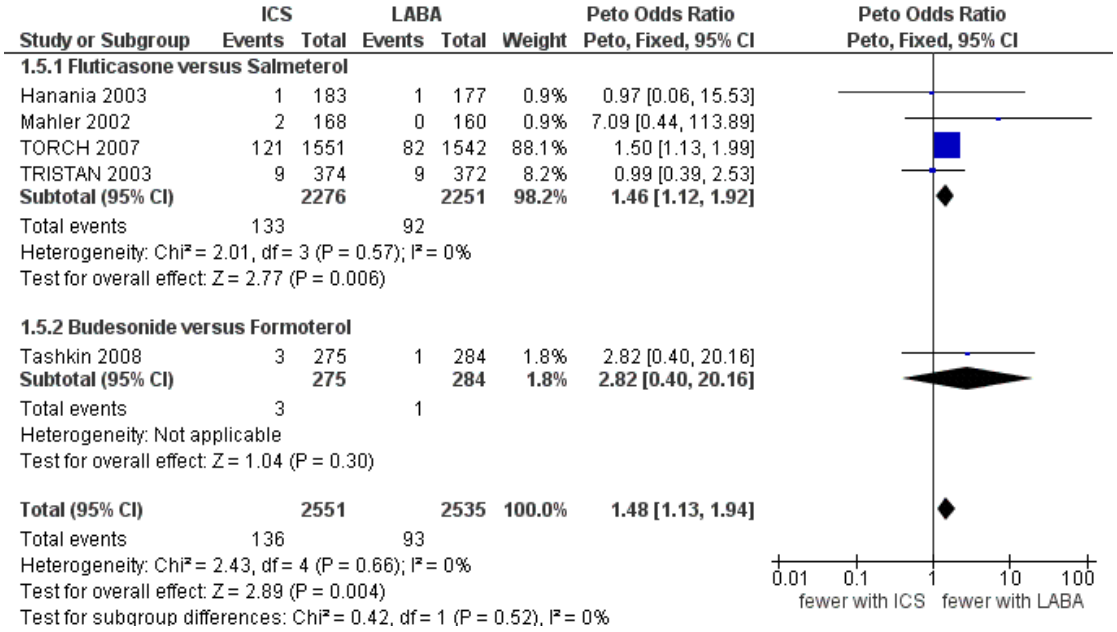


Figure 5. On LABA 7 people out of 100 had pneumonia (adverse event) over 2.4 years, compared to 9 (95% CI 8 to 12) out of 100 for the ICS group. The NNT(H) for one extra person to suffer pneumonia on ICS was 42 (95% CI: 155 to 23).



Five of the included studies (5086 participants) classified pneumonia as a serious adverse event (Mahler 2002; Hanania 2003; TRISTAN 2003; TORCH 2007; Tashkin 2008). A separate analysis was conducted for these studies as the distinction between adverse event and serious adverse event classification of pneumonia was unclear. Of these studies, four compared fluticasone versus salmeterol and one compared budesonide versus formoterol. The pooled result was again dominated by TORCH 2007 and showed a significantly greater risk of pneumonia for patients on ICS compared to patients on LABA (Peto OR 1.48; 95% CI 1.13 to 1.93), see Figure 6. There was no statistically significant difference in pneumonia, classified as a serious adverse event, between studies of $\leq$ 1 year and > 1 year of treatment (Chi^2 = 0.71, df = 1, P = 0.40), or between the studies using fluticasone/salmeterol and budesonide/formoterol (Chi^2 = 0.42, df = 1, P = 0.51).

Figure 6. Forest plot of comparison: 1 Inhaled corticosteroids versus long-acting beta$_2$-agonists by ICS and LABA, outcome: 1.5 Pneumonia serious adverse event.



Secondary outcome: mortality

All the included studies (5997 participants in seven studies) reported the number of deaths from any cause during the treatment period. The three-year TORCH 2007 study was the only one to report mortality status for all randomised participants, including study withdrawals. The number of events was generally low except for TORCH 2007, which reported significantly more deaths among patients treated with fluticasone compared to salmeterol (Peto OR 1.23; 95% CI 1.01 to 1.50). The pooled result showed that there was no statistically significant difference between ICS and LABA on mortality (Peto OR 1.17; 95% CI 0.97 to 1.42; I^2 = 37%), see Analysis 1.9. Since I^2 was greater than 20% we performed sensitivity analysis using the random-effects model (OR 0.98; 95% CI 0.59 to 1.64); this model gives much less weight to TORCH 2007, which explains the reversal of direction of the treatment effect. There was heterogeneity between the two subgroups of fluticasone versus salmeterol and budesonide versus formoterol (I^2 = 73%) but the difference was not statistically significant (Chi^2 = 3.64, df = 1, P = 0.06).

Secondary outcome: mild exacerbations

Data on mild exacerbations not necessitating treatment with antibiotics or oral corticosteroids were only reported by Hanania 2003 and Mahler 2002 (688 participants). There was no statistically significant difference between the fluticasone and salmeterol treatment groups, though the number of occurrences was low, leading to wide CIs (OR 1.51; 95% CI 0.74 to 3.08; I^2 = 57%). Because of heterogeneity between the studies we performed sensitivity analysis using the random-effects model (OR 1.63; 95% CI 0.49 to 5.39).

Secondary outcome: measures of pulmonary function

Forced expiratory volume in one second (FEV_1)

Four studies including 1993 participants reported changes in pre-dose FEV_1 (Mahler 2002; Hanania 2003; TRISTAN 2003; Tashkin 2008). TORCH 2007 was excluded from this analysis as the pre-bronchodilator FEV_1 was not reported. The combined result showed a smaller increase in FEV_1 for ICS than LABA when analysed with a fixed-effect model (MD -18.99; 95% CI -37.46 to -0.52; I^2 = 24%). However, since I^2 was greater than 20% between the studies we performed a sensitivity analysis. When analysed with a random-effects model the difference in increase in FEV_1 was not statistically significant (MD -17.36; 95% CI -39.54 to 4.82). There was moderate heterogeneity between the subgroups, fluticasone versus salmeterol and budesonide versus formoterol (I^2 = 48%), but this was not statistically significant (Chi^2 = 1.92, df = 1, P = 0.17), see Analysis 1.6.

There were also two studies (3652 participants) which reported changes in post-dose FEV_1 (TORCH 2007; Tashkin 2008). There was substantial heterogeneity between the results of the two studies (I^2 = 98%). TORCH 2007 showed no statistically significant difference in mean change in 30 minute post-bronchodilator FEV_1 between fluticasone and salmeterol after three years of treatment (MD 5 mL; 95% CI -11.46 to 21.46). Tashkin 2008 on the other hand showed a significantly smaller improvement in 60 minute post-bronchodilator FEV_1 with budesonide than with formoterol after six months of treatment (MD -140 mL; 95% CI -177.24 to -102.76). Because of the many substantial differences between the two studies, the results were not pooled.

Peak expiratory flow (PEF)

Tashkin 2008 (559 participants) reported the difference in change in morning PEF between formoterol and budesonide that was not statistically significant (MD -4.26L/min; 95% CI -9.26 to 0.74).

Secondary outcome: quality of life

We could extract data on changes in health-related quality of life from three studies involving 4398 participants that used the St George's Respiratory Questionnaire (SGRQ) (TRISTAN 2003; TORCH 2007; Tashkin 2008). Patients treated with ICS showed greater improvements in quality of life compared to those treated with LABA (MD -0.74; 95% CI -1.42 to -0.06). This difference was small in relation to the threshold of four units for a clinically significant difference. There was no heterogeneity between the subgroups, see Analysis 1.10.

Secondary outcome: symptom scores of breathlessness and other symptom scores

Dyspnoea

Data on changes in dyspnoea could be extracted from five of the included studies. Changes in dyspnoea over the treatment period were measured using either a 0 to 4 point validated dyspnoea scale (Calverley 2003; TRISTAN 2003; Tashkin 2008) in 2505 participants or the validated Transition Dyspnoea Index (TDI) (Mahler 2002; Hanania 2003) in 688 participants. On the TDI scale a higher score represents an improvement in perceived breathlessness, and on the 0 to 4 dyspnoea scale a higher score represents more breathlessness. There was no statistically significant difference (MD 0.03; 95% CI -0.02 to 0.08) between ICS and LABA using the 0 to 4 point dyspnoea scale and although there was heterogeneity between the two subgroups (fluticasone versus salmeterol and budesonide versus formoterol) (I^2 = 57%), this was not statistically significant (Chi^2 = 2.31, df = 1, P = 0.13) see Analysis 1.11. However, there was also moderate heterogeneity among the studies comparing budesonide and formoterol (I^2 = 30%) and among all the included studies (I^2 = 47%). There was no statistically significant difference between fluticasone and salmeterol treatment in studies using the TDI (Mahler 2002; Hanania 2003) in 688 participants (MD 0.26; 95% CI -0.21 to 0.74). CIs for the comparisons were wide using either dyspnoea scale.

Symptoms

Symptom score data could be extracted from three studies including 1470 participants (Calverley 2003; Szafranski 2003; Tashkin 2008). The mean improvement in symptom score was greater with LABA than ICS (MD 0.21; 95% CI 0.06 to 0.37) although there was no coherent pattern between the studies resulting in considerable heterogeneity (I^2 = 62%). When analysed with a random-effects model there was no statistically significant difference between ICS and LABA treatment (MD 0.22; 95% CI -0.03 to 0.47).

Secondary outcome: rescue medication

Tashkin 2008 (559 participants) reported a statistically significant difference in the use of rescue medication during the treatment period that favoured formoterol (MD 0.56 puffs/24 h; 95% CI 0.10 to 1.02).

Secondary outcome: adverse events

All adverse events

The number of patients suffering adverse events could be extracted from five studies including 5086 participants (Mahler 2002; Hanania 2003; TRISTAN 2003; TORCH 2007; Tashkin 2008). Patients receiving ICS had more adverse events (2122/2552) compared to those receiving LABA (2070/2537), but the difference was not statistically significant (OR 1.12; 95% CI 0.96 to 1.30). There was no heterogeneity between the subgroups.

Serious adverse events (non-fatal)

Data on the number of non-fatal, serious adverse events could be obtained from three of the included studies (Calverley 2003; Szafranski 2003; Tashkin 2008) (1470 participants). These three studies all compared the risk of serious adverse events associated with budesonide treatment versus formoterol, which was not statistically significant (OR 1.01; 95% CI 0.77 to 1.31). Data on the number of participants experiencing one or more non-fatal, serious adverse events were obtained from a further three of the included studies (Mahler 2002; Hanania 2003; TRISTAN 2003) (1434 participants). These studies all compared fluticasone versus salmeterol. There was considerable heterogeneity among the studies (I^2 = 54%), and there was no statistically significant difference between the treatments (OR 0.93; 95% CI 0.67 to 1.31). This

was consistent when analysed with a random-effects model (OR 1.17; 95% CI 0.60 to 2.28) (Analysis 1.15).

Secondary outcome: all cause hospitalisations

None of the included studies reported the number of patients admitted to hospital for any cause.

Secondary outcome: withdrawals

All seven of the included studies reported the number of participant withdrawals from each treatment arm. Overall there was no statistically significant difference in the number of withdrawals between patients on ICS and LABA (OR 1.02; 95% CI 0.92 to 1.14; I^2 = 29%) (Analysis 1.16). Subgroup analysis showed no statistically significant differences between fluticasone versus salmeterol (OR 1.05; 95% CI 0.92 to 1.18) and budesonide versus formoterol (OR 0.96; 95% CI 0.76 to 1.20). However, there was moderate heterogeneity among the studies comparing fluticasone and salmeterol (I^2 = 58%).

DISCUSSION

Summary of main results

This systematic review set out to investigate the relative effects of inhaled corticosteroids and long-acting beta$_2$-agonists on clinical endpoints in patients with stable COPD using direct comparisons from randomised trials. Seven randomised, active-control, double-blind trials involving 5997 participants were identified. The results of the review were dominated by the largest study, TORCH 2007, for many outcomes (exacerbations, pneumonia, mortality, health-related quality of life and withdrawals).

The review showed no statistically significant differences between ICS and LABA in the number of patients experiencing exacerbations or the number of exacerbation per patient year (rate ratio). This result was accompanied by narrow confidence intervals, which suggests that there may not be a big difference in exacerbation rates between ICS and LABA. Given the pharmacological differences between the drugs, it seems reasonable to conclude that they are exerting different benefits (albeit of seemingly equal clinical importance) and this endorses the assumption that exacerbations are complex in terms of their pathophysiology. Data on exacerbations leading to hospitalisation were only reported by TORCH 2007 and also showed no statistically significant difference between ICS and LABA. Exacerbation rates are often higher in patients who withdraw from a study before completion (Keene 2008) and this could suggest that the rates used in this review underestimate population exacerbation frequencies. However, this would only represent potential analytical bias in the presence of differential dropout rates, and this study has shown parity between ICS and LABA withdrawals.

The risk of pneumonia was significantly greater for patients on ICS than patients on LABA, whether classified as an adverse event (OR 1.38; 95% CI 1.10 to 1.73) or a serious adverse event (Peto OR 1.48; 95% CI 1.13 to 1.94). The increased incidence of pneumonia with ICS compared to LABA appears independent of study length. However, it should be noted that event rates were very low (3% or less) in all studies with the exception of TORCH 2007, the largest and longest of all the included studies.

Differences in mortality between ICS and LABA were not statistically significant (Peto OR 1.17; 95% CI 0.97 to 1.42). However, TORCH 2007 was the only study to record mortality status for all randomised participants, including withdrawals, and it recorded significantly more deaths on the ICS fluticasone compared to the LABA salmeterol (OR 1.23; 95% CI 1.01 to 1.50). It should be noted that very low event rates in the majority of studies may be due, in part, to follow-up limited to patients remaining in the study, and the study duration. Conversely, interpretation of mortality data is complicated by the tendency for patients who withdraw to then be given the other active study therapies, for example patients withdrawing from the LABA arm are prescribed ICS, though this is likely to reduce differences between groups rather than to enhance them.

Treatment with ICS led to a smaller improvement in lung function (pre-bronchodilator FEV_1) compared to LABA, although the difference was relatively small (MD -18.99 mL; 95% CI -37.46 to -0.52). Post-dose FEV1 was reported in two studies and gave very different results with high heterogeneity, and there were too many differences between the studies to be able to pool the outcome. The change in health-related quality of life was also significantly different between the treatment arms but with this outcome improvements were greater with ICS treatment than with LABA (SGRQ MD -0.74; 95% CI -1.42 to -0.06). However, the differences in health-related quality of life were small in comparison to the threshold for a clinically important difference (defined as a change of four units). Improvements in quality of life in favour of ICS may support the idea that the drug exerts its benefits not just in terms of alleviating or abrogating lung function impairment (noting that LABA also improves lung function). Given the possibility that COPD is a systemic disease, it may be that drug effects on airways inflammation have wider consequences, that is reductions in systemic consequences of airways inflammation.

There were no significant differences for hospitalisations due to exacerbations, mild exacerbations, peak expiratory flow, dyspnoea, symptoms scores, rescue medication, adverse events, all cause hospitalisations, and withdrawals from studies.

Overall completeness and applicability of evidence

- This review has provided evidence to suggest that differences in exacerbation rates between COPD patients treated with ICS and those treated with LABA are unlikely.

- High withdrawal rates compared to low mortality rates introduces considerable uncertainty in the analysis of mortality from the smaller, shorter studies. However, TORCH 2007, which was the only study with complete mortality data, reported higher mortality with ICS therapy compared to LABA therapy.

- The size and length of TORCH 2007 lends substantial weight to evidence for an increased risk of pneumonia with ICS treatment compared to LABA treatment. However, event rates across the remaining studies were low and the results should therefore be interpreted with caution.

- The indirect comparisons between the trials comparing budesonide with formoterol and fluticasone with salmeterol do not allow any conclusions to be drawn about the relative efficacy and safety of budesonide and fluticasone or formoterol and salmeterol.
- Data synthesis was limited by the lack of common data for several outcomes. The definition of change and impact differed substantially with studies using: a) different outcome measures, e.g. pre-bronchodilator or post-bronchodilator FEV1, b) different units of analysis, e.g. mL or % change from baseline, c) no exact measures of variability for differences between treatments, e.g. no CI, no exact P value.

Quality of the evidence

The included studies were generally of good quality, free from selective reporting of results, and all but one of the studies used intention-to-treat data analysis to control for the relatively high withdrawal rates, which are common in long (≥ six-month) COPD trials. However, because of the high number of withdrawals in the included studies, the results for the dichotomous outcomes with relatively few events (such as mortality, pneumonia and serious adverse events) are less reliable when the withdrawals have not been followed up, and must be interpreted with caution.

Potential biases in the review process

Several of the studies did not report on the statistical variance of the difference between the ICS and LABA arms as these were not the primary issues in those studies. We were able to calculate these variances from exact P values or confidence intervals (see Appendix 1). However, for some of the outcomes several studies only provided approximate P values (see Table 1) and as we were not able to obtain further information from the authors data for these outcomes could not be used in this review.

Table 1. Excluded data

	Calverley 2003	Hanania 2003	Mahler 2002	Szafranski 2003	Tashkin 2008	TRISTAN 2003
Exacerbations					X	
Pre-dose FEV_1		X	X			
Post-dose FEV_1	X	X	X			
PEF	X	X	X	X		X
Dyspnoea				X		
Symptom		X				
Rescue medication			X			

Agreements and disagreements with other studies or reviews

Several systematic reviews have tried to clarify the contribution of ICS and LABA to the benefits and risks of the combination inhalers in COPD. Treatment with ICS and LABA combination inhalers has been shown to significantly reduce exacerbation rates

in COPD patients compared to placebo (rate ratio 0.74; 95% CI 0.7 to 0.8) (Nannini 2007a). In comparison to placebo, combination therapy also significantly reduced all cause mortality (primarily based on TORCH 2007) (OR 0.79; 95% CI, 0.65 to 0.96); improved health-related quality of life, symptoms and lung function; but increased the risk of pneumonia (OR 1.83; 95% CI 1.51 to 2.21) (Nannini 2007a). Systematic reviews comparing ICS treatment with placebo have shown that ICS reduced the occurrence of exacerbations (risk ratio (RR) 0.82; 95% CI 0.73 to 0.92) (Agarwal 2010), slowed the decline in health-related quality of life (MD -1.22 units/year; 95% CI -1.83 to -0.60) and improved FEV_1 after two to six months of treatment (Yang 2007). Although long-term use of ICS (longer than six months) did not reduce the rate of decline in FEV_1 (MD 5.80 mL/year with ICS; 95% CI -0.28 to 11.88), it was not associated with a higher mortality rate compared to placebo (OR 0.98; 95% CI 0.83 to 1.16) (Yang 2007). Neither of these reviews looked at adverse events, including pneumonia. Compared to placebo, LABA treatment has also been shown to reduce exacerbations (RR 0.78; 95% CI 0.67 to 0.91) and improve health-related quality of life (MD -3.26; 95% CI -4.57 to -1.96) without a significant effect on mortality (RR 0.95; 95% CI 0.80 to 1.14) (Appleton 2006; Rodrigo 2008). The reviews of placebo-controlled studies have shown benefits for both monotherapies without an increased risk of mortality. Comparing the effects of combination inhaler to those of its components has shown that all cause mortality is lower with combined treatment than with ICS alone (OR 0.77; 95% CI 0.63 to 0.94) (Nannini 2007), whereas there was no significant difference in mortality between combined inhalers and LABA alone (RR 0.90; 95% CI 0.76 to 1.06) (Nannini 2007b; Rodrigo 2009). Quality of life and lung function favour combination treatment over both monotherapies (Nannini 2007; Nannini 2007b; Rodrigo 2009). Combination therapy also significantly reduced exacerbation rates compared to the individual monotherapies: ICS/LABA versus ICS (rate ratio 0.91; 95% CI 0.85 to 0.97) (Nannini 2007), ICS/LABA versus LABA (rate ratio 0.82; 95% CI 0.78 to 0.88) (Nannini 2007b). A recent review found that combination inhalers did not significantly decrease the number of severe exacerbations (RR 0.91; 95% CI 0.82 to 1.01) but did decrease the number of moderate exacerbations (RR 0.84; 95% CI 0.74 to 0.96) (Rodrigo 2009). No statistically significant difference in the odds of pneumonia has been shown between combination inhaler and ICS alone (OR 1.13; 95% CI 0.92 to 1.38) (Nannini 2007), whereas pneumonia occurs more commonly with combined inhalers than with LABA alone (OR 1.58; 95% CI 1.32 to 1.88 (Nannini 2007b); RR 1.63; 95% CI 1.35 to 1.98 (Rodrigo 2009)). A recent meta analysis including 24 randomised trials (16 fluticasone trials, seven budesonide trials and one mometasone trial) showed a significantly increased risk of pneumonia with ICS (RR 1.56; 95% CI 1.40 to 1.74; P = 0.0001) (Singh 2010). The elevated risk remained consistent irrespective of whether the ICS/LABA combination inhaler was compared to LABA or ICS to placebo (Singh 2010).

In summary:

- both ICS and LABA may contribute to a decrease in exacerbation rates but according to the results from this review there is not a large difference between them;
- although ICS therapy benefits COPD patients, it also increases the risk of pneumonia;
- the effect of ICS and LABA on mortality is more complicated. According to Yang 2007 and Rodrigo 2008 there is not enough evidence to say that ICS or LABA influences all cause mortality on its own. However, in combination they seem to cause a reduction in mortality both compared to placebo (Nannini 2007a) and to ICS alone (Nannini 2007) but not compared to LABA (Nannini 2007b; Rodrigo 2009). This review supports the view that there is insufficient evidence for the impact of LABA and ICS on mortality and the differential impact of ICS and LABA on mortality remains unclear. Our review showed no overall difference in mortality rates between the monotherapies but the study with the most reliable mortality data (TORCH 2007) showed lower rates for patients receiving LABA therapy;
- according to this review LABA therapy is associated with small improvements in FEV_1 compared to ICS, which is consistent with the results from the above reviews; and
- both ICS and LABA increase the patient's quality of life but ICS therapy is associated with slightly larger improvements.

AUTHORS' CONCLUSIONS

Implications for practice

The benefits of ICS therapy for COPD patients may be similar to those of LABA, but there is potentially an increased incidence of pneumonia. These data support both national and international guidelines stating that the choice of drugs should take into account the person's symptomatic response, the drug's potential to reduce exacerbations and side effects (GOLD 2010; NICE 2010).

Implications for research

Additional work is required in assessing the risks and benefits of budesonide/formoterol combination inhalers. Potential class effects between fluticasone and budesonide are still unknown as are the influence of high and low doses on benefits and risks for both drugs. The lack of key standardised outcomes is an impediment to the synthesis of trial data for systematic reviews. We strongly recommend international consensus on the identification and definition of key common outcomes, for example change from baseline in pre-bronchodilator FEV_1 (mL), change from baseline in health-related quality of life, and complete mortality data for all randomised participants including study withdrawals.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Calverley 2003

Methods	**Design:** a multi-centre, randomised, double-blind, parallel-group, placebo-controlled study. Trial duration was 2 week run-in period followed by 52 weeks treatment. The trial included 109 centres in 15 countries
Participants	**Participants:** 512 patients were randomised (budesonide 257; formoterol 255) **Baseline characteristics:** mean age 64 years; 74% male; mean FEV_1 1.0 L; mean FEV_1 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; $FEV_1/FVC \leq 70\%$ pre-bronchodilator; $FEV_1 \leq 50\%$ predicted; use of short acting $beta_2$-agonists as reliever medication; ≥ 1 COPD exacerbation requiring oral corticosteroids/antibiotics 2 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 4 weeks of run-in/during run-in phase; non-allowed medications: oxygen therapy; ICS (aside from study medication), disodium cromoglycate, leukotriene-antagonists, 5-lipoxygenase inhibitors, bronchodilators (other than study medication and terbutaline 0.5 mg as needed), antihistamines, medication containing ephedrine, β-blocking agents
Interventions	**Run-in:** all participants received 30 mg oral prednisolone twice daily and 2 x 4.5 mg formoterol twice daily (2 weeks) **1.** budesonide 800 µg per day: 2 x 200 µg twice daily **2.** formoterol 18 µg per day: 2 x 4.5 µg twice daily Inhaler device: Turbuhaler **Co-treatment:** terbutaline 0.5 mg as needed, courses of oral corticosteroids (maximum 3 weeks per course) and antibiotics in the event of exacerbations, parenteral steroids and/or nebulised treatment (single injections/inhalations) at emergency visits The following medications were disallowed from recruitment: inhaled steroids (except the study medication), disodium cromoglycate, leukotriene antagonists or 5-lipoxygenase (5-LO) inhibitors, bronchodilators (other than study medication and terbutaline 0.5 mg as needed), antihistamines, any medication containing ephedrine, and β-blockers, including eye-drops. The following medications were withheld prior to recruitment: short-acting inhaled or oral β_2-agonists (6 h before), inhaled or oral long-acting β_2-agonists (48 h), inhaled short-acting anticholinergics (8 h), inhaled long-acting anticholinergics (7 days), xanthine-containing derivatives (48 h), xanthine-containing derivatives (24 h), leukotriene antagonists or 5-LO inhibitors (48 h)
Outcomes	Number of exacerbations; time to first exacerbation; time to and number of oral corticosteroid-treated episodes; change in post-dose FEV_1; slow VC; morning and evening PEF; quality of life (SGRQ), symptoms, use of reliever medication, adverse events

Calverley 2003 (*Continued*)

Notes	P values used to calculate pooled SEMs for the following outcomes: Health-related quality of life; FEV_1; rescue medication Exacerbations defined as requiring medical intervention (oral antibiotics and/or corticosteroids or hospitalisation)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	The withdrawal rates were 40% in the inhaled corticosteroid (budesonide) group and 44% in the long-acting $beta_2$-agonist (formoterol) group. However an intention-to-treat analysis was used
Selective reporting (reporting bias)	Low risk	All collected data reported

Hanania 2003

Methods	**Design:** a multi-centre, randomised, double-blind, placebo-controlled, parallel-group study from November 1998 to August 2000. Trial duration was 2 week run-in period followed by 24 weeks treatment. The trial included 76 hospitals in the USA. Randomization was stratified by reversibility and investigative site
Participants	**Participants:** 360 patients were randomised (salmeterol 177; fluticasone 183) **Baseline characteristics:** mean age 64 years; 62% male; mean FEV_1 1.3 L; mean FEV_1 predicted 42%; mean reversibility (FEV_1% predicted) was 8.8% increase in non-reversible patients **Inclusion criteria:** stable COPD, FEV_1 40 to 65% predicted, FEV_1/FVC < 70% predicted, symptoms of chronic bronchitis and moderate dyspnoea **Exclusion criteria:** current diagnosis of asthma, use of oral steroids in past 6 weeks, abnormal ECG, long-term oxygen therapy, moderate - severe exacerbation in run-in, other significant medical disorder
Interventions	**Run-in:** 2 weeks treatment with placebo inhaler and short acting $beta_2$-agonist as needed **1.** salmeterol 100 µg per day: 50 µg twice daily **2.** fluticasone propionate 500 µg per day: 250 µg twice daily Inhaler device: Diskus **Co-treatment:** Patients were given as-needed albuterol

Hanania 2003 (*Continued*)

Outcomes	Exacerbations; change in pre-dose and 2 h post-dose FEV_1 from baseline to end of study. PEF data not stratified by reversibility; morning PEF; Quality of life: (CRDQ, CBSQ not stratified by reversibility); dyspnoea (BDI, TDI); symptoms; use of reliever medication (salbutamol); adverse events
Notes	Reversibility was defined as a $\geq$ 12% and 200 mL increase in FEV_1 from baseline following the administration of 400 µg albuterol. Change in FEV_1: mean group SE estimated from reversibility stratified SEs, then used to calculate SD Exacerbations were defined by treatment: moderate exacerbations requiring treatment with antibiotics and/or corticosteroids, and severe exacerbations requiring hospitalisation

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	In order to account for patient withdrawals, endpoint was used as the primary time point and was defined as the last on-treatment post-baseline assessment excluding any data from the discontinuation visit.
Selective reporting (reporting bias)	Low risk	All collected data reported

Mahler 2002

Methods	**Design:** a randomised, double-blind, placebo-controlled, parallel-group study. Trial duration was 2 week run-in period followed by 24 weeks treatment. The trial included 65 centres in the USA. Randomisation was stratified by reversibility and investigative site
Participants	**Participants:** 328 patients were randomised (salmeterol 160; fluticasone 168) **Baseline characteristics:** mean age 63 years; 63% male; mean predose FEV_1 1.2 L; mean FEV_1 predicted 40% **Inclusion criteria:** participants with COPD according to ATS guidelines. Baseline pre-bronchodilation FEV_1 < 65% predicted and > 0.70 L. Baseline pre-bronchodilation $FEV_1/FVC \leq$ 70% predicted. Age > 40, 20 pack-year history smoking, day or night symptoms present on 4 out of last 7 days during run-in period **Exclusion criteria:** history of asthma, corticosteroid use in last 6 weeks, abnormal ECG,

Mahler 2002 (*Continued*)

	oxygen therapy, moderate or severe exacerbation during run-in, significant concurrent disease
Interventions	**Run-in:** 2 weeks treatment with placebo inhaler and SABA as needed **1.** salmeterol 100 μg per day: 50 μg twice daily **2.** fluticasone propionate 1000 μg per day: 500 μg twice daily Inhaler device: Diskus **Co-treatment:** Patients were given as-needed albuterol
Outcomes	Exacerbations, change in FEV_1 from baseline to end of study; morning PEF; quality of life (CRDQ, CBSQ not stratified by reversibility); dyspnoea (BDI, TDI); symptoms; use of reliever medication (salbutamol); adverse events
Notes	Reversibility defined as an increase of 12% and 200 mL in FEV_1 following albuterol 400 μg Change in FEV_1: mean group SE estimated from reversibility stratified SEs, then used to calculate SD

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Endpoint analysis for both predose and post-dose FEV_1 was performed to ensure that the patients prematurely withdrawing from the trial did not impact the robustness of the FEV_1 results. The endpoint was defined as the last on-treatment post-baseline assessment excluding any data from the discontinuation visit. The appropriateness of this analysis was supported by evaluating the data using alternative methods of handling dropouts, including multiple imputation, analysis of only completers, and recursive regression imputation
Selective reporting (reporting bias)	Low risk	All collected data reported

Szafranski 2003

Methods	**Design:** a multi-centre, randomised, double-blind, placebo-controlled, parallel-group study. Trial duration was 2 week run-in period and 52 weeks treatment. The trial included 89 centres in 11 countries from Central & South America, Europe and South Africa
Participants	**Participants:** 399 patients were randomised (formoterol 201; budesonide 198). **Baseline characteristics:** mean age 64 years; 78% male; mean predose FEV_1 1.0 L; mean FEV_1 predicted 36%, mean reversibility 6% predicted normal **Inclusion criteria:** age $\geq$ 40 years; COPD for $\geq$ 2 years; smoking history $\geq$ 10 pack years; $FEV_1 \leq 50\%$ predicted; $FEV_1/FVC \leq 70\%$; Symptom score $\geq$ 2 during at least 7 days of run-in; use of bronchodilators for reliever medication; $\geq$ 1 severe COPD exacerbation within 2-12 months before study entry **Exclusion criteria:** history of asthma/rhinitis before age of 40; using beta-blockers; current respiratory tract disease other than COPD
Interventions	**Run-in:** 2 weeks. Treatment as-needed with short-acting bronchodilators only **1.** budesonide 800 µg per day: 2 x 200 µg twice daily **2.** formoterol 18 µg per day: 2 x 4.5 µg twice daily Inhaler device: Turbuhaler **Co-treatment:** Only study medication was allowed during the treatment period and terbutaline 0.5 mg when needed as reliever medication
Outcomes	Number of mild and severe exacerbations; change in post-dose FEV_1 as % from baseline; dyspnoea (MMRC); symptoms; morning and evening PEF; quality of life (SGRQ); use of reliever medication; adverse events
Notes	Classified as 'poorly reversible' subgroup Severe exacerbation defined as requirement of oral steroids and/or antibiotics and/or hospitalisation for respiratory symptoms. Mild exacerbation defined as requirement of $\geq$ 4 inhalations per day P values used to calculate pooled 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 at AstraZeneca, Lund, Sweden. At each centre, eligible patients received an enrolment code and then after run-in, participants were allocated the next consecutive patient number
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	All the Turbuhaler inhalers were identical to ensure that the patient, pharmacist and the investigator were blinded to the allo-

Szafranski 2003 (*Continued*)

		cated treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	The withdrawal rates were relatively large but even between the inhaled corticosteroid (budesonide) group (31%) and the long-acting beta$_2$-agonist (formoterol) group (32%). An intention-to-treat analysis was used
Selective reporting (reporting bias)	Low risk	All collected data reported

Tashkin 2008

Methods	**Design:** a multi-centre, randomised, double-blind, double-dummy, placebo-controlled, parallel-group study. Trial duration was 2 week run-in, 6 months treatment, and telephone follow-up 4 weeks after the last study visit. The trial included 194 centres in 5 countries (42% US)
Participants	**Participants:** 559 patients were randomised (budesonide 275; formoterol 284) **Baseline characteristics:** mean age 63 years; 67% male; mean predose FEV_1 1.03 L; mean predose FEV_1 predicted 40% **Inclusion criteria:** Current or ex-smokers aged $\geq$ 40 years; clinical diagnosis of COPD with symptoms for > 2 years; $\geq$ 1 COPD exacerbation requiring oral corticosteroids/ antibiotics 1 to 12 months before first clinic visit; use of SABAs as reliever medication; predose $FEV_1 \leq 50\%$ predicted; predose $FEV_1/FVC \leq 70\%$; smoking history $\geq$ 10 pack years; dyspnoea scale (MMRC) $\geq$ 2; breathlessness, cough and sputum scale (BCSS) score $\geq$ 2 per day for at least half of the 2-week run-in period **Exclusion criteria:** history of asthma/rhinitis before 40 years of age; significant/unstable cardiovascular disorder; clinically significant respiratory tract disorder other than COPD; homozygous α-1 antitrypsin deficiency; if the patient needed additions or alterations to their usual COPD maintenance therapy or an increment in rescue therapy due to worsening symptoms within 30 days before screening or during the run-in; oral or ophthalmic non-cardioselective beta-adrenoceptor antagonists, oral corticosteroids, pregnancy and breast-feeding
Interventions	**Run-in:** 2 weeks. Patients continued ICS mono-therapy if they had previously been receiving ICS alone or in combination with a LABA, and patients who had previously been receiving anticholinergic therapies were placed on stable doses of ipratropium bromide. A short-acting beta$_2$-adrenoceptor agonist was allowed for rescue use **1.** budesonide 640 µg per day: 2 x 160 µg twice daily (Turbuhaler) **2.** formoterol 18 µg per day: 2 x 4.5 µg twice daily (pMDI) **Co-treatment:** Allowed: Ephedrine-free (or other bronchodilator-free) antitussives and mucolytics, nasal corticosteroids, stable-dose non-nebulized ipratropium bromide, oral or ophthalmic cardioselective beta-adrenoceptor antagonists, study-provided salbutamol (albuterol) as rescue medication, medications allowed for exacerbations after randomisation: oral and parenteral corticosteroids (not depot formulations), acute use of xanthines, increased use of inhaled beta-adrenoceptor agonists and ipratropium bromide, and nebulized beta-adrenoceptor agonists and ipratropium bromide

	Disallowed: Long-acting anticholinergics, inhaled LABAs (other than study medication) , inhaled SABAs (other than salbutamol [albuterol] for rescue), oral beta-adrenoceptor agonists, ephedrine-containing medication, leukotriene receptor antagonists and 5-lipoxygenase inhibitors, xanthine-containing derivatives (except in short-term treatment of exacerbations), disodium cromoglygates, non-cardioselective beta-adrenoceptor antagonists, ICSs (other than study medication)
Outcomes	Pre- and post-dose FEV_1; inspiratory capacity; FVC; morning and evening PEF; dyspnoea (BCSS); quality of life (SGRQ); exacerbations; use of reliever medication (beta-agonist); symptoms; adverse events
Notes	Exacerbations were defined as respiratory symptoms requiring treatment with a course of oral steroids and/or hospitalisation

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Eligible patients were randomised in balanced blocks according to a computer-generated randomisation scheme at each site
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	To maintain blinding, patients received both a pressurized metered-dose inhaler (pMDI) and a dry powder inhaler (DPI) containing either active treatment or placebo, or combinations of active treatment and placebo, as appropriate
Incomplete outcome data (attrition bias) All outcomes	Low risk	The withdrawal rates were 23% in the inhaled corticosteroid (budesonide) group and 22% in the long- acting $beta_2$-agonist (formoterol) group. However the efficacy analysis set (i.e. intention-to-treat population) included all randomised patients who received at least one dose of study medication and contributed sufficient data for at least one co-primary or secondary efficacy endpoint during the randomised treatment period
Selective reporting (reporting bias)	Low risk	All collected data reported

TORCH 2007

Methods	**Design:** a multi-centre, randomised, double-blind, placebo-controlled, parallel-group study. Trial duration was 2 week run-in period and 156 weeks treatment. The trial included 444 centres in 42 countries in North America, Central America and Asia Pacific
Participants	**Participants:** 3093 patients were randomised (salmeterol: 1542; fluticasone 1551) **Baseline characteristics:** mean age 65 years; 76% male; mean FEV_1 predicted 44%, mean predose FEV_1 1.1 L, mean SGRQ score 50 **Inclusion criteria:** male/female 40-80 years of age; diagnosis of COPD (ERS); < 10% reversibility of predicted FEV_1; FEV1/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/lung transplant; requirement for > 12 h/day long term oxygen therapy; long term oral corticosteroid therapy; serious uncontrolled disease likely to interfere with medication/cause death in next three years
Interventions	**Run-in:** 2 weeks. All maintenance treatment with ICS and LABA ceased, but patients could continue other medications for COPD **1.** salmeterol 100 µg per day: 50 µg twice daily **2.** fluticasone 1000 µg per day: 500 µg twice daily Inhaler device: DPI (Diskus) **Co-treatment:** Patients could continue medications for COPD other than corticosteroids and inhaled long-acting bronchodilators
Outcomes	All cause mortality; frequency of exacerbations; health status (SGRQ); change in post-dose FEV_1 from baseline to end of study; adverse events
Notes	Exacerbation defined as symptomatic deterioration requiring treatment with antibiotics, systematic corticosteroids, hospitalisation or a combination of these

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Eligible patients were randomly assigned to study treatment in accordance with the randomisation schedule, which was generated using the GW computer program Patient Allocation for Clinical Trials (PACT). Patients were randomised in permuted blocks with stratification according to country and smoking status.
Allocation concealment (selection bias)	Low risk	Medication was allocated by the use of three numbers as follows. • Each subject who was screened was allocated a subject number. This number was unique to each subject and was assigned from a list provided to the site, in chrono-

		logical order. • Each subject who satisfied the randomisation criteria was assigned a unique treatment number from the Interactive Voice Response (IVR) system which is part of the System for Central Allocation of Drug (SCAD). Once a treatment number had been assigned to a subject, it could not be assigned to any other subject. Neither the subject nor the investigator knew to which treatment arm a subject had been allocated. • At each treatment visit the subject was provided with a treatment pack. Every pack number was unique and corresponded to the study medication pack which was dispensed to the subject at the visit A specialist IVR system company, ClinPhone, managed this system. At the randomisation visit (Visit 2) the principal investigator or designee contacted the IVR system through an automated 24-hour telephone number; upon providing their unique personal identification number (PIN) and answering a series of questions, the site was provided with the subject's treatment number as well as a pack number
Blinding (performance bias and detection bias) All outcomes	Low risk	Neither the subject nor the investigator knew to which treatment arm a subject had been allocated. At each treatment visit each subject was issued with a treatment pack containing DISKUS/ACCUHALER inhalers. The inhalers contained either of the four treatments (salmeterol/fluticasone propionate combination product, fluticasone propionate, salmeterol, or placebo) in accordance with the randomisation schedule. The inhalers were labelled in accordance with all applicable regulatory requirements. Each treatment pack and study treatment inhaler was labelled with the protocol number, storage and dosing instructions by GW Research and Development
Incomplete outcome data (attrition bias) All outcomes	Low risk	For patients who withdrew from the study prematurely, all data on exacerbations, health status, and lung function available at the time of a patient's withdrawal from

TORCH 2007 (*Continued*)

		the study were included in the analysis. All efficacy analyses were performed according to the intention-to-treat principle
Selective reporting (reporting bias)	Low risk	All collected data reported

TRISTAN 2003

Methods	**Design:** a multi-centre, randomised, double-blind, placebo-controlled, parallel-group study. Trial duration was 2 week run-in period, 52 weeks treatment, and 2-week follow-up. The trial included 196 centres in 25 countries
Participants	**Participants:** 746 patients were randomised (salmeterol: 372; fluticasone 374) **Baseline characteristics:** mean age 63 years; 70% male; mean reversibility (FEV_1% predicted) 3.7%; mean FEV_1 predicted 45%, mean predose FEV_1 1.25 L, mean SGRQ score 49 **Inclusion criteria:** male/female; poor reversibility < 10% increase of predicted FEV_1 30 minutes after inhaling 400 µg salbutamol; FEV_1/FVC ratio <70%; baseline FEV_1 25 - 75% predicted; ≥10 pack year smoking history, chronic bronchitis; history of exacerbations (at least 1 in the last year) requiring oral corticosteroids and/or antibiotics. At least one episode of acute COPD per year in the previous 3 years **Exclusion criteria:** respiratory disorders other than COPD, oxygen treatment, systemic corticosteroids, high doses of inhaled corticosteroids (> 1000 µg daily beclomethasone dipropionate, budesonide or flunisolide or > 500 µg daily fluticasone) or antibiotics in the four weeks before the 2 week run-in period
Interventions	**Run-in:** 2 weeks. All maintenance treatment with ICS and LABA ceased **1.** salmeterol 100 µg per day: 50 µg twice daily **2.** fluticasone propionate 1000 µg per day: 500 µg twice daily Inhaler device: DPI (Diskus) **Co-treatment:** Inhaled salbutamol was used as relief medication throughout the study, and regular treatment with anticholinergics, mucolytics, and theophylline was allowed. All non-COPD medications could be continued if the dose remained constant whenever possible, and if their use would not be expected to affect lung function
Outcomes	Change in pre- and post-dose FEV_1 from baseline to end of study; use of reliever medication (salbutamol); symptom scores; exacerbation rate; quality of life (SGRQ); FVC; adverse events
Notes	Exacerbations were defined a priori as a worsening of COPD symptoms that required treatment with antibiotics, oral corticosteroids, or both

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A randomisation schedule generated by the patient allocation for clinical trials (PACT)

TRISTAN 2003 (*Continued*)

		program was used to assign patients to study treatment groups. Every participating centre was supplied with a list of patient numbers (assigned to patients at their first visit) and a list of treatment numbers. Patients who satisfied the eligibility criteria were assigned the next sequential treatment number from the list
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Study drugs were labelled in a way to ensure that both the patient and the investigator were unaware of the allocated treatment. Salmeterol and fluticasone combination (50/500 µg twice daily), salmeterol (50 µg twice daily), fluticasone (500 µg twice daily) and placebo were packaged in identical inhaler devices
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The withdrawal rates were even between the inhaled corticosteroid (budesonide) group (29%) and the long-acting beta$_2$-agonist (formoterol) group (32%) and the % of patients lost to follow-up were only 2.1% and 2.2% for the two groups respectively. However, it was unclear if patients discontinuing the allocated study treatment were analysed according to an intention-to-treat principle
Selective reporting (reporting bias)	Low risk	All collected data reported

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

Study	Reason for exclusion
Barnes 2005	No ICS and LABA monocomponents
Cazzola 2003	No ICS and LABA monocomponents
Della Cioppa 2001	No ICS and LABA monocomponents
Gosman 2006	No ICS and LABA monocomponents
Jiang 2009	No ICS and LABA monocomponents

(*Continued*)

Lyseng-Williamson 2002	Review article
Mittmann 2010	No ICS and LABA monocomponents
Nungtjik 2009	No ICS and LABA monocomponents
Reynolds 2004	Review article
Tzani 2010	No ICS and LABA monocomponents
Worth 2009	No ICS monocomponent

DATA AND ANALYSES

Comparison 1. Inhaled corticosteroids (ICS) versus long-acting beta$_2$-agonists (LABA) by ICS and LABA

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Exacerbation rate ratios	4	4750	Risk Ratio (Fixed, 95% CI)	0.96 [0.89, 1.02]
1.1 Fluticasone versus Salmeterol	2	3839	Risk Ratio (Fixed, 95% CI)	0.97 [0.91, 1.05]
1.2 Budesonide versus Formoterol	2	911	Risk Ratio (Fixed, 95% CI)	0.86 [0.73, 1.03]
2 Exacerbations	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Fluticasone versus Salmeterol	2	688	Odds Ratio (M-H, Fixed, 95% CI)	1.22 [0.89, 1.67]
3 Hospitalisations due to exacerbations	1		Risk Ratio (Fixed, 95% CI)	Totals not selected
3.1 Fluticasone versus Salmeterol	1		Risk Ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Pneumonia adverse event	3	4164	Odds Ratio (M-H, Fixed, 95% CI)	1.38 [1.10, 1.73]
4.1 Fluticasone versus Salmeterol	1	3093	Odds Ratio (M-H, Fixed, 95% CI)	1.43 [1.13, 1.81]
4.2 Budesonide versus Formoterol	2	1071	Odds Ratio (M-H, Fixed, 95% CI)	0.84 [0.36, 1.96]
5 Pneumonia serious adverse event	5	5086	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.48 [1.13, 1.94]
5.1 Fluticasone versus Salmeterol	4	4527	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.46 [1.12, 1.92]
5.2 Budesonide versus Formoterol	1	559	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.82 [0.40, 20.16]
6 Pre-dose FEV1	4	1993	Mean Difference (Fixed, 95% CI)	-18.99 [-37.46, -0.52]
6.1 Fluticasone versus Salmeterol	3	1434	Mean Difference (Fixed, 95% CI)	-10.88 [-32.62, 10.87]
6.2 Budesonide versus Formoterol	1	559	Mean Difference (Fixed, 95% CI)	-40.0 [-73.00, -5.00]
7 Post-dose FEV1	2		Mean Difference (Fixed, 95% CI)	Totals not selected
7.1 Fluticasone versus Salmeterol	1		Mean Difference (Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 Budesonide versus Formoterol	1		Mean Difference (Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Mild exacerbations	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Fluticasone versus Salmeterol	2	688	Odds Ratio (M-H, Fixed, 95% CI)	1.51 [0.74, 3.08]
9 Mortality	7	5997	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.17 [0.97, 1.42]
9.1 Fluticasone versus Salmeterol	4	4527	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.23 [1.01, 1.51]
9.2 Budesonide versus Formoterol	3	1470	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.62 [0.31, 1.22]

10 Health-related quality of life SGRQ	3	4398	Mean Difference (Fixed, 95% CI)	-0.74 [-1.42, -0.06]
10.1 Fluticasone versus Salmeterol	2	3839	Mean Difference (Fixed, 95% CI)	-0.77 [-1.49, -0.04]
10.2 Budesonide versus Formoterol	1	559	Mean Difference (Fixed, 95% CI)	-0.51 [-2.63, 1.61]
11 Dyspnoea symptom score 0-4	3	1817	Mean Difference (Fixed, 95% CI)	0.03 [-0.02, 0.08]
11.1 Fluticasone versus Salmeterol	1	746	Mean Difference (Fixed, 95% CI)	-0.01 [-0.08, 0.06]
11.2 Budesonide versus Formoterol	2	1071	Mean Difference (Fixed, 95% CI)	0.07 [-0.00, 0.14]
12 Dyspnoea TDI	2		Mean Difference (Fixed, 95% CI)	Subtotals only
12.1 Fluticasone versus Salmeterol	2	688	Mean Difference (Fixed, 95% CI)	0.26 [-0.21, 0.74]
13 Symptoms	3	1470	Mean Difference (Random, 95% CI)	0.22 [-0.03, 0.47]
13.1 Budesonide versus Formoterol	3	1470	Mean Difference (Random, 95% CI)	0.22 [-0.03, 0.47]
14 Adverse events	5	5089	Odds Ratio (M-H, Fixed, 95% CI)	1.12 [0.96, 1.30]
14.1 Fluticasone versus Salmeterol	4	4530	Odds Ratio (M-H, Fixed, 95% CI)	1.14 [0.96, 1.35]
14.2 Budesonide versus Formoterol	1	559	Odds Ratio (M-H, Fixed, 95% CI)	1.03 [0.74, 1.44]
15 Serious adverse events (non-fatal)	6		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
15.1 Budesonide versus Formoterol number of SAEs	3	1470	Odds Ratio (M-H, Random, 95% CI)	1.01 [0.77, 1.31]
15.2 Fluticasone versus Salmeterol number of patients with 1 or more SAEs	3	1436	Odds Ratio (M-H, Random, 95% CI)	1.17 [0.60, 2.28]
16 Withdrawals	7	5961	Odds Ratio (M-H, Fixed, 95% CI)	1.02 [0.92, 1.14]
16.1 Fluticasone versus Salmeterol	4	4491	Odds Ratio (M-H, Fixed, 95% CI)	1.05 [0.92, 1.18]
16.2 Budesonide versus Formoterol	3	1470	Odds Ratio (M-H, Fixed, 95% CI)	0.96 [0.76, 1.20]

Comparison 2. Inhaled corticosteroids versus long-acting beta$_2$-agonists by length of study

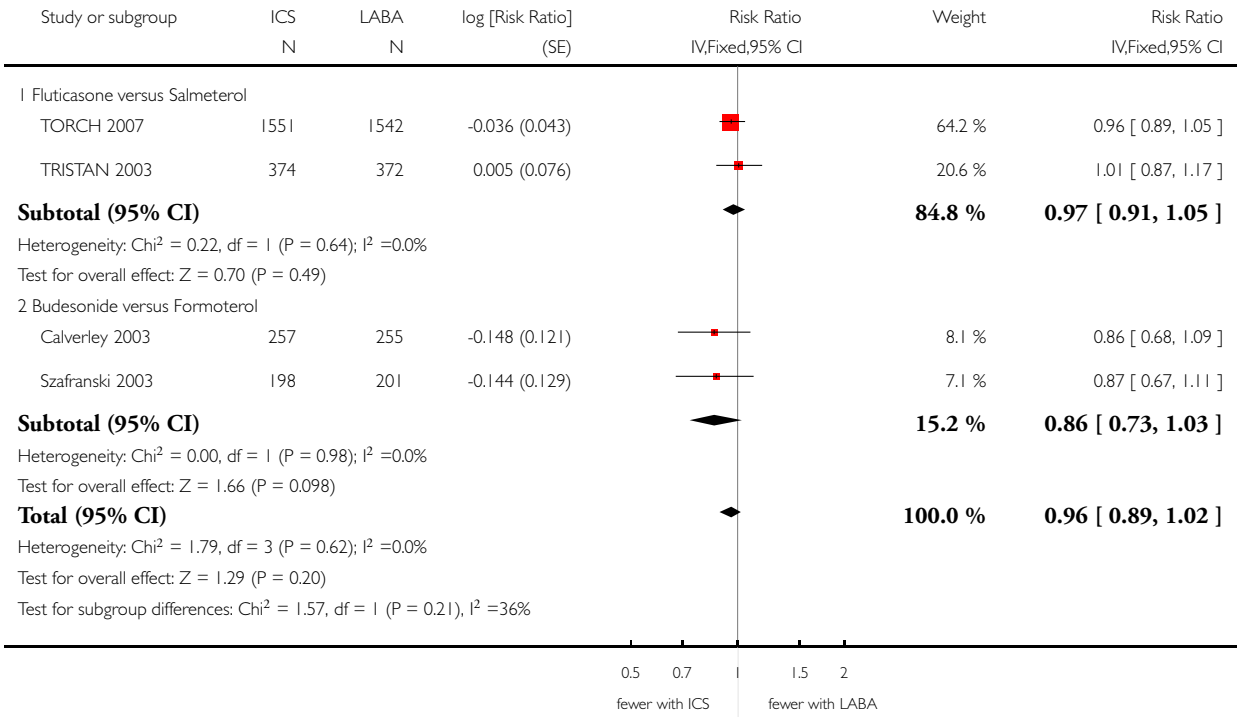
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Exacerbation rate ratios	4	4750	Risk Ratio (Fixed, 95% CI)	0.96 [0.89, 1.02]
1.1 up to 1 year	3	1657	Risk Ratio (Fixed, 95% CI)	0.94 [0.84, 1.05]
1.2 longer than 1 year	1	3093	Risk Ratio (Fixed, 95% CI)	0.96 [0.89, 1.05]
2 Pneumonia serious adverse event	6	5560	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.42 [1.10, 1.85]
2.1 up to 1 year	5	2505	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.11 [0.58, 2.10]
2.2 longer than 1 year	1	3055	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.50 [1.12, 1.99]

Analysis 1.1. Comparison 1 Inhaled corticosteroids (ICS) versus long-acting beta$_2$-agonists (LABA) by ICS and LABA, Outcome 1 Exacerbation rate ratios.

Review: Inhaled corticosteroids versus long-acting beta$_2$-agonists for chronic obstructive pulmonary disease

Comparison: 1 Inhaled corticosteroids (ICS) versus long-acting beta$_2$-agonists (LABA) by ICS and LABA

Outcome: 1 Exacerbation rate ratios



Analysis 1.2. Comparison 1 Inhaled corticosteroids (ICS) versus long-acting beta$_2$-agonists (LABA) by ICS and LABA, Outcome 2 Exacerbations.

Review: Inhaled corticosteroids versus long-acting beta$_2$-agonists for chronic obstructive pulmonary disease

Comparison: 1 Inhaled corticosteroids (ICS) versus long-acting beta$_2$-agonists (LABA) by ICS and LABA

Outcome: 2 Exacerbations

Study or subgroup	ICS n/N	LABA n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Fluticasone versus Salmeterol					
Hanania 2003	69/183	55/177		48.5 %	1.34 [0.87, 2.08]
Mahler 2002	67/168	60/160		51.5 %	1.11 [0.71, 1.72]

Analysis 1.3. Comparison 1 Inhaled corticosteroids (ICS) versus long-acting beta$_2$-agonists (LABA) by ICS and LABA, Outcome 3 Hospitalisations due to exacerbations.

Review: Inhaled corticosteroids versus long-acting beta$_2$-agonists for chronic obstructive pulmonary disease

Comparison: 1 Inhaled corticosteroids (ICS) versus long-acting beta$_2$-agonists (LABA) by ICS and LABA

Outcome: 3 Hospitalisations due to exacerbations

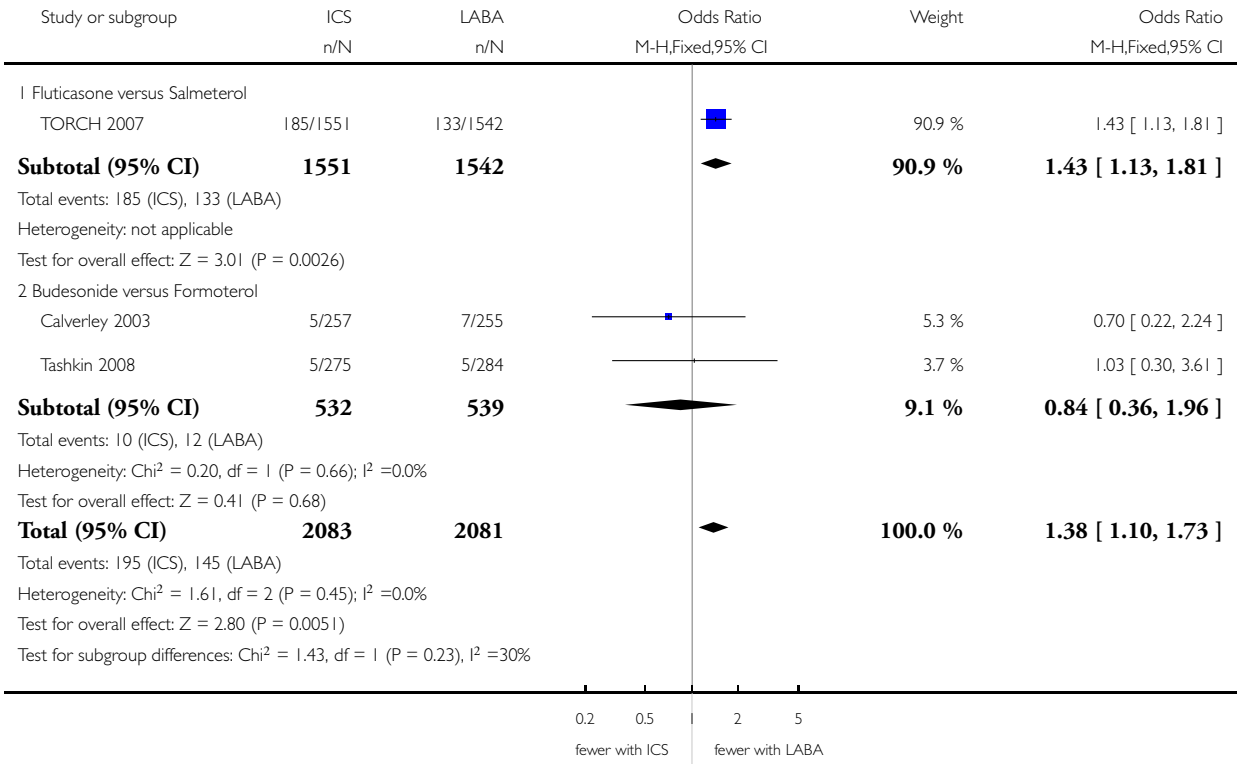
Study or subgroup	ICS N	LABA N	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
1 Fluticasone versus Salmeterol					
TORCH 2007	1534	1542	0.070618 (0.082914)		1.07 [0.91, 1.26]

Analysis 1.4. Comparison 1 Inhaled corticosteroids (ICS) versus long-acting beta$_2$-agonists (LABA) by ICS and LABA, Outcome 4 Pneumonia adverse event.

Review: Inhaled corticosteroids versus long-acting beta$_2$-agonists for chronic obstructive pulmonary disease

Comparison: 1 Inhaled corticosteroids (ICS) versus long-acting beta$_2$-agonists (LABA) by ICS and LABA

Outcome: 4 Pneumonia adverse event



Analysis 1.5. Comparison 1 Inhaled corticosteroids (ICS) versus long-acting beta$_2$-agonists (LABA) by ICS and LABA, Outcome 5 Pneumonia serious adverse event.

Review: Inhaled corticosteroids versus long-acting beta$_2$-agonists for chronic obstructive pulmonary disease

Comparison: 1 Inhaled corticosteroids (ICS) versus long-acting beta$_2$-agonists (LABA) by ICS and LABA

Outcome: 5 Pneumonia serious adverse event

Study or subgroup	ICS n/N	LABA n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Fluticasone versus Salmeterol					
Hanania 2003	1/183	1/177		0.9 %	0.97 [0.06, 15.53]
Mahler 2002	2/168	0/160		0.9 %	7.09 [0.44, 113.89]
TORCH 2007	121/1551	82/1542		88.1 %	1.50 [1.13, 1.99]
TRISTAN 2003	9/374	9/372		8.2 %	0.99 [0.39, 2.53]
Subtotal (95% CI)	**2276**	**2251**		**98.2 %**	**1.46 [1.12, 1.92]**
Total events: 133 (ICS), 92 (LABA)					
Heterogeneity: Chi^2 = 2.01, df = 3 (P = 0.57); I^2 =0.0%					
Test for overall effect: Z = 2.77 (P = 0.0056)					
2 Budesonide versus Formoterol					
Tashkin 2008	3/275	1/284		1.8 %	2.82 [0.40, 20.16]
Subtotal (95% CI)	**275**	**284**		**1.8 %**	**2.82 [0.40, 20.16]**
Total events: 3 (ICS), 1 (LABA)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.04 (P = 0.30)					
Total (95% CI)	**2551**	**2535**		**100.0 %**	**1.48 [1.13, 1.94]**
Total events: 136 (ICS), 93 (LABA)					
Heterogeneity: Chi^2 = 2.43, df = 4 (P = 0.66); I^2 =0.0%					
Test for overall effect: Z = 2.89 (P = 0.0039)					
Test for subgroup differences: Chi^2 = 0.42, df = 1 (P = 0.52), I^2 =0.0%					

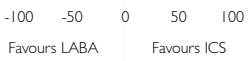
Analysis 1.6. Comparison 1 Inhaled corticosteroids (ICS) versus long-acting beta$_2$-agonists (LABA) by ICS and LABA, Outcome 6 Pre-dose FEV1.

Review: Inhaled corticosteroids versus long-acting beta$_2$-agonists for chronic obstructive pulmonary disease

Comparison: 1 Inhaled corticosteroids (ICS) versus long-acting beta$_2$-agonists (LABA) by ICS and LABA

Outcome: 6 Pre-dose FEV1

Study or subgroup	ICS N	LABA N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Fluticasone versus Salmeterol						
TRISTAN 2003	374	372	-22 (13.771)		46.8 %	-22.00 [-48.99, 4.99]
Mahler 2002	168	160	2 (26)		13.1 %	2.00 [-48.96, 52.96]
Hanania 2003	183	177	18 (27)		12.2 %	18.00 [-34.92, 70.92]
Subtotal (95% CI)					**72.1 %**	**-10.88 [-32.62, 10.87]**
Heterogeneity: Chi^2 = 2.04, df = 2 (P = 0.36); I^2 =2%						
Test for overall effect: Z = 0.98 (P = 0.33)						
2 Budesonide versus Formoterol						
Tashkin 2008	275	284	-40 (17.857)		27.9 %	-40.00 [-75.00, -5.00]
Subtotal (95% CI)					**27.9 %**	**-40.00 [-75.00, -5.00]**
Heterogeneity: not applicable						
Test for overall effect: Z = 2.24 (P = 0.025)						
Total (95% CI)					**100.0 %**	**-18.99 [-37.46, -0.52]**
Heterogeneity: Chi^2 = 3.96, df = 3 (P = 0.27); I^2 =24%						
Test for overall effect: Z = 2.01 (P = 0.044)						
Test for subgroup differences: Chi^2 = 1.92, df = 1 (P = 0.17), I^2 =48%						

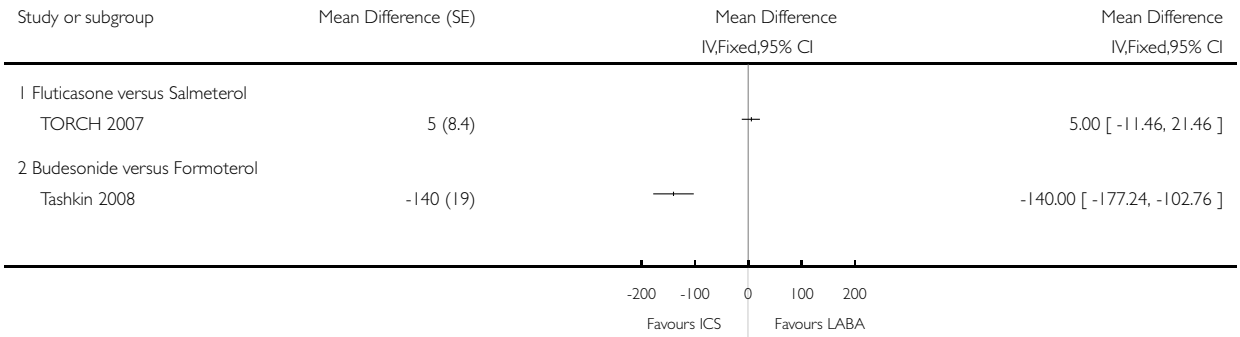


Analysis 1.7. Comparison 1 Inhaled corticosteroids (ICS) versus long-acting beta$_2$-agonists (LABA) by ICS and LABA, Outcome 7 Post-dose FEV1.

Review: Inhaled corticosteroids versus long-acting beta$_2$-agonists for chronic obstructive pulmonary disease

Comparison: 1 Inhaled corticosteroids (ICS) versus long-acting beta$_2$-agonists (LABA) by ICS and LABA

Outcome: 7 Post-dose FEV1

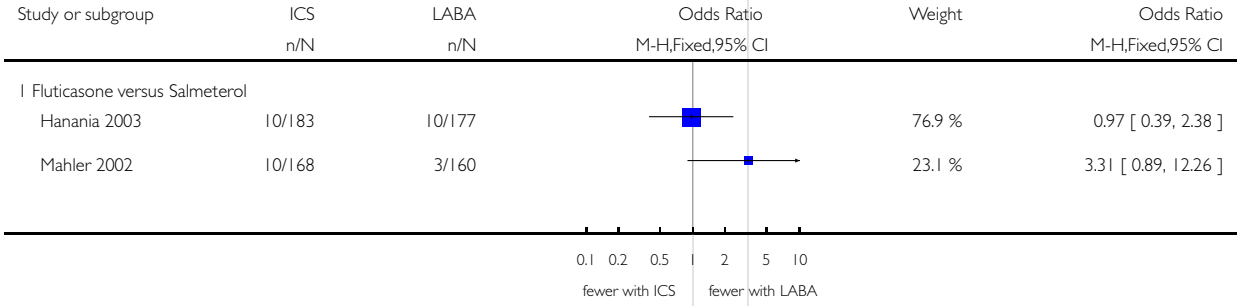


Analysis 1.8. Comparison 1 Inhaled corticosteroids (ICS) versus long-acting beta$_2$-agonists (LABA) by ICS and LABA, Outcome 8 Mild exacerbations.

Review: Inhaled corticosteroids versus long-acting beta$_2$-agonists for chronic obstructive pulmonary disease

Comparison: 1 Inhaled corticosteroids (ICS) versus long-acting beta$_2$-agonists (LABA) by ICS and LABA

Outcome: 8 Mild exacerbations



Analysis 1.9. Comparison 1 Inhaled corticosteroids (ICS) versus long-acting beta$_2$-agonists (LABA) by ICS and LABA, Outcome 9 Mortality.

Review: Inhaled corticosteroids versus long-acting beta$_2$-agonists for chronic obstructive pulmonary disease

Comparison: 1 Inhaled corticosteroids (ICS) versus long-acting beta$_2$-agonists (LABA) by ICS and LABA

Outcome: 9 Mortality

Study or subgroup	ICS n/N	LABA n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
1 Fluticasone versus Salmeterol				
Hanania 2003	0/183	0/177		0.0 [0.0, 0.0]
Mahler 2002	0/168	0/160		0.0 [0.0, 0.0]
TORCH 2007	246/1551	205/1542		1.23 [1.01, 1.50]
TRISTAN 2003	1/374	0/372		7.35 [0.15, 370.40]
Subtotal (95% CI)	**2276**	**2251**		**1.23 [1.01, 1.51]**
Total events: 247 (ICS), 205 (LABA)				
Heterogeneity: Chi^2 = 0.80, df = 1 (P = 0.37); I^2 =0.0%				
Test for overall effect: Z = 2.07 (P = 0.038)				
2 Budesonide versus Formoterol				
Calverley 2003	6/257	14/255		0.43 [0.18, 1.06]
Szafranski 2003	5/198	6/201		0.84 [0.25, 2.79]
Tashkin 2008	2/275	1/284		2.02 [0.21, 19.47]
Subtotal (95% CI)	**730**	**740**		**0.62 [0.31, 1.22]**
Total events: 13 (ICS), 21 (LABA)				
Heterogeneity: Chi^2 = 1.92, df = 2 (P = 0.38); I^2 =0.0%				
Test for overall effect: Z = 1.38 (P = 0.17)				
Total (95% CI)	**3006**	**2991**		**1.17 [0.97, 1.42]**
Total events: 260 (ICS), 226 (LABA)				
Heterogeneity: Chi^2 = 6.36, df = 4 (P = 0.17); I^2 =37%				
Test for overall effect: Z = 1.60 (P = 0.11)				
Test for subgroup differences: Chi^2 = 3.64, df = 1 (P = 0.06), I^2 =73%				

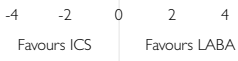
Analysis 1.10. Comparison 1 Inhaled corticosteroids (ICS) versus long-acting beta$_2$-agonists (LABA) by ICS and LABA, Outcome 10 Health-related quality of life SGRQ.

Review: Inhaled corticosteroids versus long-acting beta$_2$-agonists for chronic obstructive pulmonary disease

Comparison: 1 Inhaled corticosteroids (ICS) versus long-acting beta$_2$-agonists (LABA) by ICS and LABA

Outcome: 10 Health-related quality of life SGRQ

Study or subgroup	ICS N	LABA N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Fluticasone versus Salmeterol						
TORCH 2007	1551	1542	-1 (0.471)		54.5 %	-1.00 [-1.92, -0.08]
TRISTAN 2003	374	372	-0.4 (0.587)		35.1 %	-0.40 [-1.55, 0.75]
Subtotal (95% CI)					**89.6 %**	**-0.77 [-1.49, -0.04]**
Heterogeneity: Chi² = 0.64, df = 1 (P = 0.43); I² =0.0%						
Test for overall effect: Z = 2.08 (P = 0.037)						
2 Budesonide versus Formoterol						
Tashkin 2008	275	284	-0.51 (1.08)		10.4 %	-0.51 [-2.63, 1.61]
Subtotal (95% CI)					**10.4 %**	**-0.51 [-2.63, 1.61]**
Heterogeneity: not applicable						
Test for overall effect: Z = 0.47 (P = 0.64)						
Total (95% CI)					**100.0 %**	**-0.74 [-1.42, -0.06]**
Heterogeneity: Chi² = 0.69, df = 2 (P = 0.71); I² =0.0%						
Test for overall effect: Z = 2.12 (P = 0.034)						
Test for subgroup differences: Chi² = 0.05, df = 1 (P = 0.82), I² =0.0%						

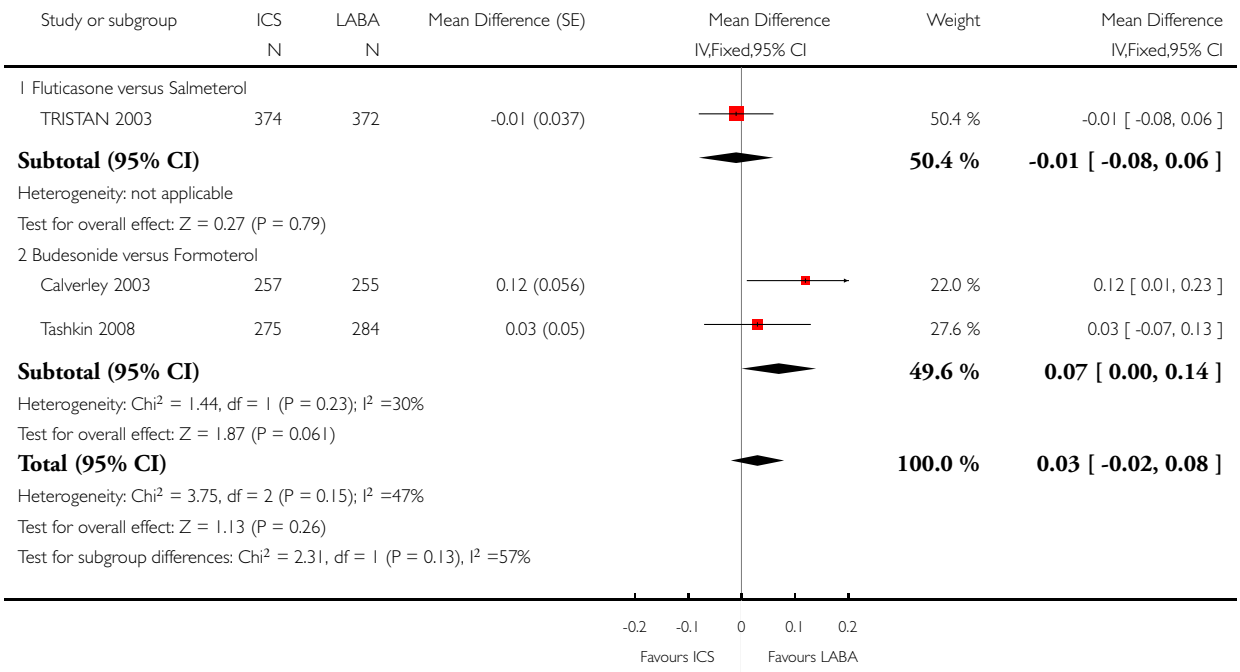


Analysis 1.11. Comparison 1 Inhaled corticosteroids (ICS) versus long-acting beta$_2$-agonists (LABA) by ICS and LABA, Outcome 11 Dyspnoea symptom score 0-4.

Review: Inhaled corticosteroids versus long-acting beta$_2$-agonists for chronic obstructive pulmonary disease

Comparison: 1 Inhaled corticosteroids (ICS) versus long-acting beta$_2$-agonists (LABA) by ICS and LABA

Outcome: 11 Dyspnoea symptom score 0-4



Analysis 1.12. Comparison 1 Inhaled corticosteroids (ICS) versus long-acting beta$_2$-agonists (LABA) by ICS and LABA, Outcome 12 Dyspnoea TDI.

Review: Inhaled corticosteroids versus long-acting beta$_2$-agonists for chronic obstructive pulmonary disease

Comparison: 1 Inhaled corticosteroids (ICS) versus long-acting beta$_2$-agonists (LABA) by ICS and LABA

Outcome: 12 Dyspnoea TDI

Study or subgroup	ICS N	LABA N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Fluticasone versus Salmeterol						
Hanania 2003	183	177	0.1 (0.361)		45.1 %	0.10 [-0.61, 0.81]
Mahler 2002	168	160	0.4 (0.327)		54.9 %	0.40 [-0.24, 1.04]

Analysis 1.13. Comparison 1 Inhaled corticosteroids (ICS) versus long-acting beta$_2$-agonists (LABA) by ICS and LABA, Outcome 13 Symptoms.

Review: Inhaled corticosteroids versus long-acting beta$_2$-agonists for chronic obstructive pulmonary disease

Comparison: 1 Inhaled corticosteroids (ICS) versus long-acting beta$_2$-agonists (LABA) by ICS and LABA

Outcome: 13 Symptoms

Study or subgroup	ICS N	LABA N	Mean Difference (SE)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Budesonide versus Formoterol						
Calverley 2003	257	255	0.24 (0.15)		30.8 %	0.24 [-0.05, 0.53]
Szafranski 2003	198	201	0.43 (0.134)		33.7 %	0.43 [0.17, 0.69]
Tashkin 2008	275	284	0.01 (0.125)		35.4 %	0.01 [-0.23, 0.25]
Total (95% CI)					**100.0 %**	**0.22 [-0.03, 0.47]**
Heterogeneity: Tau^2 = 0.03; Chi^2 = 5.29, df = 2 (P = 0.07); I^2 =62%						
Test for overall effect: Z = 1.74 (P = 0.081)						

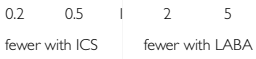
Analysis 1.14. Comparison 1 Inhaled corticosteroids (ICS) versus long-acting beta$_2$-agonists (LABA) by ICS and LABA, Outcome 14 Adverse events.

Review: Inhaled corticosteroids versus long-acting beta$_2$-agonists for chronic obstructive pulmonary disease

Comparison: 1 Inhaled corticosteroids (ICS) versus long-acting beta$_2$-agonists (LABA) by ICS and LABA

Outcome: 14 Adverse events

Study or subgroup	ICS n/N	LABA n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Fluticasone versus Salmeterol					
Hanania 2003	129/183	114/177		10.7 %	1.32 [0.85, 2.05]
Mahler 2002	138/168	119/160		6.8 %	1.58 [0.93, 2.70]
TORCH 2007	1395/1552	1381/1542		43.8 %	1.04 [0.82, 1.31]
TRISTAN 2003	302/374	295/374		17.7 %	1.12 [0.79, 1.61]
Subtotal (95% CI)	**2277**	**2253**		**79.0 %**	**1.14 [0.96, 1.35]**
Total events: 1964 (ICS), 1909 (LABA)					
Heterogeneity: Chi^2 = 2.56, df = 3 (P = 0.46); I^2 =0.0%					
Test for overall effect: Z = 1.53 (P = 0.12)					
2 Budesonide versus Formoterol					
Tashkin 2008	158/275	161/284		21.0 %	1.03 [0.74, 1.44]
Subtotal (95% CI)	**275**	**284**		**21.0 %**	**1.03 [0.74, 1.44]**
Total events: 158 (ICS), 161 (LABA)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.18 (P = 0.86)					
Total (95% CI)	**2552**	**2537**		**100.0 %**	**1.12 [0.96, 1.30]**
Total events: 2122 (ICS), 2070 (LABA)					
Heterogeneity: Chi^2 = 2.84, df = 4 (P = 0.59); I^2 =0.0%					
Test for overall effect: Z = 1.45 (P = 0.15)					
Test for subgroup differences: Chi^2 = 0.28, df = 1 (P = 0.60), I^2 =0.0%					

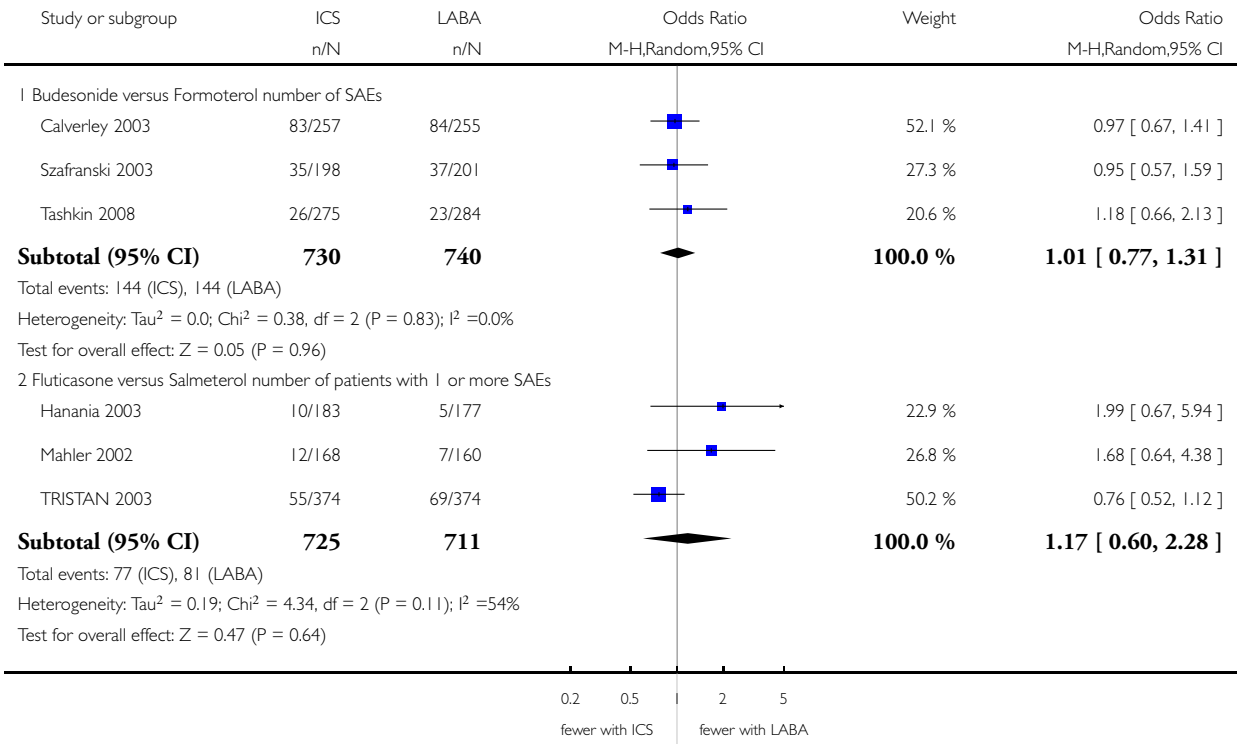


Analysis 1.15. Comparison 1 Inhaled corticosteroids (ICS) versus long-acting beta$_2$-agonists (LABA) by ICS and LABA, Outcome 15 Serious adverse events (non-fatal).

Review: Inhaled corticosteroids versus long-acting beta$_2$-agonists for chronic obstructive pulmonary disease

Comparison: 1 Inhaled corticosteroids (ICS) versus long-acting beta$_2$-agonists (LABA) by ICS and LABA

Outcome: 15 Serious adverse events (non-fatal)

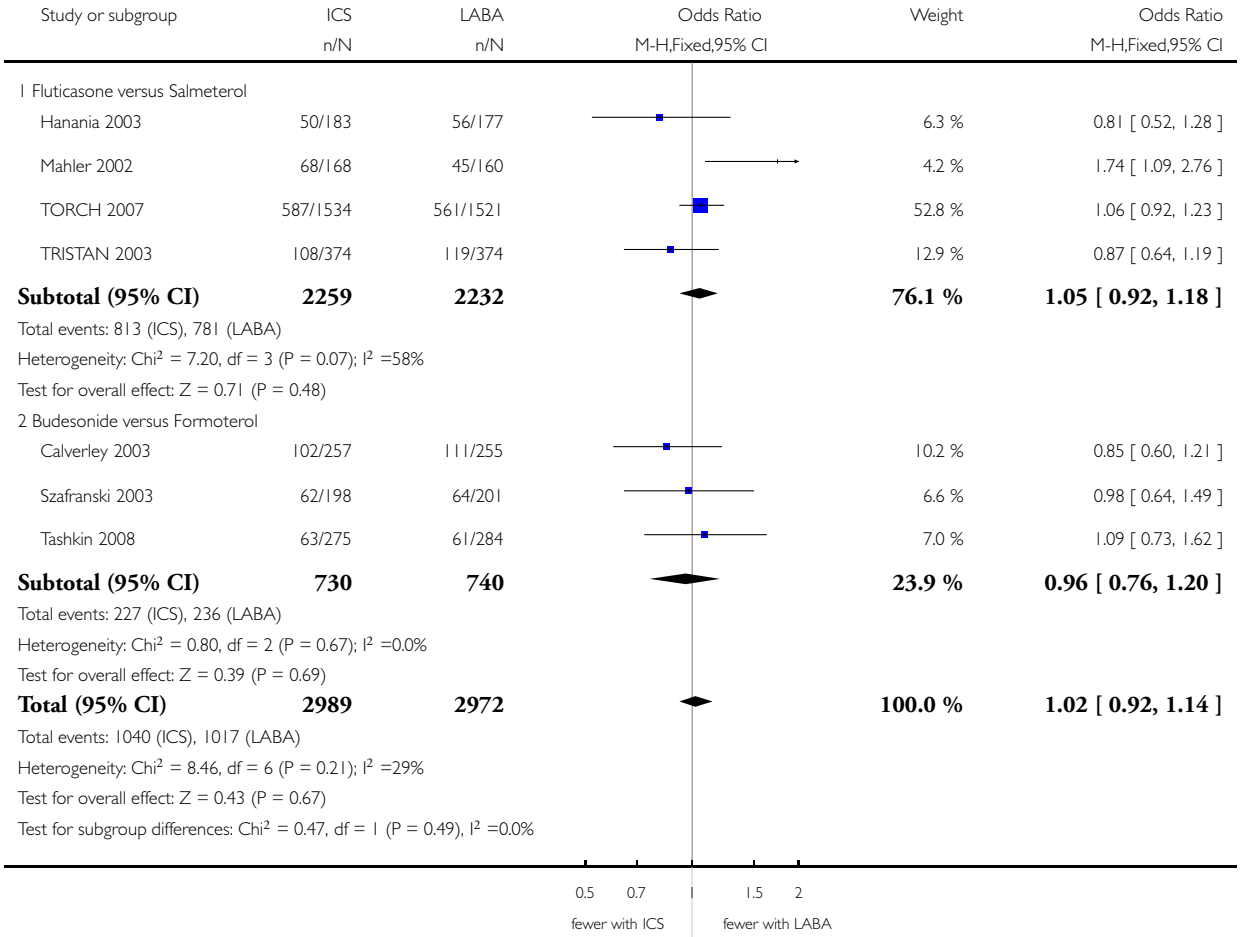


Analysis 1.16. Comparison 1 Inhaled corticosteroids (ICS) versus long-acting beta$_2$-agonists (LABA) by ICS and LABA, Outcome 16 Withdrawals.

Review: Inhaled corticosteroids versus long-acting beta$_2$-agonists for chronic obstructive pulmonary disease

Comparison: 1 Inhaled corticosteroids (ICS) versus long-acting beta$_2$-agonists (LABA) by ICS and LABA

Outcome: 16 Withdrawals



Analysis 2.1. Comparison 2 Inhaled corticosteroids versus long-acting beta$_2$-agonists by length of study, Outcome 1 Exacerbation rate ratios.

Review: Inhaled corticosteroids versus long-acting beta$_2$-agonists for chronic obstructive pulmonary disease

Comparison: 2 Inhaled corticosteroids versus long-acting beta$_2$-agonists by length of study

Outcome: 1 Exacerbation rate ratios

Study or subgroup	Inhaled corticosteroid N	Long acting beta-agonist N	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
1 up to 1 year						
Calverley 2003	257	255	-0.148 (0.121)		8.1 %	0.86 [0.68, 1.09]
Szafranski 2003	198	201	-0.144 (0.129)		7.1 %	0.87 [0.67, 1.11]
TRISTAN 2003	374	372	0.005 (0.076)		20.6 %	1.01 [0.87, 1.17]
Subtotal (95% CI)					**35.8 %**	**0.94 [0.84, 1.05]**
Heterogeneity: Chi^2 = 1.68, df = 2 (P = 0.43); I^2 =0.0%						
Test for overall effect: Z = 1.03 (P = 0.30)						
2 longer than 1 year						
TORCH 2007	1551	1542	-0.036 (0.043)		64.2 %	0.96 [0.89, 1.05]
Subtotal (95% CI)					**64.2 %**	**0.96 [0.89, 1.05]**
Heterogeneity: not applicable						
Test for overall effect: Z = 0.84 (P = 0.40)						
Total (95% CI)					**100.0 %**	**0.96 [0.89, 1.02]**
Heterogeneity: Chi^2 = 1.79, df = 3 (P = 0.62); I^2 =0.0%						
Test for overall effect: Z = 1.29 (P = 0.20)						
Test for subgroup differences: Chi^2 = 0.11, df = 1 (P = 0.75), I^2 =0.0%						

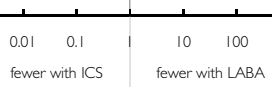
Analysis 2.2. Comparison 2 Inhaled corticosteroids versus long-acting beta$_2$-agonists by length of study, Outcome 2 Pneumonia serious adverse event.

Review: Inhaled corticosteroids versus long-acting beta$_2$-agonists for chronic obstructive pulmonary disease

Comparison: 2 Inhaled corticosteroids versus long-acting beta$_2$-agonists by length of study

Outcome: 2 Pneumonia serious adverse event

Study or subgroup	Inhaled corticosteroid n/N	Long acting beta-agonist n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 up to 1 year					
Calverley 2003	5/257	7/255		5.2 %	0.71 [0.22, 2.22]
Hanania 2003	1/183	1/177		0.9 %	0.97 [0.06, 15.53]
Mahler 2002	2/168	0/160		0.9 %	7.09 [0.44, 113.89]
Tashkin 2008	3/275	1/284		1.8 %	2.82 [0.40, 20.16]
TRISTAN 2003	9/374	9/372		7.8 %	0.99 [0.39, 2.53]
Subtotal (95% CI)	**1257**	**1248**		**16.4 %**	**1.11 [0.58, 2.10]**
Total events: 20 (Inhaled corticosteroid), 18 (Long acting beta-agonist)					
Heterogeneity: Chi^2 = 3.24, df = 4 (P = 0.52); I^2 =0.0%					
Test for overall effect: Z = 0.31 (P = 0.76)					
2 longer than 1 year					
TORCH 2007	121/1534	82/1521		83.6 %	1.50 [1.12, 1.99]
Subtotal (95% CI)	**1534**	**1521**		**83.6 %**	**1.50 [1.12, 1.99]**
Total events: 121 (Inhaled corticosteroid), 82 (Long acting beta-agonist)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.77 (P = 0.0056)					
Total (95% CI)	**2791**	**2769**		**100.0 %**	**1.42 [1.10, 1.85]**
Total events: 141 (Inhaled corticosteroid), 100 (Long acting beta-agonist)					
Heterogeneity: Chi^2 = 3.95, df = 5 (P = 0.56); I^2 =0.0%					
Test for overall effect: Z = 2.66 (P = 0.0079)					
Test for subgroup differences: Chi^2 = 0.71, df = 1 (P = 0.40), I^2 =0.0%					



APPENDICES

Appendix 1. Data analysis

None of the included trials directly compared inhaled corticosteroids (ICS) alone to long-acting beta$_2$-agonists (LABA) alone for treatment of COPD. However, the studies included these treatment arms which were compared to the treatment effect of ICS/LABA combination treatment and/or placebo. We have used the direct comparison of ICS and LABA where this has been available and complemented this with indirect estimates of treatment effects.

For dichotomous data we obtained the log risk ratio (LRR) for ICS vs LABA from trials comparing either:

ICS/LABA vs ICS and ICS/LABA vs LABA

$LRR_{ICSvsLABA}$ =

$LRR_{ICS/LABA\ vs\ LABA}$

- $LRR_{ICS/LABAvsICS}$

or ICS vs placebo and LABA vs placebo

$LRR_{ICSvsLABA} = LRR_{ICSvsplacebo} - LRR_{LABAvsplacebo}$

For continuous data the indirect estimation of treatment effect of ICS vs LABA was calculated similarly.

The exact standard error (SE) for ICS vs LABA could be calculated when SE or confidence intervals (CI) were available for the following five indirect comparisons:

ICS/LABA vs placebo

ICS/LABA vs LABA

ICS/LABA vs ICS

LABA vs placebo

ICS vs placebo

The variance (VAR) for ICS vs LABA could then be calculated from:

ICS/LABA = A

ICS = B

LABA = C

Placebo = D

$VAR_{BC} = (VAR_{AB} + VAR_{AC} + VAR_{BD} + VAR_{CD} - 2*VAR_{AD})/2$

When the treatment effect of ICS and LABA were only compared to either ICS/LABA or placebo, but comparisons to both were not available, the variance for ICS vs LABA was calculated through either of following ways:

$VAR_{BC} = VAR_{AB} + VAR_{AC} - VAR_{AD}$

$VAR_{BC} = VAR_{BD} + VAR_{CD} - VAR_{AD}$

These calculations were only used if exact P values or CI for each comparison were available. We assumed that the contribution of the individual groups to the variance of ICS/LABA vs placebo (VAR_{AD}) was equal. When not all reported P values for the different comparisons were exact we assumed that the SE for each comparison was similar to the SE for comparisons with an exact P value.

HISTORY

Protocol first published: Issue 2, 2008

Review first published: Issue 10, 2011

CONTRIBUTIONS OF AUTHORS

SS and DJE collated the articles. SS, DJE and CK extracted the data. CK, CC and SS performed the statistical analysis. SS, DJE, CK and CC wrote the review.

DECLARATIONS OF INTEREST

Sally Spencer has had consultancy arrangements with GlaxoSmithKline who make long-acting beta$_2$-agonists and inhaled corticosteroids. She has also previously been funded by GlaxoSmithKline. David Evans, Christopher Cates and Charlotta Karner do not have any known conflicts of interest.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Post-bronchodilator FEV1 was added as an outcome at the suggestion of a peer reviewer.

In the protocol we planned to assess study quality according to whether studies met the following pre-specified quality criteria (Handbook 2005):

I) adequacy of the randomisation procedure;

ii) demographic balance of study participants at baseline;

iii) adequacy of blinding procedures for concealing treatment allocation;

iv) adequacy of the reporting and handling of participants who withdrew from treatment.

By the time the review was written the guidelines for assessing study quality had been updated (Higgins 2008). We assessed the risk of bias for all included studies according to recommendations outlined in The Handbook for Systematic Reviews of Interventions (Higgins 2008) for the following items:

1. allocation sequence generation;
2. concealment of allocation;
3. blinding of participants and investigators;
4. incomplete outcome data;
5. selective outcome reporting.

We graded each potential source of bias as low, high or unclear risk of bias.