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

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Abstract

Background—Long-acting beta-agonists and inhaled corticosteroids have both been recommended in guidelines for the treatment of chronic obstructive pulmonary disease. Their co-administration in a combined inhaler may facilitate adherence to medication regimens, and improve efficacy.

Objectives—To assess the efficacy of combined inhaled corticosteroid and long-acting beta-agonist preparations, compared to placebo, in the treatment of adults with chronic obstructive pulmonary disease.

Search methods—We searched the Cochrane Airways Group Specialised Register of trials. The date of the most recent search is April 2007.

Selection criteria—Studies were included if they were randomised and double-blind. Studies could compare any combined inhaled corticosteroids and long-acting beta-agonist preparation with placebo.

Data collection and analysis—Two authors independently assessed study risk of bias and extracted data. The primary outcomes were exacerbations, mortality and pneumonia. Health-related quality of life (measured by validated scales), lung function and side-effects were

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CONTRIBUTIONS OF AUTHORS

LN and PP developed the protocol. Studies were assessed by LN and TJL. TJL and LN checked data and entered into RevMan. TJL and LN conducted the analysis. TJL and LN developed the discussion with input from PP. CJC participated in the 2004 and 2007 updates of the review and offered statistical advice and input with calculating SEMs and SDs for the included studies where appropriate.

DECLARATIONS OF INTEREST

The authors who have been involved in this review have done so without any known conflicts of interest. None of the authors is considered a paid consultant by any pharmaceutical company which produces agents discussed in this review.

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secondary outcomes. Dichotomous data were analysed as fixed effect odds ratios or rate ratios with 95% confidence intervals, and continuous data as mean differences and 95% confidence intervals.

Main results—Eleven studies met the inclusion criteria (6427 participants randomised). Two different combination preparations (fluticasone/salmeterol and budesonide/formoterol) were used. Study quality was good. Fluticasone/salmeterol and budesonide/formoterol both reduced the rate of exacerbations. Pooled analysis of both combination therapies indicated that exacerbations were less frequent when compared with placebo, Rate Ratio: 0.74 (95% CI 0.7 to 0.8). The clinical impact of this effect depends on the frequency of exacerbations experienced by patients. The patients included in these trials had on average 1-2 exacerbations per year which means that treatment with combination therapy would lead to a reduction of one exacerbation every two to four years in these individuals. There is an overall reduction in mortality, but this outcome is dominated by the results of TORCH and further studies on budesonide/formoterol are required. The three year number needed to treat to prevent one extra death is 36 (95% CI 21 to 258), using a baseline risk of 15.2% from the placebo arm of TORCH. Both treatments led to statistically significant improvement in health status measurements, although the clinical importance of the differences observed is open to interpretation. Symptoms and lung function assessments favoured combination treatments. There was an increase in the risk of pneumonia with combined inhalers. The three year number needed to treat for one extra case of pneumonia is 13, using a baseline risk of 12.3% from the placebo arm of TORCH. Fewer participants withdrew from studies assessing combined inhalers due to adverse events and lack of efficacy.

Authors' conclusions—Compared with placebo, combination therapy led to a significant reduction of a quarter in exacerbation rates. There was a significant reduction in all-cause mortality with the addition of data from the TORCH trial. The increased risk of pneumonia is a concern, and better reporting of this outcome in future studies would be helpful. In order to draw firmer conclusions about the effects of combination therapy in a single inhaler more data are necessary, particularly in relation to the profile of adverse events and benefits in relation to different doses of inhaled corticosteroids.

Medical Subject Headings (MeSH)

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

MeSH check words

Humans

BACKGROUND

Both inhaled corticosteroids and long-acting beta-agonists (LABAs) have been shown to be effective in chronic obstructive pulmonary disease (COPD). The evidence available indicates that there is a consistent, statistically significant difference in FEV1 of around 50 mL, and significant differences in health status measurements in favour of salmeterol in patients with a poor response to short-acting bronchodilators (Appleton 2006). Inhaled

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steroids have not been shown to reduce the rate of decline in FEV1 although short-term increases in FEV_1 and significant reductions in exacerbations have been reported (Yang 2007). The impact of these effects on morbidity and mortality remain uncertain. LABAs are recommended by NICE 2004 and GOLD (GOLD 2006) when patients continue to experience problems on short-acting bronchodilators.

The evidence base for the addition of long-acting beta-agonists to inhaled steroids in asthma is well established (Ni Chroinin 2004; Ni Chroinin 2005). There are several possible advantages to fixed combination therapy. The most obvious benefit is in terms of patient convenience with the expectation that this may lead to greater treatment adherence. Therefore, it is important to know whether inhaled corticosteroids combined with long-acting beta-agonist (LABAs) preparations reduce the number of exacerbations and improve other endpoints such as quality of life, despite the lack of effect on FEV_1 decline.

This is an update of a previous review which considered the effect of combination therapy compared with placebo, and both monocomponents in people with chronic obstructive pulmonary disease (COPD) (Nannini 2004). The availability of several new studies has prompted us to split the review between comparisons with placebo and those with monocomponents. This review summarises the evidence from clinical trials comparing combination inhaled steroids and long-acting beta-agonists with placebo. Reviews of combination therapy with inhaled steroids (Nannini 2007a) and long-acting beta-agonists (Nannini 2007b) are published separately. Recent concerns have been raised regarding the safety of long-acting beta-agonists in asthma (Walters 2007) and also the validity of summary estimates from clinical trials which assess exacerbation rates without taking account of follow-up time or adjustment for between-patient variability (Suissa 2006).

OBJECTIVES

To determine the efficacy of combined inhaled corticosteroid and long-acting beta-agonists for stable COPD in comparison with placebo.

METHODS

Criteria for considering studies for this review

Types of studies—Randomised, double-blind clinical trials.

Types of participants—Adult patients (age > 45 years) with known, stable COPD fulfilling American Thoracic Society (ATS), European Respiratory Society (ERS) or Global Initiative for Chronic Obstructive Lung Disease (GOLD) diagnostic criteria. Patients were to be clinically stable, without evidence of an exacerbation for one month prior to study entry. Patients with significant diseases other than COPD, (for example with a diagnosis of asthma, cystic fibrosis, bronchiectasis, or other lung diseases) were excluded. However patients with partial reversibility on pulmonary function testing were included.

Types of interventions

1. Fluticasone/salmeterol versus placebo

2. Budesonide/formoterol versus placebo Concomitant therapy was permitted, as long as there was no systematic difference between treatment groups.

Types of outcome measures

Primary outcomes

1. Exacerbations & hospitalisations
2. Mortality
3. Pneumonia has been added as a primary outcome for this update.

Secondary outcomes

1. Change in forced expiratory volume in 1 second (FEV_1) and change in forced ventilatory capacity (FVC): trough, peak and average; and other measures of pulmonary function
2. Exercise performance - six minute walk and other measures
3. Quality of life scales - St George's Respiratory Questionnaire (SGRQ), Chronic Respiratory Disease Questionnaire (CRDQ)
4. Symptoms
5. Inhaled rescue medication used during the treatment period and other concomitant medication usage including antibiotics and steroids
6. Adverse events - palpitations, tremor, hoarseness/dysphonia, oral candidiasis, cataracts, skin bruising, bone fracture, bone density, plasma cortisol level

Search methods for identification of studies

Electronic searches—Trials were identified using the Cochrane Airways Group Specialised Register of trials, which is derived from systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED and PsycINFO, and handsearching of respiratory journals and meeting abstracts. All records in the Specialised Register coded as 'COPD' were searched using the following terms:

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

The most recent search on the Register was run in April 2007. In addition, we performed a search of LILACS (all years to March 2005) and CENTRAL (The Cochrane Library Issue 1, 2006).

Searching other resources—We reviewed reference lists of all primary studies and review articles for additional references. We also contacted authors of identified randomised trials about other published and unpublished studies. In addition, we consulted the online

trial registries of GSK and AstraZeneca, manufacturers of FPS and BUDF respectively (www.ctr.gsk.co.uk; www.astrazenecaclinicaltrials.com).

Data collection and analysis

Selection of studies—Two reviewers independently identified abstracts of trials which appeared potentially relevant. Using the full text of each study, two reviewers independently selected trials for inclusion in the review. Agreement was by simple agreement; third party adjudication was used to resolve differences.

Data extraction and management—Two reviewers independently extracted data from included trials and entered results into the Cochrane Collaboration software program (Review Manager). In some cases, we estimated information regarding outcomes from graphs. This was performed independently by the two reviewers. Data extraction included the following items:

Population: Age, gender, smoking status, study setting (country, practice setting), inclusion and exclusion criteria.

Intervention: Dose, delivery device, duration

Control: Concurrent treatments (ipratropium, beta-2 agonist, inhaled and systemic corticosteroids)

Outcomes: Pulmonary function measures (baseline and follow-up FEV_1 and FVC), timing of pulmonary function measures, 6-minute walk, urgent visits, admissions, self-rated symptom score/symptoms, quality-of-life instruments, adverse events (palpitations, dry mouth, blurred vision, urinary obstruction and constipation), assessors, adjudicator of clinical endpoints. Mortality outcome data were collected from studies of greater than one year's duration where these were available.

Design: method of randomisation, presence and type of run-in period, study design (parallel, cross-over)

Assessment of risk of bias in included studies—We assessed the risk of bias for each study according to the extent to which the design of the trial had protected the findings from bias. Our assessments we made on the basis of allocation, its concealment and blinding.

Dealing with missing data—The reported confidence interval or P value were used to calculate standard deviations, or standard errors, for results when these were not reported and could not be obtained from the authors of the papers.

Assessment of heterogeneity—For pooled effects, heterogeneity was to be tested using I^2 measurement of the degree of variation between the studies, not attributable by the play of chance.

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Data synthesis—For continuous variables, a fixed effects weighted mean difference (MD) was used for outcomes measured on the same metric. Standardised mean difference (SMD) and 95% confidence interval (CI) was calculated for outcomes where data were combined from studies using different metrics. All similar studies were to be pooled using fixed effect MD/SMD and 95% CIs.

For dichotomous variables, a fixed effect odds ratio (OR) with 95% confidence intervals (95% CI) were calculated for individual studies. All similar studies were pooled using fixed effect OR and 95% CIs. Where mean treatment differences were reported, data were entered as generic inverse variance (GIV), provided a standard error for the difference could be extracted or imputed. Where this method was used the effect size was reported from the original papers, for example as Rate Ratio. This method (GIV) was not available when the protocol was written for the review so was not pre-specified.

Subgroup analysis and investigation of heterogeneity—Whilst we separated the type of steroid and long-acting beta-agonist, we pooled studies with differing dosages of the same drug. We planned *a priori* subgroups as:

1. Disease severity (related to baseline FEV_1 and placebo group exacerbation rate) according to the GOLD staging = IIA, IIB (moderate COPD, characterised by deteriorating lung function (A = FEV1</=80% predicted; B = </=50% predicted) and progression of symptoms) and III (severe COPD, characterised by severe airflow limitation (FEV1<30% predicted) and presence of respiratory failure or clinical signs of right heart failure (GOLD 2006).
2. Prior inhaled corticosteroid plus long-acting beta agonists use (dichotomised as yes/no).
3. Concurrent therapy with routine beta-agonist use (short or long-acting), corticosteroid (systemic or inhaled) or theophylline use (dichotomised as yes/no).
4. Reversibility of airflow obstruction with beta-2-agonist therapy (dichotomised as partial/none). Definition: >12% and > 200 ml from baseline FEV_1 or > 12% as a per cent of the predicted normal value following MDI salbutamol 200 to 400
5. Dose, duration and delivery method of therapy.

Sensitivity analysis—For pooled effects, heterogeneity was to be tested using I^2 measurement of the degree of variation between the studies, not attributable by the play of chance. If heterogeneity was found, (I^2 statistic more than 20%), a random effects model was also used to determine the impact of heterogeneity on the overall pooled effect. In addition, the robustness of the results was tested using a sensitivity analysis based on the quality of the trials where possible.

RESULTS

Description of studies

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

Results of the search—For details of search history, see Table 1. An overview of the division of our original review into three and description of the search results is given in Figure 1.

Included studies—Eleven studies are included in this review. One study is ongoing (Morgan 2004). For a full description of baseline characteristics, methods used and inclusion and exclusion entry criteria. individual studies, see Characteristics of included studies.

Design: All trials had a randomised, double-blind parallel group design. Methods of randomisation were described in one study (Mahler 2002). Method of blinding was not fully described in all studies. Following correspondence from GSK, trial methodology was confirmed for TRISTAN, and AstraZeneca confirmed methodology for Szafranski 2003. Study characteristics were sufficiently described in three data sets without journal publication to justify their inclusion in the review (O'Donnell 2006; SFCT01; SCO100540).

Participants: A total of 6427 participants were randomised to studies in the review. Participants suffered from COPD, with variable definition of COPD and reversibility. COPD was defined by national or international criteria: ATS (Hanania 2003; Mahler 2002) ERS (TORCH; TRISTAN) and GOLD (Barnes 2006; Calverley 2003; Dal Negro 2003; SCO100540; Szafranski 2003). In two studies, definitions were based on lung function tests and smoking history (O'Donnell 2006; SFCT01). Patient populations in the studies suffered from moderate and severe COPD. Hanania 2003 and Mahler 2002 enrolled participants with reversible and non-reversible COPD. In TORCH the participants were not required to have had previous exacerbations requiring oral steroids or antibiotics to be included in the study.

Interventions: All eleven studies compared combination therapy with placebo.

In one study all participants had a two-week run-in treatment with oral corticosteroids, inhaled formoterol and prn SABA (Calverley 2003).

Concomitant therapy was as-needed short-acting beta agonist, or oral steroids and/or antibiotics in the case of exacerbations. However in three studies, theophylline was also used. Eleven percent of participants in Hanania 2003, and all 18 participants in Dal Negro 2003 received theophylline, in addition to the study drugs. The exact proportion of patients in TRISTAN who were taking theophylline was not reported.

In two studies the combination of inhaled corticosteroid/long-acting beta-agonist was fluticasone/salmeterol (FPS) was 250 mcg/50 mcg twice daily (Dal Negro 2003; Hanania 2003). In the remainder of the FPS studies the dose was 500 mcg/50 mcg twice daily. In

Calverley 2003 and Szafranski 2003 the combination inhaled corticosteroid/long-acting beta agonist was budesonide/formoterol (BDF) (320 mcg/9 mcg twice daily).

Duration: 13 weeks or less: Barnes 2006; O'Donnell 2006.

24 weeks: Hanania 2003; Mahler 2002; SCO100540.

52 weeks: Calverley 2003; Dal Negro 2003; Szafranski 2003; SFCT01; TRISTAN.

156 weeks: TORCH.

Outcomes: Exacerbations were stratified by medication given (oral steroid and/or antibiotic treatment in Barnes 2006; Calverley 2003; Dal Negro 2003; SCO100540; SFCT01; Szafranski 2003; TORCH; TRISTAN) or hospitalisation (Barnes 2006; Dal Negro 2003; SCO100540; TORCH; TRISTAN). O'Donnell 2006 did not record/report exacerbation data. Hanania 2003 and Mahler 2002 withdrew participants who exacerbated. Lung function was measured as FEV1 or PEF in all the studies. Quality of life assessment by the SGRQ or CRDQ were available for Calverley 2003; Hanania 2003; Kardos 2007; Mahler 2002; SCO100540; SFCT01; Szafranski 2003; TORCH; TRISTAN. All cause mortality was reported by TORCH.

Excluded studies—Studies that did not meet the entry criteria of this review are listed in Characteristics of excluded studies.

Risk of bias in included studies

Our assessments of the risk of bias for allocation and blinding are provided in Figure 2. The majority of our judgements on allocation procedures were unclear due to paucity of this information in the trial reports. We were able to ascertain that these were at a low risk of bias in three large studies (Szafranski 2003; TORCH; TRISTAN). All studies used identical inhaler devices to deliver therapy in the treatment groups.

Effects of interventions

See Summary of Findings table (See Figure 3).

Primary outcomes: Exacerbations, Mortality and Pneumonia

Rate of exacerbations

FPS versus placebo: There was a significant reduction in the rate of exacerbations with combination therapy when compared with placebo (0.74; 95% CI 0.69 to 0.8, three trials, N = 4222). This result was not altered by removing TRISTAN whose summary estimate may have been biased by inadequate adjustment for between patient variability (Suissa 2006), see Figure 4. Additional analysis was performed on exacerbations by specific definitions. Compared with placebo, FPS led to fewer exacerbations requiring oral steroids (rate ratio 0.57; 95% CI 0.52 to 0.63, three studies), less requirement for antibiotics (rate ratio 0.6 95% CI 0.43 to 0.84, one study) and fewer hospitalisations (rate ratio 0.83; 95% CI 0.7 to 0.97, two studies).

BDF versus placebo: There was a significant effect on pooled exacerbation rates in favour of BDF when expressed as a rate ratio compared with placebo (0.74; 95% CI 0.62 to 0.88) (see Figure 4). These results are based on 913 participants from two trials (Calverley 2003; Szafranski 2003).

When combined together the overall reduction in rate ratio of exacerbations using either FPS or BDF is 0.74; 95% CI 0.69 to 0.79, five trials, N = 5135.

Dichotomous data (number of people experiencing an exacerbation)

FPS versus placebo: No significant difference: OR 0.91; 95% CI 0.69 to 1.19, four studies, N = 1109.

Mortality

FPS versus placebo: The adjusted hazard ratio from TORCH did not identify a significant effect of FPS over placebo (0.825, 0.681 to 1.002, P = 0.052). Analysed as number of deaths in each treatment group by odds ratio and combined with data from other four other studies, there was a significant reduction in the odds of death in favour of FPS versus placebo (Odds Ratio 0.79, 95% CI 0.65 to 0.98, N = 4829). Data were separated according to the time point and subgrouped for data at three years, data reported at 1-3 years, data at 1 year and data at 6 months.

BDF versus placebo: The two studies of one year duration did not detect a significant difference between BDF and placebo. The point estimate (Odds Ratio 0.78, 95%CI 0.35 to 1.73) was similar to that for FPS and the was no significant difference in the odds ratio for mortality between FPS and BDF.

When combined together the overall reduction in the odds ratio for mortality with either FPS or BDF was 0.79, 95% CI 0.65 to 0.96, N = 5752, see Figure 5. Since differing lengths of follow-up across the studies hinders the calculation of a pooled NNT, we have tabulated this for each study individually (see Table 2). The three year NNT (using the baseline risk of 15.2% in the placebo arm of TORCH) to prevent one extra death is 36 (95% CI 21 to 258).

Pneumonia

FPS versus placebo: Addition of data from TORCH shows a significant increase in pneumonia with FPS in comparison with placebo. The pooled OR is 1.80 (95% CI 1.48 to 2.18).

BDF versus placebo: Calverley 2003 reported data on pneumonia and although the increase was not statistically significant (OR 4.13, 95% CI 0.87 to 19.64) the direction of effect was similar to FPS and there is no significant difference between the increase in pneumonia when BDF is compared to FPS.

For combined inhalers, the pooled OR for pneumonia is 1.83 (95% CI 1.51 to 2.21). Table 3 gives the range of NNT(H) across the studies for pneumonia. A pooled NNT(H) was not calculated due to the wide differences in duration and the likely impact this would have on the calculation of a pooled event rate. The three year NNT(H) (using the baseline risk of

12.3% in the combination therapy arm of TORCH) for one extra patient to suffer pneumonia was 13.

Secondary outcomes

Quality of life

St George Respiratory Questionnaire (results collected from end of study)

FPS versus placebo: Treatment with FPS improved SGRQ scores by an average of −2.9 units versus placebo (95% CI: −3.61 to −2.18, four studies, N = 3346).

BDF versus placebo: There was a significant effect in favour of BDF compared with placebo of −6.06 units on the SGRQ (95%CI −7.90 to −4.22). There was a high level of heterogeneity when these data were pooled (I square 71.8%). Random effects modelling also generated a significant effect (MD −5.8 units [95%CI −9.32 to −2.28]). The magnitude of improvement in the Szafranski 2003 BDF group was 3.9 units from baseline, and was not dissimilar to the change scores from post run-in treatment in the Calverley 2003 (see graphical presentation of data in the published article, P 916). However, the placebo group deteriorated more in Calverley 2003, which possibly reflects the withdrawal of active treatment, with the subsequent loss of the pre-dosing effects achieved with high dose OCS and LABAs. In comparison, BDF may have maintained the pre-dosing treatment effects of QoL more successfully.

Chronic Respiratory Disease Questionnaire (results collected from end of study)

FPS versus placebo: Pooled data from Mahler 2002 and Hanania 2003 indicated a statistically significant improvement in CRDQ for those treated with FPS compared with placebo (5 units (95% CI 2.48 to 7.52).

Symptom score

FPS versus placebo: FPS led to improved symptom scores (transitional dysponea index) when compared with placebo (MD 1.04 (95% CI 0.56 to 1.53) Mahler 2002 and Hanania 2003 gave a significant difference in change scores in favour FPS .

TRISTAN reported improvements in symptoms after treatment in favour of FPS versus placebo on breathlessness scores (P < 0.001), and night time awakenings (FPS mean number of nights per week: 2.31; placebo mean: 3.01 (P = 0.006). Cough scores also favoured FPS (P = 0.018).

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

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Lung function

Predose & post-dose FEV_1 - Change from baseline

FP versus placebo: Pooled analysis of data were conducted without findings from the Dal Negro 2003 study. Owing to the small size of this study, we were concerned that the SDs represented an inaccurate estimate for the SDs of the population, and the small variance increased the weight of the study, out of all proportion to its size. Data pooled from seven studies gave a MD in predose FEV_1 of 0.16 Litres; 95% CI 0.14 to 0.19, N = 1408. Analysis of post-dose FEV_1 from TORCH indicated a significant improvement in favour of FPS over placebo of 0.09 L.

BDF versus placebo: FEV_1 data were reported as % change. There was a significant increase in FEV_1 in favour of BDF versus placebo of 14.40% (95%CI 11.91 to 16.90, two studies).

Predose FEV_1-Absolute values

FPS versus placebo: TRISTAN and SFCT01 reported data as mL and Dal Negro 2003 reported % predicted.

The results of this analysis have not been pooled due to concern over the small number of similar patients in Dal Negro 2003, and the very low variance. It is therefore not appropriate to combine the results on an SMD scale.

Pooled data from TRISTAN and SFCT01 led to a significant difference in favour of FPS of 0.13 Litres; 95% CI 0.10 to 0.16.

Rescue medication

FPS versus placebo: Pooled data from Mahler 2002 and Hanania 2003 indicated a significant reduction in mean puffs per day of short-acting beta-agonist usage for FPS versus placebo (MD −1.19 puffs/day; 95% CI: −1.83 to −0.55).

Mahler 2002 reported significant increases in the percentage of nights with no awakenings requiring short-acting beta-agonist in favour of FPS versus placebo (5.7% versus −4.3% respectively, $P < 0.031$).

TRISTAN reported a significant difference in median % of days without use of relief medication: FPS: 14% versus placebo: 0% ($P < 0.001$).

BDF versus placebo: BDF treatment reduced the requirement for reliever medication when compared with placebo. The combined results of Calverley 2003; Szafranski 2003, MD −0.87 puffs per day (95%CI −1.15 to −0.58), I^2 29.1%; Random effects modelling: MD −0.92 puffs per day (95% CI −1.34 to −0.50).

Safety & tolerability

FPS versus placebo: There was no significant difference in the occurrence of overall reported adverse events between FPS and placebo: OR 1.10; 95% CI 0.96 to 1.27; eight studies, N = 5493.

Pneumonia, candidiasis, nasopharyngitis, hoarseness and upper respiratory tract infections (URTI) occurred more frequently in FPS treated participants:

Pneumonia: OR 1.80; 95% CI 1.48 to 2.18; seven studies, N = 5229.

Candidiasis: OR 5.73; 95%CI 3.07 to 10.67; six studies, N = 1958.

Hoarseness: OR 8.79; 95% CI 1.11 to 69.62; two studies, N = 585.

Nasopharyngitis: OR 1.28; 95% CI 1.05 to 1.56; two studies, N = 3535.

URTI: OR 1.23; 95% CI 1.04 to 1.47; five studies, N = 4963.

Withdrawals

FPS versus placebo: There were significantly fewer withdrawals from treatment with FPS than placebo (OR 0.69; 95% confidence interval 0.62 to 0.78). Withdrawals due to adverse events and lack of efficacy also occurred less frequently on treatment with FPS than placebo (withdrawal due to adverse event: OR 0.76; 95% confidence interval 0.65 to 0.88; eight studies, 5110 participants; withdrawal due to lack of efficacy: OR 0.30; 95% confidence interval 0.21 to 0.42; five studies, 4620 participants).

BDF versus placebo: Data were pooled from Calverley 2003 and Szafranski 2003 for withdrawals due to worsening COPD symptoms and adverse events.

There was a significant difference in withdrawals due to worsening of COPD symptoms when BDF was compared with placebo, OR 0.40 [95%CI 0.28 to 0.58].

There was no significant difference between BDF and placebo on the likelihood withdrawal due to adverse events other than COPD deterioration, OR 1.30 [95%CI 0.78 to 2.18].

DISCUSSION

We have reviewed data from 11 randomised controlled trials (6427 participants) assessing the effectiveness of combined inhaled corticosteroid and long-acting beta-agonist in the treatment of chronic obstructive pulmonary disease (COPD). Whilst the consensus regarding the definitions of COPD and COPD exacerbations evolve, the trial evidence to date indicates that in severe COPD where this is defined by low FEV1, significant smoking history, and a recent history of reduced disease control there is a role for combination therapy in reducing exacerbations which lead to unscheduled additional treatment, including courses of oral steroid therapy and hospitalisation.

Patient populations

There is much debate as whether ‘chronic obstructive pulmonary disease’ includes patients who have a significant bronchodilator response to short-acting beta-agonists, although recent definitions permit some reversibility. In this review, we have attempted to stratify data according to baseline reversibility. There is debate as to whether such a distinction is a clinically valid dichotomy (Burge 2003; Calverley 2003a). We have opted to pool data from

both these populations as there remains little consensus on this issue (ATS 1995), but for some outcomes (such as FEV_1) a sub-group analysis has been carried out on the basis of reversibility. It is also of interest that Calverley 2003 and Szafranski 2003 were classified as low reversibility on the basis of change in FEV1 following short acting beta-agonists, but nevertheless achieved a mean change in FEV1 of around 15% following pre-treatment with oral steroids and long-acting beta-agonist treatment in the studies.

Baseline FEV1 data from the studies indicate that the effects observed in the analyses were measured in populations who were over-whelmingly severe. Intention-to-treat analyses were conducted in all the studies, but on outcomes such as mean exacerbation rates, the withdrawal of severe frequent exacerbators in the studies may have distorted study findings due to the lower exacerbation rates on active treatment. The loss of these patients from the studies may thus limit the accuracy of mean event rates.

There was also a high proportion of current smokers in Mahler 2002 and TRISTAN. A recent study has demonstrated a diminished response to dexamethasone in vitro following the simulation of smoking effects. Smoke effects induced the inhibition of the histone deacetylases (HDAC) enzyme which is necessary in the process of gene repression (Ito 2001). Whilst one in vivo study has demonstrated the resistance to steroid action in asthmatic smokers (Pedersen 1996), there may nevertheless be a similar inhibition of the expression of corticosteroids when inhaled or systemic steroids are used in current smokers with COPD, resulting in compromised corticosteroid effectiveness.

Clinical endpoints

The outcomes identified *a priori* to be of primary significance related to exacerbations and hospitalisations. Limited data were presented in the trials on hospitalisations as a separate outcome although the evidence available did indicate that combination treatment reduced the rate of this event. Previous studies have indicated that ICS reduces the mean rate of exacerbations requiring oral steroid or antibiotics in patients with moderate and severe COPD (Yang 2007). However, the dose at which ICS is considered to efficacious, and the patients most likely to respond to this therapy remain unclear. The magnitude of these differences and their clinical impact depends upon the frequency of patients exacerbations. In severe patients with a history of one or more exacerbations in the previous year, the difference of 24% may translate to one exacerbation less every 4 years. Further assessment of the impact of the combination therapy upon hospitalisations and exacerbations is required.

There is growing interest in the definition and analysis of exacerbations which occur in clinical trials of therapies in COPD (Roisin 2000; Suissa 2006; Calverley 2005). The role of any maintenance therapy in this population should be assessed in terms of the burden of deteriorating disease control to both the individual patient and the healthcare system which rationalises resources in treating the debilitating effects of chronic disease progression. The relationship between event defined exacerbations (such as short courses of oral steroids or antibiotics, unscheduled presentation) and other markers of health such as symptoms and quality of life continue to present trialists and guideline developers with the dilemma of when to recommend initiating additional therapy based on the trial evidence available, and

the extent to which varying definitions of endpoint alter external validity in applying evidence to the needs of an individual patient. The question of exacerbations, and the appropriate statistical analysis of rate ratios, casts some doubt over the validity of some of the findings in this review. In particular, the large long-term studies (i.e. those in excess of six months) which are adequately powered to detect statistically significant findings may overestimate the treatment effects of this therapy (Suissa 2006). The method of weighting counts of exacerbations described by Suissa 2006 (using duration of person follow-up time as a denominator in calculating the mean group rate of exacerbations rather than an unweighted approach) was undertaken in Calverley 2003; Szafranski 2003 and TORCH. In these studies the effects were consistent and significantly favoured combination therapy over placebo.

Mortality was recorded in many of the studies, but was collected and analysed as a primary outcome in TORCH. Cause-specific mortality was reported, but the definition of a primary cause of death continues to pose challenges in a population of patients who suffer from comorbidities such as lung cancer (McGarvey 2007). The findings in the original trial publication as a hazard ratio (HR). The HR reported in TORCH was adjusted for repeated measurements, and was not statistically significant (ratio: 0.825, P = 0.052). The significant finding in our review of a ratio of odds of death overall of 0.79 in favour of treatment probably reflects the fact that our analyses were not subject to adjustment for repeated measurement. Furthermore, this estimate encompasses data from studies with considerably shorter lengths of follow-up which provide only limited long-term prognostic value. This explains why TORCH provides 53% participants, and 89% of the weight. The three year NNT (from the baseline risk in TORCH) to prevent one extra death is 36 (95% CI 21 to 258).

Both the CRDQ and the SGRQ were used to measure the effect of combination therapy on health status. There was a high level of statistical variation in the FPS studies for total SGRQ scores, although the reasons for this are not clear. Differing treatment protocols in the two budesonide/formoterol combination studies may explain the differences between health status scores. Although differences between combination therapy and placebo in Calverley 2003 and Szafranski 2003 were statistically significant, the difference from Calverley 2003 suggested that combination treatment led to a clinically meaningful advantage compared with placebo (i.e. greater than 4 units, Jones 2002). This difference should be interpreted with some caution due to the effects of pre-treatment with high dose prednisolone and formoterol, which led to a clinically meaningful increase of 4.5 units on the SGRQ. These effects were sustained with combination treatment when compared with placebo, but statistical tests on the comparisons with component therapy were not available.

Side-effects were more common on treatment than placebo. The increased risk of pneumonia with combination therapy is of particular concern since this frequently leads to hospitalisation in elderly patients. The association between prescription of inhaled fluticasone and pneumonia in people with COPD has been identified from a case-control study (Ernst 2007). The rate ratio from that study indicated an increase in risk of pneumonia leading to hospitalisation of 70% (RR 1.7). From RCT data in this review the combination of salmeterol and fluticasone also led to an increase in the odds of pneumonia of 1.8

(representing an increase in the risk of pneumonia of 65%). The NNT(h) for this outcome varies considerably, with three long-term studies (i.e. one year or greater) showing the lowest NNT(H) (Calverley 2003: 36; TORCH: 13; TRISTAN: 153, see Table 3).

The advantages associated with combination therapy extend beyond potentially greater patient compliance with a convenient delivery system of two therapies. The component treatments have complementary mechanisms of action, whereby the smooth muscle relaxation of the beta-agonist combined with the anti-inflammatory action of the steroid offer greater scope of clinical benefits than they would do alone. Cazzola 2000 reported a single-blind trial assessing the additive benefit of long-acting beta-agonist and inhaled steroids. When administered in separate inhalers there was no significant improvement in lung function until three months of treatment. The results from the trials in this review have not addressed the question of synergistic effects, and further research comparing combination therapy in a single versus separate inhaler devices could elucidate this issue more clearly.

Fixed dose therapy may be an effective pharmacological strategy in clinically stable moderately severe COPD, but if patients become unstable other approaches would be needed (GOLD 2006). Consensus guidelines recommend oral corticosteroids and/or antibiotics depending on the cardinal symptoms of the exacerbation of COPD (GOLD 2006). At this time it would be inappropriate to manage a clinically unstable situation with combined fixed therapy on its own.

AUTHORS' CONCLUSIONS

Implications for practice

In participants with moderate and severe COPD, there is clinical benefit when long acting beta-agonist and inhaled corticosteroid are co-administered compared to treatment with placebo, with fewer exacerbations and better quality of life. The effect on all cause mortality with active treatment is statistically significant. Fluticasone/salmeterol also led to increased harm with an increased risk of pneumonia with active treatment. In order to draw firmer conclusions about the effects of combination therapy in a single inhaler, assessment of the comparative effects of different doses of inhaled corticosteroids is necessary. Ongoing and future trials should allow better clarification of any additional benefits of combined therapy.

Implications for research

Assessment of budesonide/formoterol in large trials is required to assess whether this preparation confers similar benefits when compared with placebo on mortality. Combined therapy should be compared with separate administration of long acting beta-agonist and inhaled corticosteroid at different doses in a double-dummy design study in large scale multi-centre studies, in order to assess whether combined therapy confers benefits over the simple addition of beta-agonist to different doses of inhaled steroid treatment in separate inhalers. This should include an evaluation of patient compliance. A pharmacoeconomic analysis would be very helpful to assist purchasers of healthcare. Documentation of serious adverse events such as hospitalisation, intensive care support and also standardised

collection and reporting of deaths and pneumonia would offer very valuable insights in to the long-term effects of this form of therapy.

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External sources

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CHARACTERISTICS OF STUDIES

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

Barnes 2006

Methods	Parallel group design Randomisation: not clear Blinding: double blind, identical inhaler devices used Allocation concealment: unclear Excluded: not described Withdrawals: described Trial duration: 13 weeks Baseline characteristics: comparable Intention to treat analysis stated Jadad Score: 4	
Participants	**1**	Setting: 18 centres in Western and Eastern Europe.
	2	Participants randomised: 141 (two groups: FP/SAL combination: 74; placebo: 67).
	3	Baseline characteristics: 64 years. mean FEV1 L: 1.68; mean FEV1 % predicted: 59; mean FEV1 reversibility: 3.9 (of predicted)
	4	Inclusion criteria: M/F 40-80 years of age; diagnosis of COPD (according to GOLD criteria); >/= 2 on MRC dyspnea scale; poor reversibility of <10% predicted normal.
	5	Exclusion criteria: Current diagnosis of asthma; recent exacerbation (within 4 weeks); LTOT; Pulmonary rehabilitation; ICS, anti-leukotriene or tiotropium within 14 days of visit 1
Interventions	Run-in phase: 4 weeks. Treatment during this phase of the study not described	
	1	FPS 500/50mcg bid.
	2	Placebo

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	Inhaler device: DPI
Outcomes	Exacerbations; withdrawals; adverse events
Notes	
Risk of bias	

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Described as randomised; no other information available
Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	Yes	Identical inhaler devices

Calverley 2003

Methods	Parallel group study. Randomisation: unclear Blinding: double-blind (identical inhaler devices) Trial duration: 52 weeks with two week run-in of treatment optimisation. Allocation concealment: unclear Withdrawals: stated Intention to treat analysis: stated Jadad score: 4
Participants	**1** Setting: 109 centres in 15 countries **2** Participants randomised: 510 (BDF: 254; PLA: 256) Additional treatment groups not covered in this review: BUD: 257; F: 255 **3** Baseline characteristics: mean age: 64; mean FEV1 L: 1; mean FEV1 % predicted: 36; mean SGRQ: 48 **4** Inclusion criteria: GOLD defined COPD (stages III and IV); >/= 40 years; COPD symptoms >2 years; smoking history >/= 10 pack years; FEV1/VC </= 70% pre-BD; FEV1 </= 50% predicted; use of SABAs as reliever medication; >/= 1 COPD exacerbation requiring OCS/antibx 2-12 months before 1st clinic visit. **5** 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: O2 therapy; ICS - (aside from study medication), disodium cromoglycate, leukotriene-antagonists, 5-LO inhibitors, BD (other than study medication and prn terbutaline 0.5mg), antihistamines, medication containing ephedrine, ß-blocking agents
Interventions	Run-in phase: All participants received 30mg oral prednisolone BiD and 2×4.5mg formoterol BiD (2 weeks) 1) BDF: 320/9mcg bid. 2)Placebo (lactose monohydrate). Additional treatment groups not covered in this review: 3) BUD: 400mcg bid. 3) F: 9mcg bid. Inhaler device: Turbuhaler.
Outcomes	Time to first exacerbation; change in post-medication FEV1; number of exacerbations; time to and number of OCS-treated episodes; am and pm PEF, slow VC, HRQL, symptoms, use of reliever medication, AEs
Notes	Classified as 'poorly reversible population'. P values used to calculate pooled SEMs for the following outcomes: Health related quality of life; FEV1; rescue medication
Risk of bias	

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Described as randomised; no other information available
Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	Yes	Identical inhaler devices

Dal Negro 2003

Methods	Parallel group study. Randomisation: unclear Blinding: double-blind Method of randomisation: Not reported. Allocation concealment: unclear Trial duration: 52 weeks. Withdrawals: Stated. Baseline characteristics: Comparable Intention to treat analysis: Yes Jadad score: 3
Participants	**1** Setting: Single centre in Italy **2** Participants randomised: 12 (FPS: 6; PLA: 6) Additional treatment groups not covered in this review: SAL: 6 **3** Baseline characteristics: Age range: 53-78; moderate COPD; mean FEV1 (L): 1.46; mean FEV1 (% predicted): 48; mean PEF (L/min): 180; mean reversibility (% baseline): 3.2 **4** Inclusion criteria: baseline FEV1 % predicted: </= 80%; FEV1 >800 mL; FEV1/FVC ratio: </= 70% predicted; FEV1 change of </= 12% predicted post 400mg SAL; regular treatment with oral theophylline 20mg BiD; SABA prn (for at least 6 months); current/ex-smokers with smoking history of at least 10 pack years. **5** Exclusion criteria: Current evidence of asthma or other pulmonary diseases; regular treatment with ICS; unstable respiratory disease requiring oral/parenteral CS within 4 weeks prior to the beginning of the study; changes in COPD medication in last 4 weeks before entering run-in; upper/lower respiratory tract infection within 4 weeks before last screening visit; unstable angina/unstable arrhythmias; recent MI/heart failure; insulin-dependent diabetes mellitus; neuropsychiatric disorders; concurrent use of medications that affect COPD (e.g. ß-blockers), or interact with methylxanthine products, e.g. macrolides or fluoroquinolones; known/suspected hypersensitivity to ICS, ß-agonist or lactose; evidence of alcohol abuse
Interventions	Run-in: 2 weeks treatment with theophylline and prn SABA. **1** FPS 50/250 mcg bid. **2** Placebo. Additional treatment groups not covered in this review **3** SAL 50mcg bid. Participants were on concomitant therapy: SABA prn and theophylline 400ug/day, for 12 months Inhaler device: Diskus.
Outcomes	FEV1, Delta FEV1, PEF am, symptom scores, rescue medication use, exacerbations (event rate and mean number per year)
Notes	Classified as 'poorly reversible population'. Jadad score: 3 Mild exacerbation: requirement for increase in SABA prn by >2 occasions/24hrs on two or more consecutive days compared with baseline mean of last seven days of run-in Moderate exacerbation: condition requiring treatment with antibiotics and/or oral corticosteroids

	Severe exacerbation: Condition requiring emergency hospital treatment and/or hospitalisation

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Described as randomised; no other information available
Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	Yes	Identical inhaler devices

Hanania 2003

Methods	Parallel group study. Randomisation: method unclear. Blinding: double blind. Allocation concealment: unclear Excluded: described. Withdrawals: described. Trial duration: 24 weeks with 2-week run-in period. Baseline characteristics: comparable. Intention to treat analysis: not stated. Jadad score: 4
Participants	**1** Setting: USA, Multi-centre (76 hospitals) **2** Patients randomised: 368 (FPS: 183; PLA: 185). Additional treatment groups not covered in this review; SAL: 177; FP: 183 **3** Baseline characteristics: Mean age: 64; mean FEV1: 1.27L (42% predicted) **4** Inclusion criteria: stable COPD, FEV1 40-65% predicted, FEV1/FVC < 70% predicted, symptoms of chronic bronchitis and moderate dyspnoea **5** Exclusion criteria: current diagnosis of asthma, use of oral steroids in past 6 weeks, abnormal ECG, LTOT, moderate - severe exacerbation in run in. Other significant medical disorder
Interventions	Run-in: 2 weeks treatment with placebo inhaler and prn SABA. **1** FPS 50/250 mcg bid. **2** Placebo Additional treatment groups not covered in this review **3** SAL 50 mcg bid. **4** FP 250 mcg bid. Inhaler device: Diskus.
Outcomes	Lung function: Change in FEV1 from baseline to end of study (M). PEF data not stratified by reversibility. Quality of life: CRDQ, CBSQ not stratified by reversibility. Dyspnoea and symptoms: Transitional dyspnoea index, Baseline dyspnoea index not stratified by reversibility. Exacerbations. Rescue salbutamol use
Notes	FEV1 reversibility < 12% or 200ml (of baseline FEV1) Reversibility stratified data. Mean % increase non-reversible patients = 8.8

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Described as randomised; no other information available

Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	Yes	Identical inhaler devices

Mahler 2002

Methods	Parallel group study. Randomisation: stratified by reversibility and investigative site. Blinding: Double blind. Allocation concealment: unclear Excluded: described. Withdrawals: described. Trial duration: 24 weeks. Baseline characteristics: comparable Intention to treat analysis: stated Jadad score: 3
Participants	**1** Setting: Multi-centre study (65 centres) **2** Patients randomised: 346 (FPS: 165; PLA: 181). Additional treatment groups not covered in this review; SAL: 160; FP: 168. **3** Baseline characteristics: Mean age: 63; FEV1: 1.2-3 L **4** Inclusion criteria: Participants with COPD according to ATS guidelines. Baseline pre-bronchodilation FEV1 < 65% predicted and > 0.70L. Baseline pre-bronchodilation FEV1/FVC < 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. **5** Exclusion criteria: history of asthma, corticosteroid use in last 6 weeks, abnormal ECG, oxygen therapy, moderate or severe exacerbation during run-in, significant concurrent disease
Interventions	Run-in: 2 weeks treatment with placebo inhaler and prn SABA. **1** FPS 500/50 mcg bid. **2** Placebo Additional treatment groups not covered in this review: **3** SAL 50 mcg bid. **4** FP 500 mcg bd. Inhaler device: Diskus.
Outcomes	Lung function: Change in FEV1 from baseline to end of study (M). Quality of life: CRDQ, CBSQ not stratified by reversibility. Dyspnoea and symptoms: End of study dyspnoea (TDI). Exacerbations. Rescue salbutamol use
Notes	COPD subjects reversible and non-reversible, < 15% (baseline) improvement in FEV1 to salbutamol. Reversibility stratified data. Mean FEV1 reversibility 11.0%

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Described as randomised; stratified by reversibility and investigative site
Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	Yes	Identical inhaler devices

O'Donnell 2006

Methods	Parallel group design Randomisation: not clear Blinding: double blind Allocation concealment: unclear Excluded: not described Withdrawals: described Trial duration: 8 weeks Baseline characteristics: comparable Intention to treat analysis stated Jadad Score: 3
Participants	**1** Setting: 22 centres in North America **2** Participants randomised: 126 (FP/SAL: 62; placebo: 64) Additional treatment groups not covered in this review: salmeterol: 59 **3** Baseline characteristics: 65 years; FEV1: 1.12L **4** Inclusion criteria: M/F >/=40 years of age; diagnosis of COPD; >/=10 pack year; baseline Borg dyspnoea index <7; FEV1 <70% predicted; FRC >/= 120% predicted **5** Exclusion criteria: Current diagnosis of asthma; use of xanthines/ LABAs/OCS/ICS
Interventions	Run-in: 2 weeks. Single-blind placebo. **1** FPS 500/50mcg bid. **2** Placebo Additional treatment groups not covered in this review: **3** SAL 50mcg bid. Inhaler device: DPI.
Outcomes	Withdrawals; exercise time; FEV1; adverse events
Notes	Study downloaded from ctr.gsk.co.uk

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Described as randomised; no other information available
Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	Yes	Identical inhaler devices

SCO100540

Methods	Parallel group design Randomisation: not clear Blinding: double blind (identical inhaler devices) Allocation concealment: unclear Excluded: not described Withdrawals: described Trial duration: 24 weeks Baseline characteristics: comparable Intention to treat analysis: stated Jadad Score: 4
Participants	**1** Setting: 12 centres in China **2** Subjects randomised: 445 (two groups: FP/SAL combination: 297; PLA: 148) **3** Baseline characteristics: 66 years; Male: 89%

	4 Inclusion criteria: M/F 40-80 years of age; diagnosis of COPD according to GOLD criteria; <10% reversibility of predicted FEV1; FEV1/FVC ratio <70%; FEV1 <60% predicted 5 Exclusion criteria: Respiratory disease other than COPD; requirement for >12hrs/day LTOT; Received >1000mcg/d BDP; 500mcg/d FP in 4 weeks prior to run-in; hospitalisation with exacerbation of COPD
Interventions	Run-in phase: 2 weeks. Treatment during this phase of the study not described 1 FP/SAL combination 500/50mcg BID 2 Placebo Inhaler device: DPI
Outcomes	FEV1; SGRQ; Symptoms; Bronchodilator usage; Exacerbations (requirement for antibiotics; OCS and hospitalisations); withdrawals; adverse events
Notes	Study downloaded from ctr.gsk.co.uk

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Described as randomised; no other information available
Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	Yes	Identical inhaler devices

SFCT01

Methods	Parallel group design. Randomisation: not clear. Blinding: double blind. Allocation concealment: unclear. Excluded: not described. Withdrawals: described. Trial duration: 52 weeks. Baseline characteristics: comparable. Intention to treat analysis stated. Jadad Score: 3
Participants	1 Setting: 49 centres in Italy, 7 in Poland. 2 Participants randomised: 256 (FP/SAL: 131; placebo: 125) Additional treatment groups not covered in this review: fluticasone: 131. 3 Baseline characteristics: 65 years; FEV1: not reported. 4 Inclusion criteria: M/F >/=40 years of age; diagnosis of COPD; >/=10 pack year; FEV1 <70% predicted and >800ml; Reversibility <10% predicted normal (and <200ml). 5 Exclusion criteria: Not described.
Interventions	Run-in: 2 weeks. All maintenance LABA and ICS treatment ceased 1 FPS 500/50mcg bid. 2 Placebo Additional treatment groups not covered in this review: 3 FP 500mcg bid. Inhaler device: MDI
Outcomes	Withdrawals; exacerbations; FEV1; adverse events
Notes	Unpublished study downloaded from ctr.gsk.co.uk

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Described as randomised; no other information available
Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	Yes	Identical inhaler devices

Szafranski 2003

Methods	Parallel group study. Randomisation: Randomised, double-blind, placebo-controlled parallel group trial. Duration: 52 weeks. Methods of randomisation: 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: adequate. Blinding: All the Turbuhaler inhalers were identical to ensure that the patient, pharmacist and the investigator were blinded to the allocated treatment Excluded: Not stated Withdrawals: Stated Intention to treat analysis: Stated
Participants	**1** Setting: 89 centres in Central & South America, Europe and South Africa. **2** Participants: 413 (BDF: 208; PLA: 205). Additional treatment groups not covered in this review: F: 201; BUD: 198. **3** Baseline characteristics: Mean age: 64 years; mean FEV1 % predicted: 36%, mean reversibility 6% predicted normal. **4** Inclusion criteria: Age >/= 40 years; COPD for >/= 2 years; smoking history >/= 10 pack years; FEV1 </= 50% predicted; FEV1/FVC </ =70%; Symptom score >/= 2 during at least 7 days of run-in; use of bronchodilators for reliever medication; >/= 1 severe COPD exacerbation within 212 months before study entry. **5** 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 with prn SABA only. **1** BDF 320/9 mcg bid. **2** Placebo Additional treatment groups not covered in this review: **3** BUD 400ug bid. **4** F 9ug bid. Inhaler device: Turbuhaler
Outcomes	Symptoms, adverse events, exacerbations, lung function.
Notes	Classified as 'poorly reversible' subgroup. Jadad score: 5. Exacerbation defined as requirement of oral steroids and/or antibiotics and/or hospitalisation for respiratory symptoms. Mild exacerbation defined as requirement of >/= 4 inhalations per day P values used to calculate pooled SEMs for following outcomes: Symptoms; rescue medication usage

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated scheme
Allocation concealment?	Yes	At each centre, eligible patients received an enrolment code and then after run-in,

		participants were allocated the next consecutive patient number
Blinding? All outcomes	Yes	Identical inhaler devices

TORCH

Methods	Parallel group design Randomisation: Permuted block randomisation with stratification for smoking status and country Blinding: double blind (identical inhaler devices) Allocation concealment: Adequate Excluded: described Withdrawals: described Trial duration: 156 weeks Baseline characteristics: comparable Intention to treat analysis: stated Jadad Score: 5
Participants	**1** Setting: 444 centres in North America, Central America and Asia Pacific **2** Subjects randomised: 3091 (FP/SAL: 1546; PLA: 1545) Additional treatment groups not covered in this review: SAL: 1542; FP: 1551. **3** Baseline characteristics: 65 years; Male: 76% **4** Inclusion criteria: M/F 40-80 years of age; diagnosis of COPD (ERS); <10% reversibility of predicted FEV1; FEV1/FVC ratio <70%; FEV1< 60% predicted; >/=10 pack year smoking history **5** Exclusion criteria: Asthma or respiratory diseases other than COPD; LVRS/lung transplant; requirement for >12hrs/day LTOT; long term OCS 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 **1** FP/SAL combination 500/50mcg BID **2** Placebo Additional treatment groups not covered in this review: **3** FP 500mcg BID **4** SAL 50mcg BID Inhaler device: DPI
Outcomes	All cause mortality; change in SGRQ; exacerbations (requiring antibiotics, steroids, hospitalisation or combination of these); lung function; withdrawals; adverse events
Notes	

Risk of bias

Item	Authors’ judgement	Description
Adequate sequence generation?	Yes	Computer generated scheme. Permuted block randomisation with stratification for smoking status and country
Allocation concealment?	Yes	Centralised randomisation schedule
Blinding? All outcomes	Yes	Identical inhaler devices

TRISTAN

Methods	Parallel group design. Randomisation: computer generated. Numbers were generated off-site. Once a treatment number had been assigned to a participant it could not be assigned to any other participant. Blinding: Double blind. Participants received identically packaged and presented placebos. Excluded: Described. Withdrawals: Described. Trial duration: 2 week run-in period, 52 weeks treatment, 2-week follow-up Baseline characteristics: Comparable Intention to treat analysis: stated Jadad Score: 5
Participants	**1** Setting: 196 centres in Europe, South Africa and Australia. **2** Participants randomised: 719 (FPS: 358; PLA: 361) Additional treatment groups not covered in this review: SAL: 372; FP: 375. **3** Baseline characteristics: Mean age 63 years, mean FEV1 = 1.26L (44% predicted). **4** Inclusion criteria: Baseline FEV1 25 - 75% predicted; FEV1/FVC ratio </= 70%; Poor reversibility: < 10% increase of predicted FEV1 30 minutes after inhaling 400 mcg salbutamol; at least 10 pack years smoking history; history of exacerbations (at least 1 in the last year) requiring OCS and/or antibiotics. At least one episode of acute COPD per year in the previous 3 years. **5** Exclusion criteria: respiratory disorders other than COPD. Oxygen treatment, systemic corti-costeroids, high doses of inhaled corticosteroids (>1000 mcg daily beclomethasone dipropionate, budesonide or flunisolide or > 500 mcg daily fluticasone) or antibiotics in the four weeks before the 2 week run-in period
Interventions	Run-in: 2 weeks. All maintenance treatment with ICS and LABA ceased **1** FPS 50 mcg/500 mcg bid. **2** Placebo Additional treatment groups not covered in this review: **3** SAL 50 mcg bid. **4** FP 500 mcg bid. Inhaler device: DPI
Outcomes	FEV1; PEF; exercise tolerance; quality of life: SGRQ; dyspnoea and symptoms (symptom score for shortness of breath, cough and sputum production); exacerbations (defined as requirement for antibiotics, oral steroids or both); rescue salbutamol use
Notes	FEV1 reversibility (% predicted normal) Mean Reversibility (% predicted) = 3.8

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer generated randomisation schedule.
Allocation concealment?	Yes	Numbers were generated off-site. Once a treatment number had been assigned to a participant it could not be assigned to any other participant
Blinding? All outcomes	Yes	Identical inhaler device

BD: bronchodilator; BDF: Budesonide/formoterol combination; bid: twice daily; BUD: Busesonide; CBSQ: Chronic bronchitis symptom questionnaire; CRDQ: Canadian respiratory disease questionnaire; F: Formoterol; FEV1: Forced expiratory volume in one second; FP: Fluticasone; FPS: Fluticasone/salmeterol combination; FVC: Forced vital capacity; ICS: inhaled corticosteroid; LABA: long acting beta agonist; LTOT: Long-term oxygen therapy; MMRC: Modified Medical Research Council; OCS: oral corticosteroids; PLA: Placebo; PRN: as needed; SABA: short acting beta agonist SAL: Salmeterol; SGRQ: St George respiratory questionnaire;

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

Study	Reason for exclusion
Aaron 2004	Irrelevant comparison
Borgstrom 2003	Healthy volunteers
Cazzola 2000	Single-blind assessment of additive benefit of inhaled fluticasone to salmeterol. Although dosage was identical to Seretide/Advair (ie FP 500ug: SAL 50mcg), treatment was administered through separate inhalers
Cazzola 2002a	Single-blind randomised crossover study comparing combination salmeterol and fluticasone with formoterol and budesonide - excluded as duration of study was too short (12 hours)
Cazzola 2003	Acute phase COPD.
Cazzola 2004	Randomised trial comparing combination salmeterol/fluticasone with separately administered fluticasone and theophylline for 4 months. Excluded as the comparison was not within the scope of the review
Cazzola 2004b	The duration of this study was too short (<1 week).
Chapman 2002	Review article.
Donohue 2004	Irrelevant comparison
Kardos 2007	Comparison of combination therapy long-acting beta-agonist
Noschese 2003	Non-randomised study.
SAM40116	Within study treatment group imbalances in dosage of steroids/combination therapy based upon historical steroid dose
SCO100470	Comparison of combination therapy long-acting beta-agonist
SCO40034	Comparison of tiotropium and combination therapy
Soriano 2002	Non-randomised retrospective survival analysis.
Sun 2004	Irrelevant comparison
Vestbo 2004	Review article.
Wouters 2005	Study excluded as it assessed the withdrawal of FP from combination therapy

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

Morgan 2004

Trial name or title	None given
Methods	
Participants	People with COPD
Interventions	Combination versus single administration of ICS and LABA
Outcomes	
Starting date	
Contact information	
Notes	

DATA AND ANALYSES

Comparison 1
Combined inhalers versus Placebo (Primary Outcomes)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Exacerbation Rates with combined inhalers v. placebo	5		Rate Ratio (Fixed, 95% CI)	0.74 [0.69, 0.79]
1.1 Fluticasone/salmeterol	3		Rate Ratio (Fixed, 95% CI)	0.74 [0.69, 0.80]
1.2 Budesonide/formoterol	2		Rate Ratio (Fixed, 95% CI)	0.74 [0.62, 0.88]
2 Mortality	7	5752	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.65, 0.96]
2.1 Fluticasone/salmeterol	5	4829	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.65, 0.97]
2.2 Budesonide/formoterol	2	923	Odds Ratio (M-H, Fixed, 95% CI)	0.78 [0.35, 1.73]
3 Pneumonia	8	5739	Odds Ratio (M-H, Fixed, 95% CI)	1.83 [1.51, 2.21]
3.1 FPS	7	5229	Odds Ratio (M-H, Fixed, 95% CI)	1.80 [1.48, 2.18]
3.2 BDF	1	510	Odds Ratio (M-H, Fixed, 95% CI)	4.13 [0.87, 19.64]

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

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants with one or more exacerbation	5	1235	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.67, 1.15]
1.1 Reversible population	1	126	Odds Ratio (M-H, Fixed, 95% CI)	0.32 [0.06, 1.66]
1.2 Partially reversible population (mixed population)	2	713	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.69, 1.44]
1.3 Poorly reversible population	2	396	Odds Ratio (M-H, Fixed, 95% CI)	0.80 [0.53, 1.21]
2 End of treatment mean number of exacerbations per participant	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 Partially reversible population (mixed population)	0		Mean Difference (IV, Fixed, 95% CI)	Not estimable
2.2 Poorly reversible population	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
3 Exacerbations	3		Rate ratio (Fixed, 95% CI)	0.74 [0.69, 0.80]
3.1 Partially reversible population (mixed population)	0		Rate ratio (Fixed, 95% CI)	Not estimable
3.2 Poorly reversible population	3		Rate ratio (Fixed, 95% CI)	0.74 [0.69, 0.80]
4 Number of exacerbations by type	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Requirement for oral steroids	2	417	Odds Ratio (M-H, Fixed, 95% CI)	1.01 [0.61, 1.68]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.2 Requirement for antibiotic treatment	1	140	Odds Ratio (M-H, Fixed, 95% CI)	0.80 [0.26, 2.44]
4.3 Requirement for oral steroid or antibiotic treatment	1	140	Odds Ratio (M-H, Fixed, 95% CI)	3.32 [0.13, 82.80]
4.4 Hospitalisation	1	140	Odds Ratio (M-H, Fixed, 95% CI)	3.32 [0.13, 82.80]
5 Exacerbations by type	3		Rate ratio (Fixed, 95% CI)	Subtotals only
5.1 Requirement for oral steroids	3		Rate ratio (Fixed, 95% CI)	0.57 [0.52, 0.63]
5.2 Requirement for antibiotic treatment	1		Rate ratio (Fixed, 95% CI)	0.60 [0.43, 0.84]
5.3 Requirement for oral steroid or antibiotic treatment	0		Rate ratio (Fixed, 95% CI)	Not estimable
5.4 Hospitalisation	2		Rate ratio (Fixed, 95% CI)	0.83 [0.70, 0.97]
6 Mortality	5	4829	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.65, 0.97]
6.1 Mortality: three year data	1	3057	Odds Ratio (M-H, Fixed, 95% CI)	0.81 [0.66, 0.99]
6.2 Mortality: >one and <three year data	0	0	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
6.3 Mortality: one year data	3	1426	Odds Ratio (M-H, Fixed, 95% CI)	0.63 [0.21, 1.90]
6.4 Mortality: 6 month data	1	346	Odds Ratio (M-H, Fixed, 95% CI)	0.15 [0.01, 3.01]
7 Change from baseline in St George's Respiratory Questionnaire (total score)	4		SGRQ units (Fixed, 95% CI)	−2.90 [−3.61, −2.18]
7.1 Partially reversible population (mixed population)	0		SGRQ units (Fixed, 95% CI)	Not estimable
7.2 Poorly reversible population	4		SGRQ units (Fixed, 95% CI)	−2.90 [−3.61, −2.18]
8 Change from baseline in St George's Respiratory Questionnaire (domain - symptoms)	1		SGRQ units (Fixed, 95% CI)	Totals not selected
8.1 Partially reversible population (mixed population)	0		SGRQ units (Fixed, 95% CI)	Not estimable
8.2 Poorly reversible population	1		SGRQ units (Fixed, 95% CI)	Not estimable
9 Change from baseline in St George's Respiratory Questionnaire (domain - activity)	1		SGRQ units (Fixed, 95% CI)	Totals not selected
9.1 Partially reversible population (mixed population)	0		SGRQ units (Fixed, 95% CI)	Not estimable
9.2 Poorly reversible population	1		SGRQ units (Fixed, 95% CI)	Not estimable
10 Change from baseline in St George's Respiratory Questionnaire (domain - impact)	1		SGRQ units (Fixed, 95% CI)	Totals not selected
10.1 Partially reversible population (mixed population)	0		SGRQ units (Fixed, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.2 Poorly reversible population	1		SGRQ units (Fixed, 95% CI)	Not estimable
11 End of treatment St George's Respiratory Questionnaire scores (total score)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
11.1 Partially reversible population (mixed population)	0		Mean Difference (IV, Fixed, 95% CI)	Not estimable
11.2 Poorly reversible population	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
12 End of treatment St George's Respiratory Questionnaire scores (domain - breathlessness)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
12.1 Partially reversible population (mixed population)	0		Mean Difference (IV, Fixed, 95% CI)	Not estimable
12.2 Poorly reversible population	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
13 Change from baseline in Canadian Respiratory Disease Questionnaire scores	2	712	Mean Difference (IV, Fixed, 95% CI)	5.0 [2.48, 7.52]
13.1 Partially reversible population (mixed population)	2	712	Mean Difference (IV, Fixed, 95% CI)	5.0 [2.48, 7.52]
13.2 Poorly reversible population	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
14 Change from baseline in Transitional Dyspnoea Index (TDI) scores	2	707	Mean Difference (IV, Fixed, 95% CI)	1.04 [0.56, 1.53]
14.1 Partially reversible population (mixed population)	2	707	Mean Difference (IV, Fixed, 95% CI)	1.04 [0.56, 1.53]
14.2 Poorly reversible population	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
15 End of treatment symptom scores	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
15.1 Partially reversible population (mixed population)	0		Mean Difference (IV, Fixed, 95% CI)	Not estimable
15.2 Poorly reversible population	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
16 Change from baseline in predose FEV1	5		Litres (Fixed, 95% CI)	0.16 [0.14, 0.19]
16.1 Reversible population	3		Litres (Fixed, 95% CI)	0.19 [0.15, 0.24]
16.2 Partially reversible population (mixed population)	0		Litres (Fixed, 95% CI)	Not estimable
16.3 Poorly reversible population	4		Litres (Fixed, 95% CI)	0.15 [0.11, 0.18]
16.4 Unclear reversibility	0		Litres (Fixed, 95% CI)	Not estimable
17 Change from baseline in postdose FEV1	1		Litres (Fixed, 95% CI)	Totals not selected
17.1 Reversible population	0		Litres (Fixed, 95% CI)	Not estimable
17.2 Partially reversible population (mixed population)	0		Litres (Fixed, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
17.3 Poorly reversible population	1		Litres (Fixed, 95% CI)	Not estimable
17.4 Unclear reversibility	0		Litres (Fixed, 95% CI)	Not estimable
18 End of treatment FEV1 (% predicted)	1		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
18.1 Partially reversible population (mixed population)	0		Std. Mean Difference (IV, Fixed, 95% CI)	Not estimable
18.2 Poorly reversible population	1		Std. Mean Difference (IV, Fixed, 95% CI)	Not estimable
19 End of treatment FEV1 (Litres)	2		Litres (Fixed, 95% CI)	0.13 [0.10, 0.16]
19.1 Partially reversible population (mixed population)	0		Litres (Fixed, 95% CI)	Not estimable
19.2 Poorly reversible population	2		Litres (Fixed, 95% CI)	0.13 [0.10, 0.16]
20 End of treatment am PEF (L/min)	1		L/min (Fixed, 95% CI)	Totals not selected
20.1 Partially reversible population (mixed population)	0		L/min (Fixed, 95% CI)	Not estimable
20.2 Poorly reversible population	1		L/min (Fixed, 95% CI)	Not estimable
21 End of treatment shuttle walk test	1		Metres (Fixed, 95% CI)	Totals not selected
21.1 Partially reversible population (mixed population)	0		Metres (Fixed, 95% CI)	Not estimable
21.2 Poorly reversible population	1		Metres (Fixed, 95% CI)	Not estimable
22 End of treatment rescue medication usage (puffs/day)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
22.1 Partially reversible population (mixed population)	0		Mean Difference (IV, Fixed, 95% CI)	Not estimable
22.2 Poorly reversible population	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
23 Change from baseline in rescue medication usage (puffs/day)	2	703	Mean Difference (IV, Fixed, 95% CI)	−1.19 [−1.83, −0.55]
23.1 Partially reversible population (mixed population)	2	703	Mean Difference (IV, Fixed, 95% CI)	−1.19 [−1.83, −0.55]
23.2 Poorly reversible population	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
24 Adverse events - any event	8	5493	Odds Ratio (M-H, Fixed, 95% CI)	1.10 [0.96, 1.27]
24.1 Reversible population	1	126	Odds Ratio (M-H, Fixed, 95% CI)	1.20 [0.59, 2.46]
24.2 Partially reversible population (mixed population)	2	717	Odds Ratio (M-H, Fixed, 95% CI)	1.42 [1.03, 1.96]
24.3 Poorly reversible population	5	4650	Odds Ratio (M-H, Fixed, 95% CI)	1.03 [0.88, 1.21]
25 Adverse events - candidiasis	6	1958	Odds Ratio (M-H, Fixed, 95% CI)	5.73 [3.07, 10.67]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
25.1 Reversible population	1	126	Odds Ratio (M-H, Fixed, 95% CI)	1.03 [0.06, 16.88]
25.2 Partially reversible population (mixed population)	2	717	Odds Ratio (M-H, Fixed, 95% CI)	11.13 [3.36, 36.90]
25.3 Poorly reversible population	3	1115	Odds Ratio (M-H, Fixed, 95% CI)	4.40 [2.01, 9.62]
25.4 Unclear reversibility	0	0	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
26 Withdrawals due to adverse events	8	5110	Odds Ratio (M-H, Fixed, 95% CI)	0.76 [0.65, 0.88]
26.1 Partially reversible population (mixed population)	1	354	Odds Ratio (M-H, Fixed, 95% CI)	0.69 [0.31, 1.51]
26.2 Poorly reversible population	6	4630	Odds Ratio (M-H, Fixed, 95% CI)	0.76 [0.65, 0.89]
26.3 Unclear reversibility	1	126	Odds Ratio (M-H, Fixed, 95% CI)	0.34 [0.01, 8.47]
27 Withdrawals due to lack of efficacy/exacerbations	5	4620	Odds Ratio (M-H, Fixed, 95% CI)	0.30 [0.21, 0.42]
27.1 Partially reversible population (mixed population)	0	0	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
27.2 Poorly reversible population	5	4620	Odds Ratio (M-H, Fixed, 95% CI)	0.30 [0.21, 0.42]
27.3 Unclear reversibility	0	0	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
28 Withdrawals	8	5450	Odds Ratio (M-H, Fixed, 95% CI)	0.70 [0.62, 0.78]
28.1 Reversible population	1	121	Odds Ratio (M-H, Fixed, 95% CI)	2.95 [0.30, 29.18]
28.2 Partially reversible population (mixed population)	2	709	Odds Ratio (M-H, Fixed, 95% CI)	0.82 [0.60, 1.13]
28.3 Poorly reversible population	5	4620	Odds Ratio (M-H, Fixed, 95% CI)	0.68 [0.60, 0.76]
28.4 Unclear reversibility	0	0	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
29 Adverse events - pneumonia	7	5229	Odds Ratio (M-H, Fixed, 95% CI)	1.80 [1.48, 2.18]
29.1 Reversible population	1	126	Odds Ratio (M-H, Fixed, 95% CI)	0.34 [0.01, 8.47]
29.2 Partially reversible population (mixed population)	2	709	Odds Ratio (M-H, Fixed, 95% CI)	5.55 [0.26, 116.46]
29.3 Poorly reversible population	4	4394	Odds Ratio (M-H, Fixed, 95% CI)	1.80 [1.48, 2.18]
29.4 Unclear reversibility	0	0	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
30 Adverse events - nasopharyngitis	2	3535	Odds Ratio (M-H, Fixed, 95% CI)	1.28 [1.05, 1.56]
30.1 Partially reversible population (mixed population)	0	0	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
30.2 Poorly reversible population	2	3535	Odds Ratio (M-H, Fixed, 95% CI)	1.28 [1.05, 1.56]
30.3 Unclear reversibility	0	0	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
31 Adverse events - pharyngolaryngeal pain	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
31.1 Partially reversible population (mixed population)	0		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
31.2 Poorly reversible population	1		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
31.3 Unclear reversibility	0		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
32 Adverse events - upper respiratory tract infection	5	4963	Odds Ratio (M-H, Fixed, 95% CI)	1.23 [1.04, 1.47]
32.1 Partially reversible population (mixed population)	2	709	Odds Ratio (M-H, Fixed, 95% CI)	1.25 [0.81, 1.92]
32.2 Poorly reversible population	3	4254	Odds Ratio (M-H, Fixed, 95% CI)	1.23 [1.02, 1.48]
32.3 Unclear reversibility	0	0	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
33 Adverse events - headache	5	4367	Odds Ratio (M-H, Fixed, 95% CI)	1.06 [0.85, 1.32]
33.1 Reversible population	1	123	Odds Ratio (M-H, Fixed, 95% CI)	0.22 [0.02, 2.01]
33.2 Partially reversible population (mixed population)	2	709	Odds Ratio (M-H, Fixed, 95% CI)	1.38 [0.91, 2.10]
33.3 Poorly reversible population	2	3535	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.75, 1.27]
33.4 Unclear reversibility	0	0	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
34 Adverse events - hoarseness	2	585	Odds Ratio (M-H, Fixed, 95% CI)	8.79 [1.11, 69.62]
34.1 Partially reversible population (mixed population)	0	0	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
34.2 Poorly reversible population	2	585	Odds Ratio (M-H, Fixed, 95% CI)	8.79 [1.11, 69.62]
34.3 Unclear reversibility	0	0	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
35 Adverse events - pyrexia	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
35.1 Partially reversible population (mixed population)	0		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
35.2 Poorly reversible population	1		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
35.3 Unclear reversibility	0		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
36 Adverse events - cough	4	1057	Odds Ratio (M-H, Fixed, 95% CI)	0.61 [0.29, 1.29]
36.1 Reversible population	1	126	Odds Ratio (M-H, Fixed, 95% CI)	3.15 [0.13, 78.72]
36.2 Partially reversible population (mixed population)	1	346	Odds Ratio (M-H, Fixed, 95% CI)	0.49 [0.18, 1.31]
36.3 Poorly reversible population	2	585	Odds Ratio (M-H, Fixed, 95% CI)	0.66 [0.18, 2.44]
36.4 Unclear reversibility	0	0	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
37 Adverse events - palpitations	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
37.1 Partially reversible population (mixed population)	0		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
37.2 Poorly reversible population	1		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
37.3 Unclear reversibility	0		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
38 Adverse events - mouth ulceration	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
38.1 Partially reversible population (mixed population)	0		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
38.2 Poorly reversible population	1		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
38.3 Unclear reversibility	0		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
39 Adverse events - toothache	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
39.1 Partially reversible population (mixed population)	0		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
39.2 Poorly reversible population	1		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
39.3 Unclear reversibility	0		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
40 Adverse events - urinary tract infection	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
40.1 Partially reversible population (mixed population)	0		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
40.2 Poorly reversible population	1		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
40.3 Unclear reversibility	0		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
41 Adverse events - dyspnoea	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
41.1 Partially reversible population (mixed population)	0		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
41.2 Poorly reversible population	1		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
41.3 Unclear reversibility	0		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
42 Adverse events - blood glucose increased	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
42.1 Partially reversible population (mixed population)	0		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
42.2 Poorly reversible population	1		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
42.3 Unclear reversibility	0		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
43 Adverse events - insomnia	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
43.1 Partially reversible population (mixed population)	0		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
43.2 Poorly reversible population	1		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
43.3 Unclear reversibility	0		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
44 Adverse events - bronchitis	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
44.1 Partially reversible population (mixed population)	0		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
44.2 Poorly reversible population	1		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
44.3 Unclear reversibility	0		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable

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

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Severe Exacerbations	2		Rate ratio (Fixed, 95% CI)	0.74 [0.62, 0.88]
1.1 Partially reversible	0		Rate ratio (Fixed, 95% CI)	Not estimable
1.2 Poorly reversible	2		Rate ratio (Fixed, 95% CI)	0.74 [0.62, 0.88]
2 Mean severe exacerbation rates per patient per year	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 Partially reversible population (mixed population)	0		Mean Difference (IV, Fixed, 95% CI)	Not estimable
2.2 Poorly reversible population	2		Mean Difference (IV, Fixed, 95% CI)	Not estimable
3 Quality of life - SGRQ (change scores)	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 Partially reversible population (mixed population)	0		Mean Difference (IV, Fixed, 95% CI)	Not estimable
3.2 Poorly reversible population	2		Mean Difference (IV, Fixed, 95% CI)	Not estimable
4 Quality of life - change scores	2		SGRQ (Fixed, 95% CI)	−6.06 [−7.90, −4.22]
4.1 Partially reversible (mixed population)	0		SGRQ (Fixed, 95% CI)	Not estimable
4.2 Poorly reversible	2		SGRQ (Fixed, 95% CI)	−6.06 [−7.90, −4.22]
5 Rescue medication usage	2		Puffs per day (Fixed, 95% CI)	−0.87 [−1.15, −0.58]
5.1 Partially reversible (mixed population)	0		Puffs per day (Fixed, 95% CI)	Not estimable
5.2 Poorly reversible	2		Puffs per day (Fixed, 95% CI)	−0.87 [−1.15, −0.58]
6 Symptoms (change scores)	2		Symptom scale (Fixed, 95% CI)	−0.63 [−0.90, −0.37]
6.1 Partially reversible (mixed population)	0		Symptom scale (Fixed, 95% CI)	Not estimable
6.2 Poorly reversible	2		Symptom scale (Fixed, 95% CI)	−0.63 [−0.90, −0.37]
7 Mean FEV1 (% change from baseline)	2		% increase (Fixed, 95% CI)	14.40 [11.91, 16.90]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Partially reversible (mixed population)	0		% increase (Fixed, 95% CI)	Not estimable
7.2 Poorly reversible	2		% increase (Fixed, 95% CI)	14.40 [11.91, 16.90]
8 Adverse events - 'serious events'	2	923	Odds Ratio (M-H, Fixed, 95% CI)	1.06 [0.78, 1.45]
8.1 Partially reversible population (mixed population)	0	0	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
8.2 Poorly reversible population	2	923	Odds Ratio (M-H, Fixed, 95% CI)	1.06 [0.78, 1.45]
9 Adverse events - candidiasis	0		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
9.1 Partially reversible population (mixed population)	0		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
9.2 Poorly reversible population	0		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
10 Adverse events - pneumonia	1	510	Odds Ratio (M-H, Fixed, 95% CI)	4.13 [0.87, 19.64]
11 Withdrawals due to worsening COPD symptoms	2	923	Odds Ratio (M-H, Fixed, 95% CI)	0.40 [0.28, 0.58]
11.1 Partially reversible population (mixed population)	0	0	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
11.2 Poorly reversible population	2	923	Odds Ratio (M-H, Fixed, 95% CI)	0.40 [0.28, 0.58]
12 Withdrawals due to adverse events	2	923	Odds Ratio (M-H, Fixed, 95% CI)	1.30 [0.78, 2.18]
12.1 Partially reversible population (mixed population)	0	0	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
12.2 Poorly reversible population	2	923	Odds Ratio (M-H, Fixed, 95% CI)	1.30 [0.78, 2.18]
13 Mortality	2	923	Odds Ratio (M-H, Fixed, 95% CI)	0.78 [0.35, 1.73]
13.1 Mortality as primary outcome	0	0	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
13.2 Mortality data collected as secondary/ unpublished outcome	2	923	Odds Ratio (M-H, Fixed, 95% CI)	0.78 [0.35, 1.73]

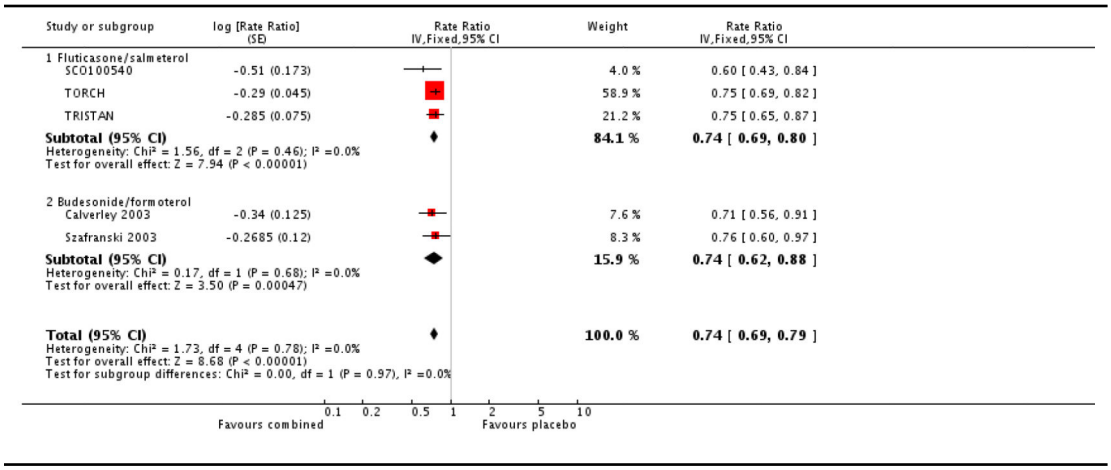
Analysis 1.1

Comparison 1 Combined inhalers versus Placebo (Primary Outcomes), Outcome 1 Exacerbation Rates with combined inhalers v. placebo

Review: Combined corticosteroid and long-acting beta-agonist in one inhaler versus placebo for chronic obstructive pulm onary disease

Comparison: 1 Combined inhalers versus Placebo (Primaiy Outcomes)

Outcome: 1 Exacebation Rates with combined inhalers v. placebo



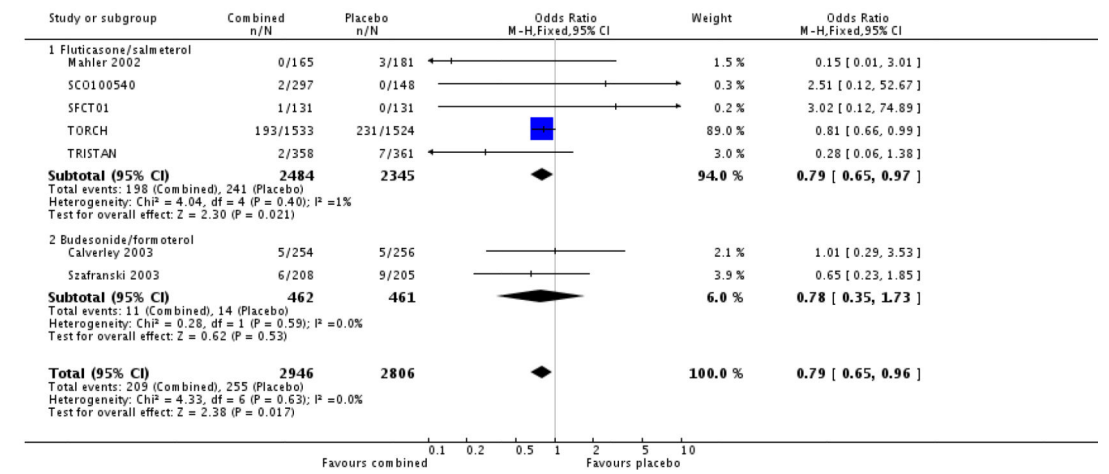
Analysis 1.2

Comparison 1 Combined inhalers versus Placebo (Primary Outcomes), Outcome 2 Mortality

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

Comparison: 1 Combined inhalers versus Placebo (Primaiy Outcomes)

Outcome: 2 Mortality



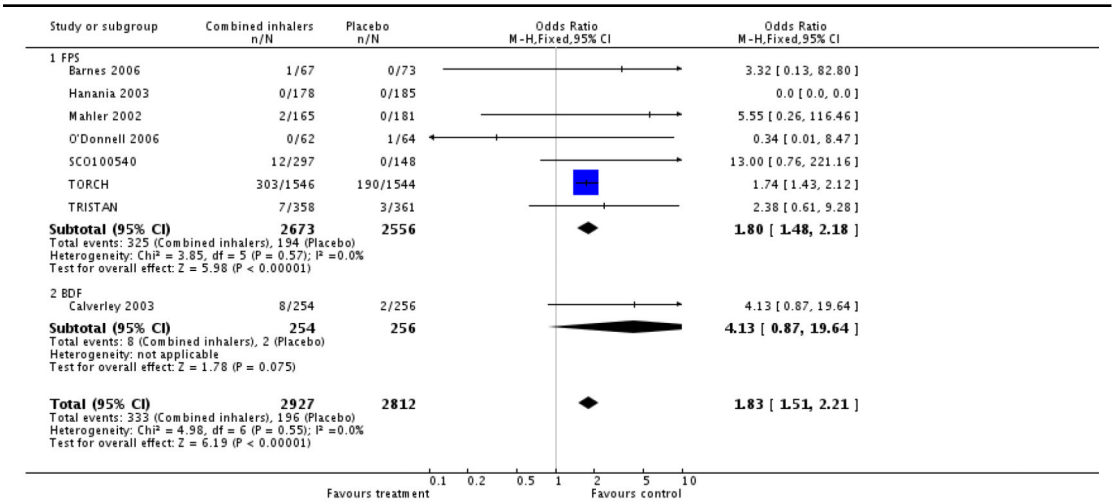
Analysis 1.3

Comparison 1 Combined inhalers versus Placebo (Primary Outcomes), Outcome 3 Pneumonia

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

Comparison: 1 Combined inhalers versus Placebo (Primary Outcomes)

Outcome: 3 Pneumonia



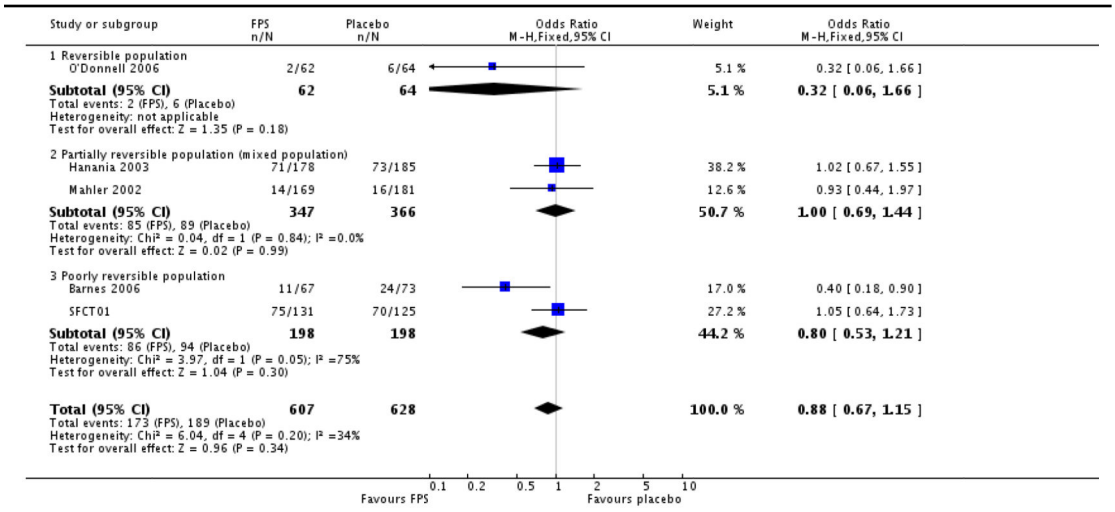
Analysis 2.1

Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 1 Number of participants with one or more exacerbation

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

Comparison: 2 Fluticasone/salmeterol (FPS) versus placebo (PLS)

Outcome: 1 Number of participants with one or more exacerbation



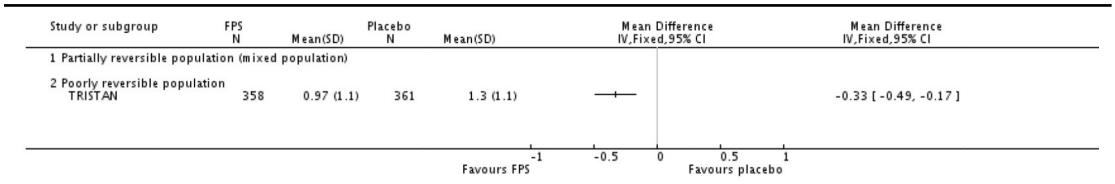
Analysis 2.2

Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 2 End of treatment mean number of exacerbations per participant

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

Comparison: 2 Fluticasone/salmeterol (FPS) versus placebo (PLS)

Outcome: 2 End of treatment mean number of exacerbations per paiticipant



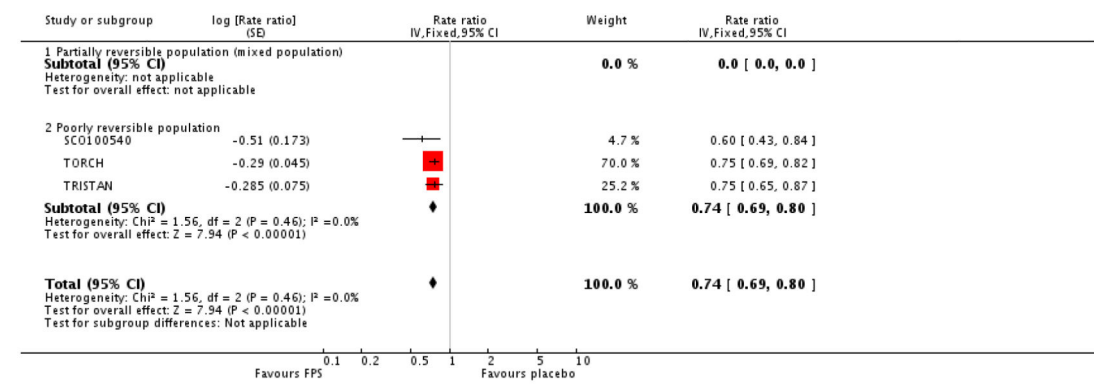
Analysis 2.3

Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 3 Exacerbations

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

Comparison: 2 Fluticasone/salmeterol (FPS) versus placebo (PLS)

Outcome: 3 Exacerbations



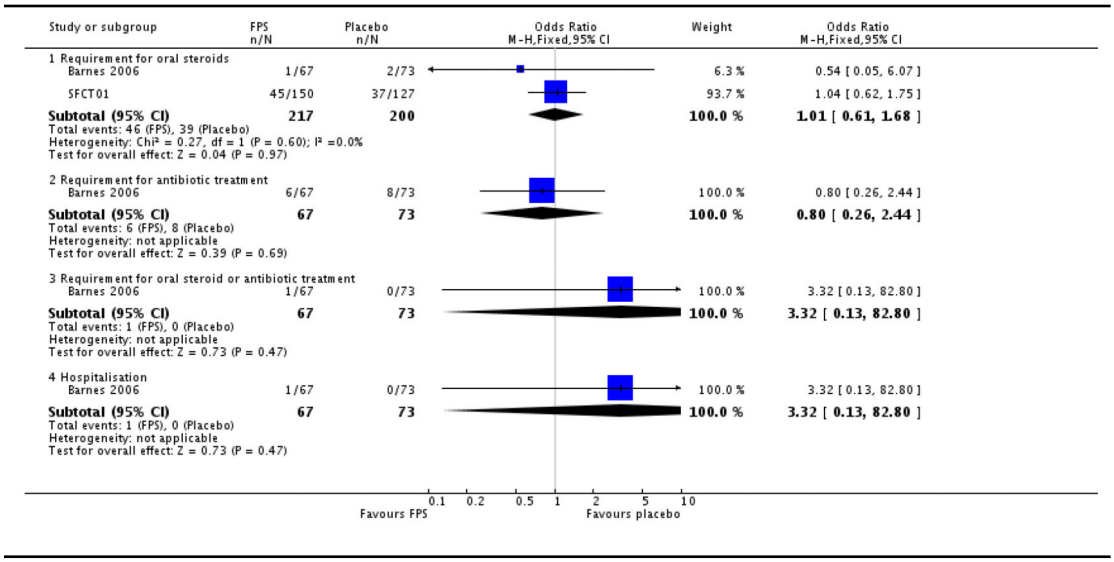
Analysis 2.4

Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 4 Number of exacerbations type

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

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

Outcome: 4 Number of exacerbations by type



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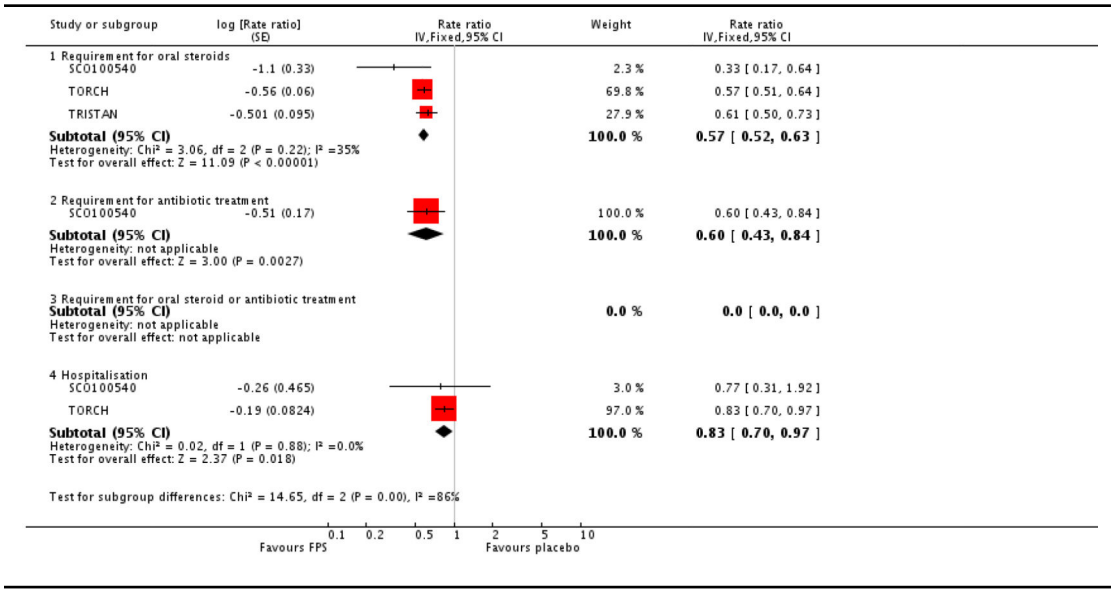
Analysis 2.5

Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 5 Exacerbations type

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

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

Outcome: 5 Exacerbations by type



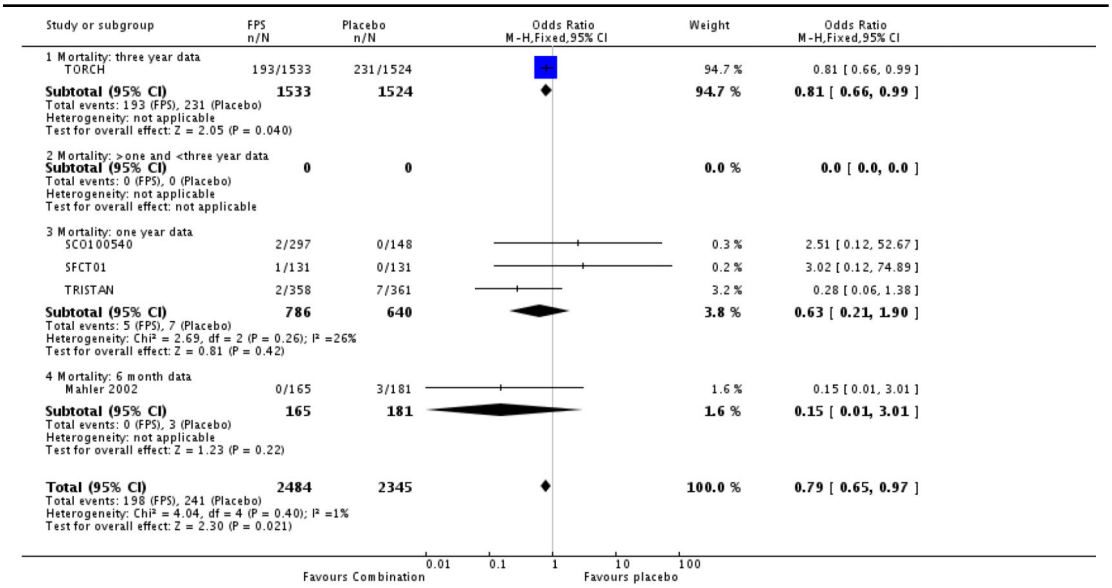
Analysis 2.6

Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 6 Mortality

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

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

Outcome: 6 Mortality



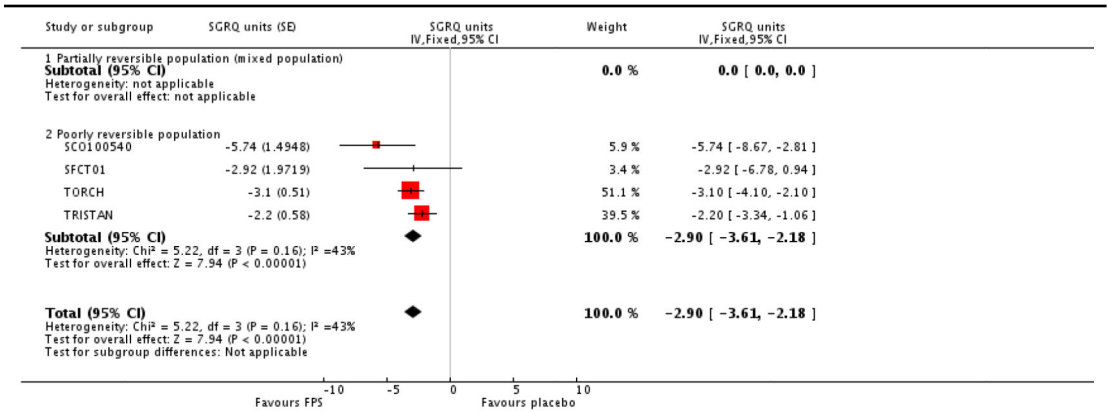
Analysis 2.7

Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 7 Change from baseline in St George's Respiratory Questionnaire (total score)

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

Comparison: 2 Fluticasone/salmeterol (FPS) versus placebo (PLS)

Outcome: 7 Change from baseline in St George's Respiratory Questionnaire (total score)



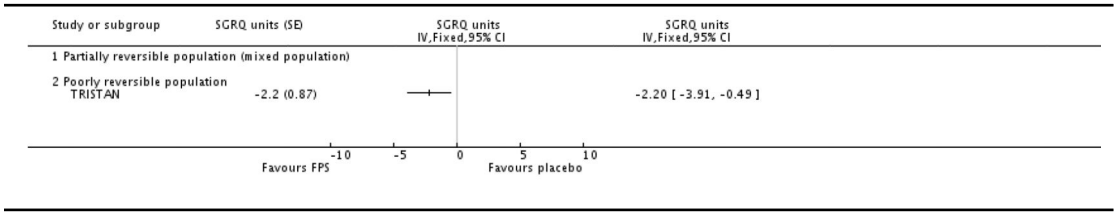
Analysis 2.8

Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 8 Change from baseline in St George's Respiratory Questionnaire (domain - symptoms)

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

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

Outcome: 8 Change from baseline in St George's Respiratory Questionnaire (domain - symptoms)



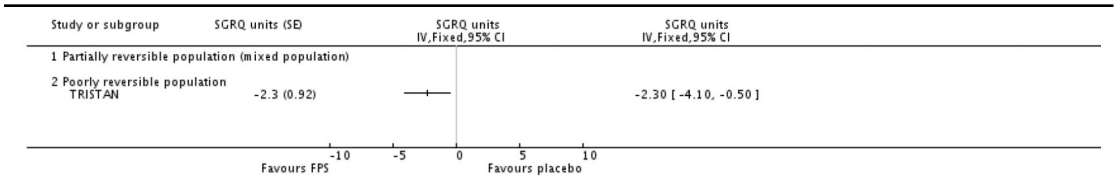
Analysis 2.9

Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 9 Change from baseline in St George's Respiratory Questionnaire (domain - symptoms)

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

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

Outcome: 9 Change from baseline in St George's Respiratory Questionnaire (domain - symptoms)



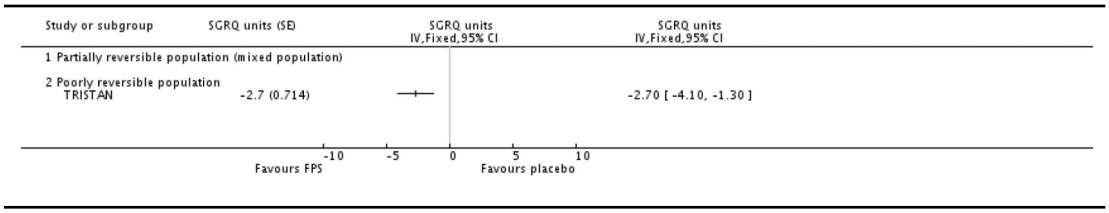
Analysis 2.10

Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 10 Change from baseline in St George's Respiratory Questionnaire (domain - impact)

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

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

Outcome: 10 Change from baseline in St George's Respiratory Questionnaire (domain - impact)



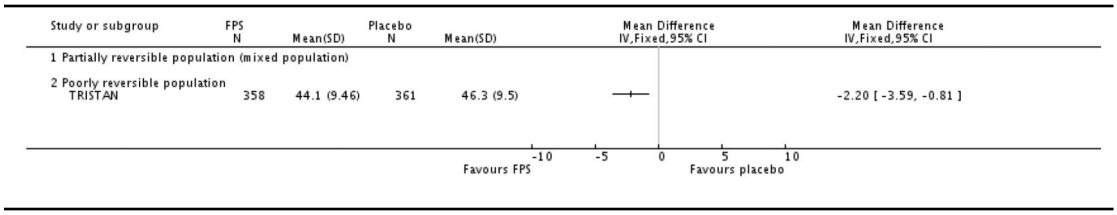
Analysis 2.11

Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 11 End of treatment St George's Respiratory Questionnaire scores (total score)

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

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

Outcome: 11 End of treatment St George's Respiratory Questionnaire scores (total score)



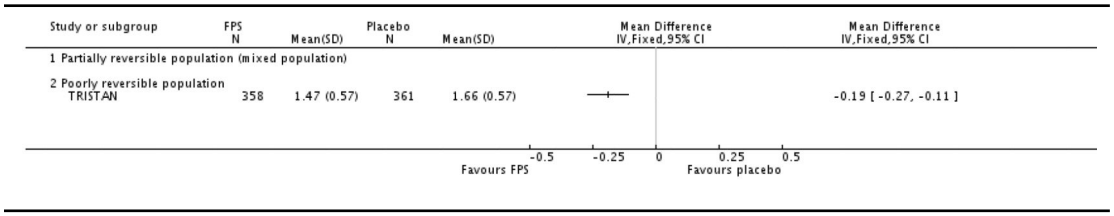
Analysis 2.12

Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 12 End of treatment St George's Respiratory Questionnaire scores (domain - breathlessness)

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

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

Outcome: 12 End of treatm ent St George's Respiratory Questionnaire scores (domain - breathlessness)



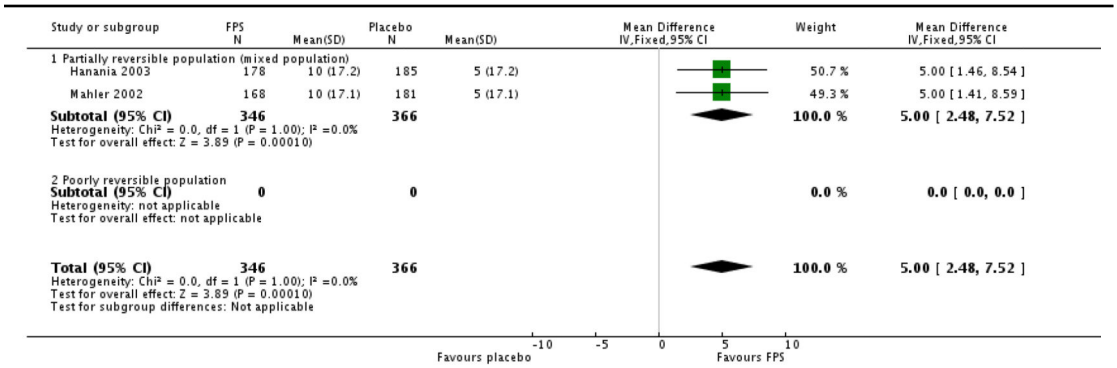
Analysis 2.13

Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 13 Change from baseline in Canadian Respiratory Disease Questionnaire scores

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

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

Outcome: 13 Change from baseline in Canadian Respiratoiy Disease Questionnaire scores



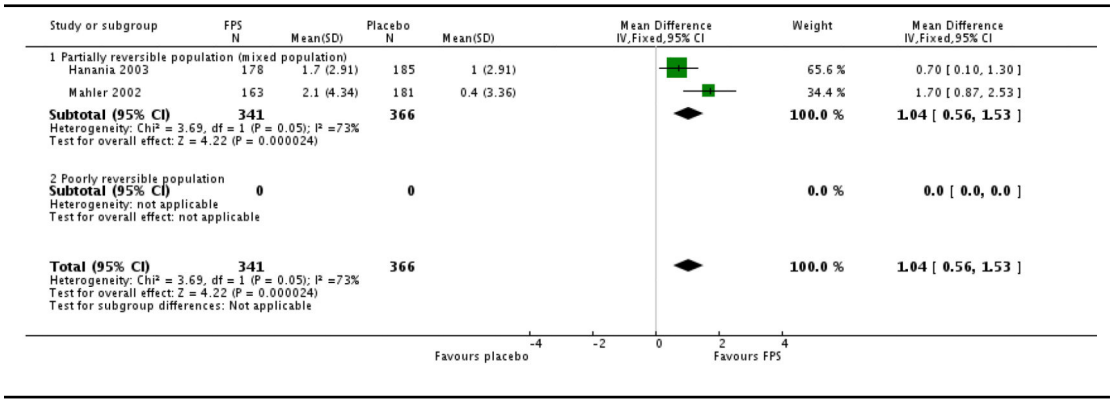
Analysis 2.14

Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 14 Change from baseline in Transitional Dyspnoea Index (TDI)

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

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

Outcome: 14 Change from baseline in Transitional Dyspnoea Index (TDI) scores



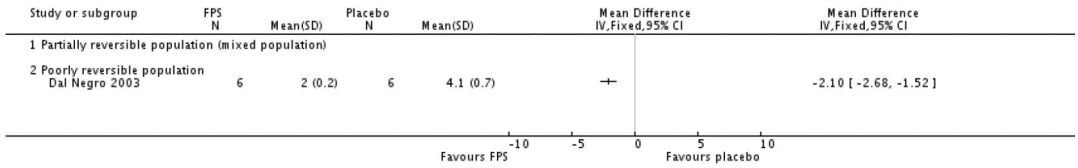
Analysis 2.15

Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 15 End of treatment symptom scores

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

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

Outcome: 15 End of treatment symptom scores



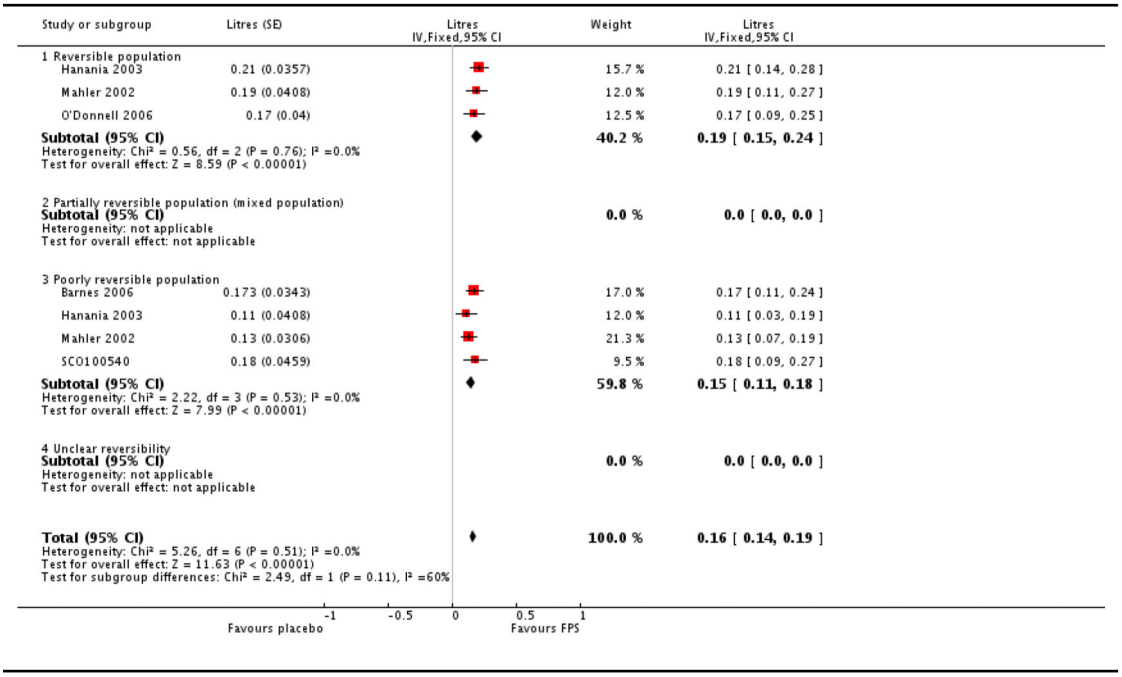
Analysis 2.16

Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 16 Change from baseline in predose FEV1

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

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

Outcome: 16 Change from baseline in predose FEV1



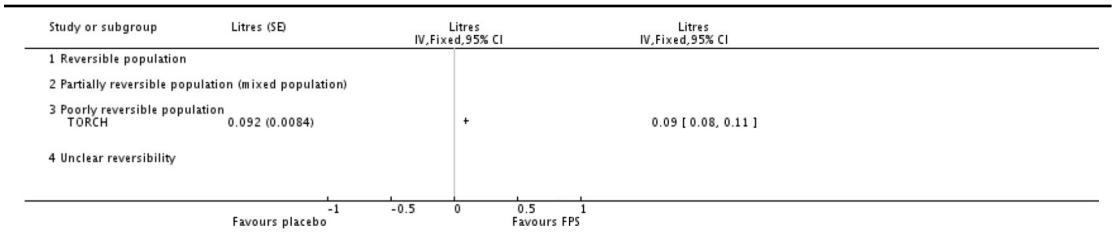
Analysis 2.17

Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 17 Change from baseline in postdose FEV1

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

Comparison: 2 Fluticasone/salm eterol (FPS) versus placebo (PLA)

Outcome: 17 Change from baseline in postdose FEV1



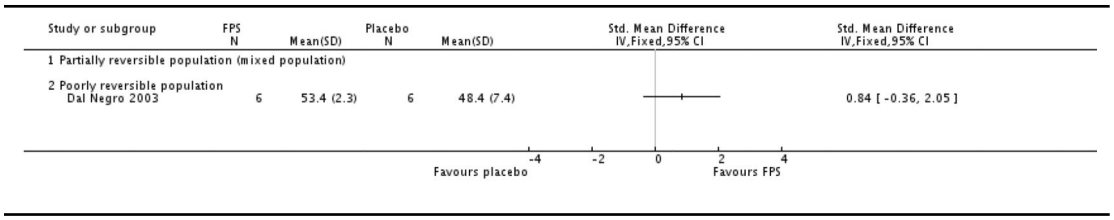
Analysis 2.18

Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 18 End of treatment FEV1 (% predicted)

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

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

Outcome: 18 End of treatment FEV1 (% predicted)



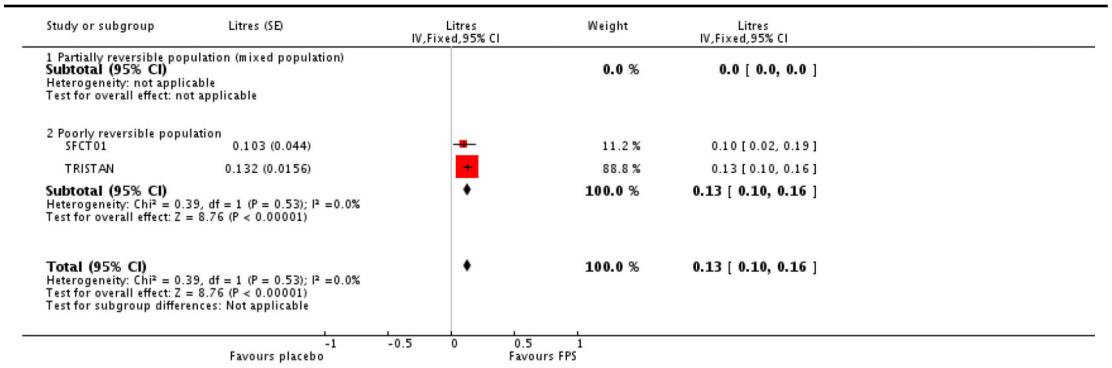
Analysis 2.19

Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 19 End of treatment FEV1 (Litres)

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

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

Outcome: 19 End of treatment FEV1 (Litres)



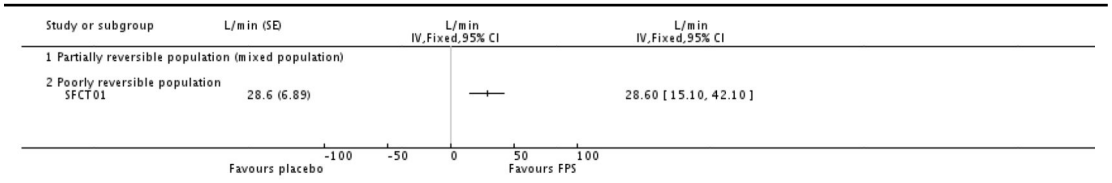
Analysis 2.20

Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 20 End of treatment am PEF (L/min)

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

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

Outcome: 20 End of treatment am PEF (L/min)



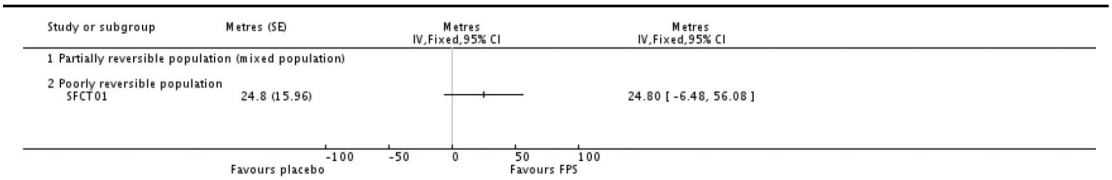
Analysis 2.21

Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 21 End of treatment shuttle walk test

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

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

Outcome: 21 End of treatment shuttle walk test



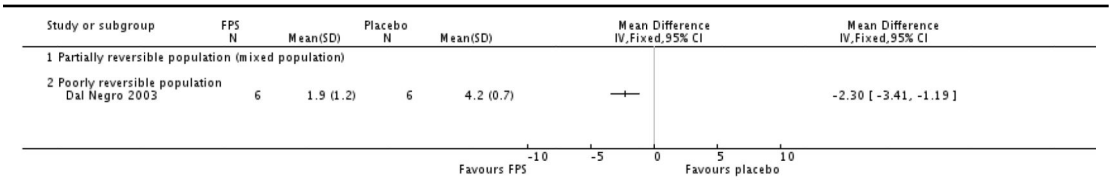
Analysis 2.22

Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 2 End of treatment rescue medication usage (puffs/day)

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

Comparison: 2 Fluticasone/salmeterol (FPS) versus placebo (PLS)

Outcome: 22 End of treatment rescue medication usage (puffs/day)



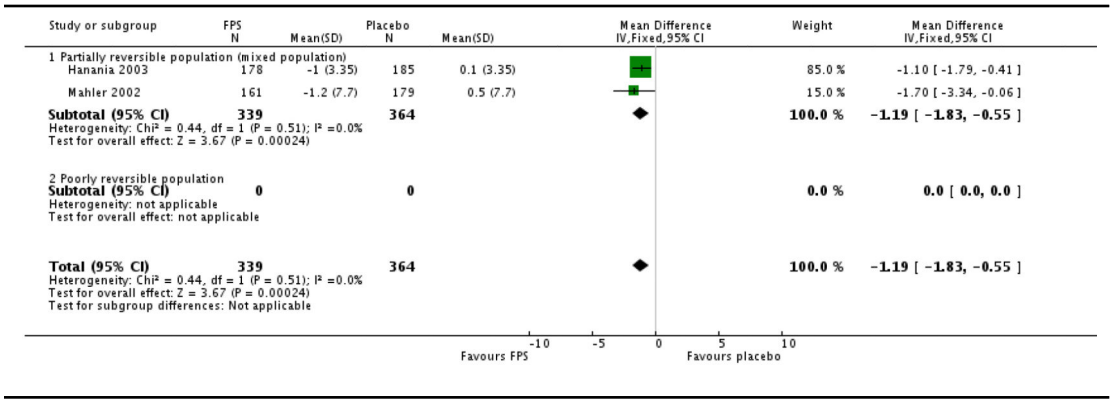
Analysis 2.23

Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 23 Change from baseline in rescue medication usage (puffs/day)

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

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

Outcome: 23 Change from baseline in rescue medication usage (puffs/day)



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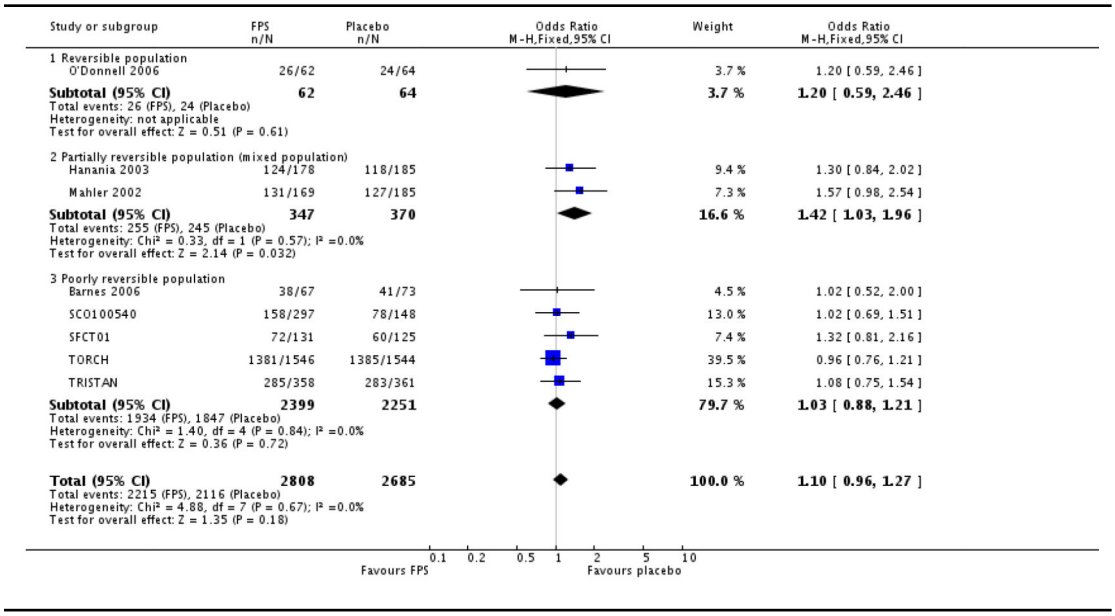
Analysis 2.24

Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 24 Adverse events- any event

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

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

Outcome: 24 Adverse events - any event



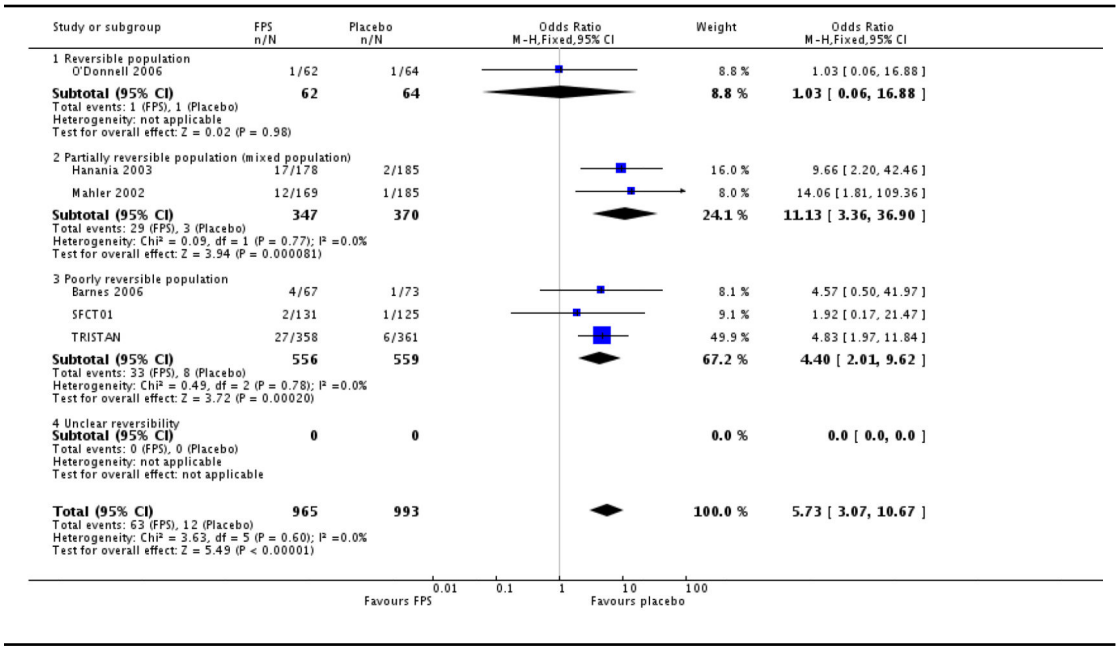
Analysis 2.25

Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 25 Adverse events - candidiasis

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

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

Outcome: 25 Adverse events - candidiasis



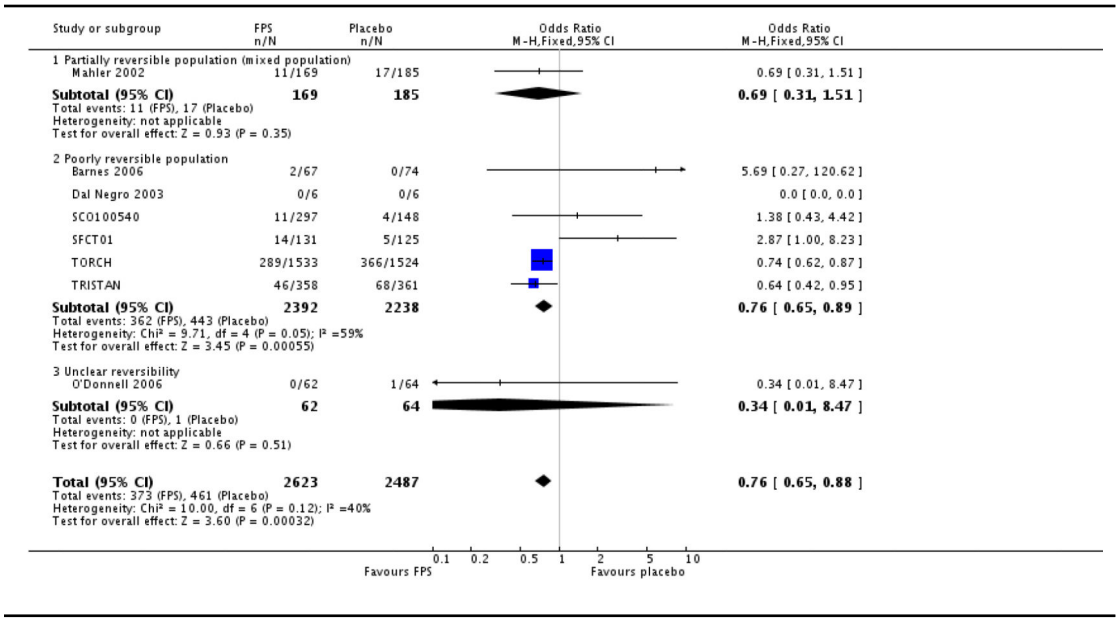
Analysis 2.26

Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 26 Withdrawals due to adverse events

Review: Com bine d corticosteroid and long-acting beta-agonist in one inhaler versus placebo for chronic obstructive pulmonary disease

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

Outcome: 26 Withdrawals due to adverse events



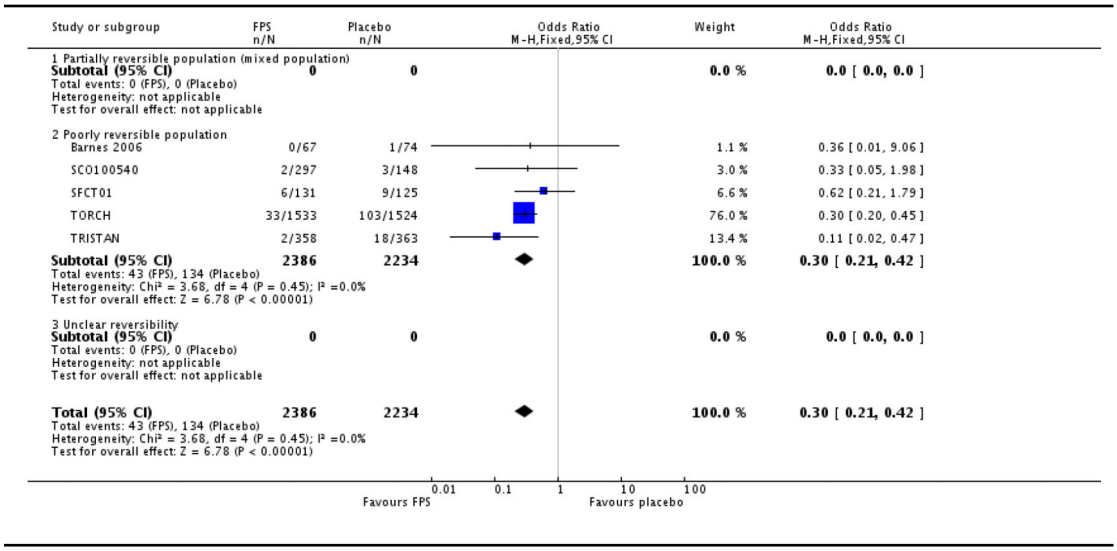
Analysis 2.27

Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 27 Withdrawals due to lack of efficacy/exacerbations

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

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

Outcome: 27 Withdrawals due to lack of efficacy/exacerbations



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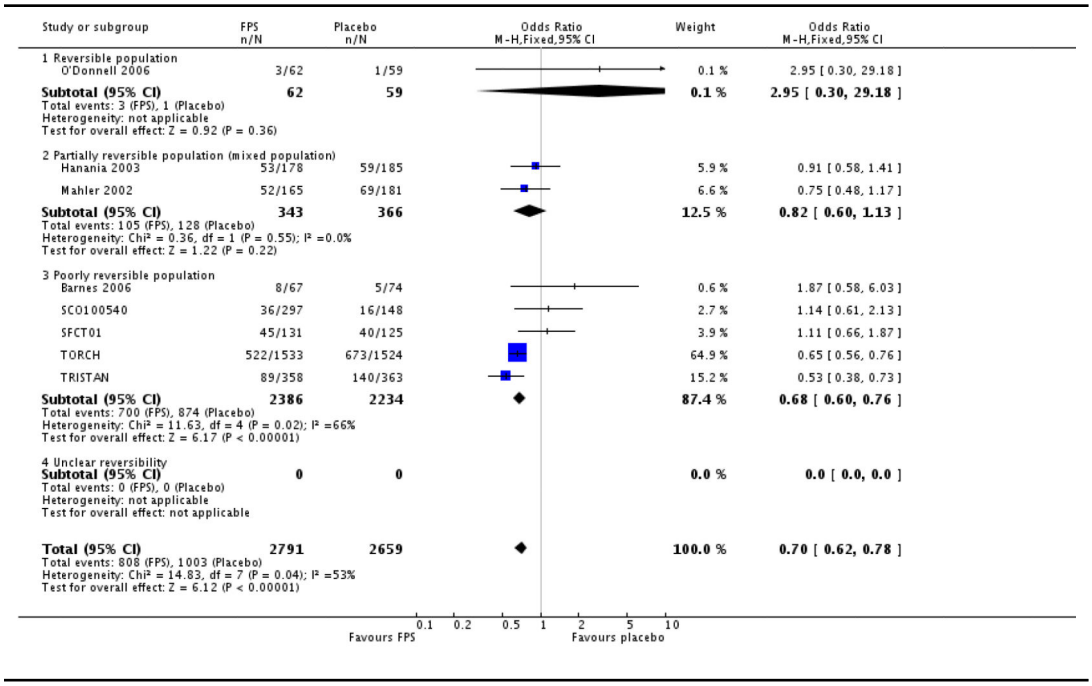
Analysis 2.28

Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 28 Withdrawals

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

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

Outcome: 28 Withdrawals



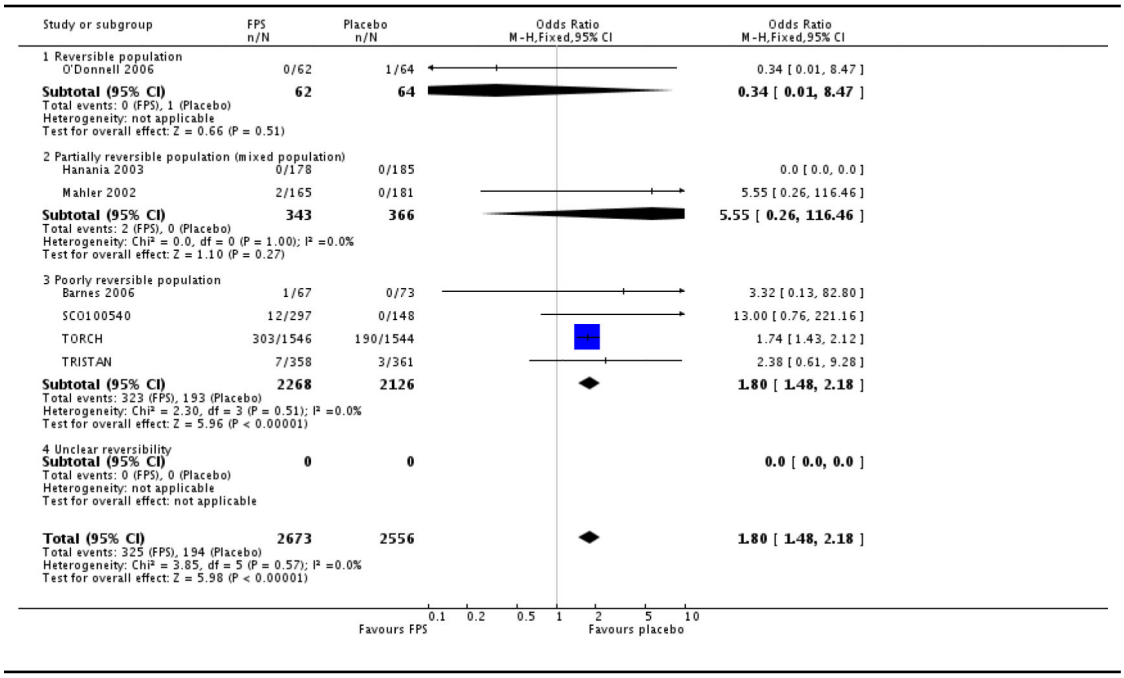
Analysis 2.29

Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 29 Withdrawals due to adverse events - pneumonia

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

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

Outcome: 29 Withdrawals due to adverse events - pneumonia



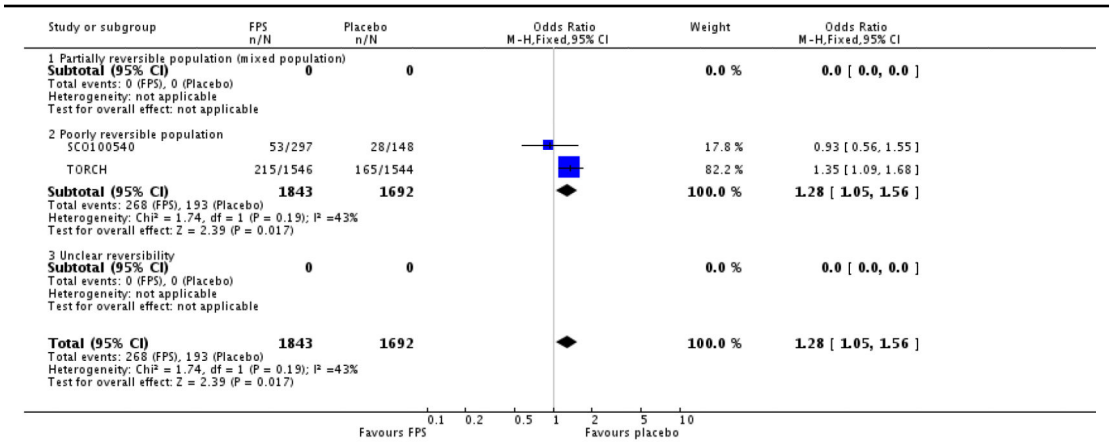
Analysis 2.30

Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 30 Adverse event - nasopharyngitis

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

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

Outcome: 30 Adverse event - nasopharyngitis



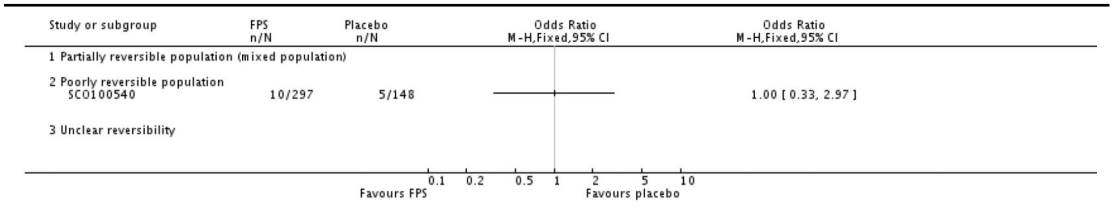
Analysis 2.31

Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 31 Adverse events - pharyngolaryngeal pain

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

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

Outcome: 31 Adverse events - pharyngolaryngeal pain



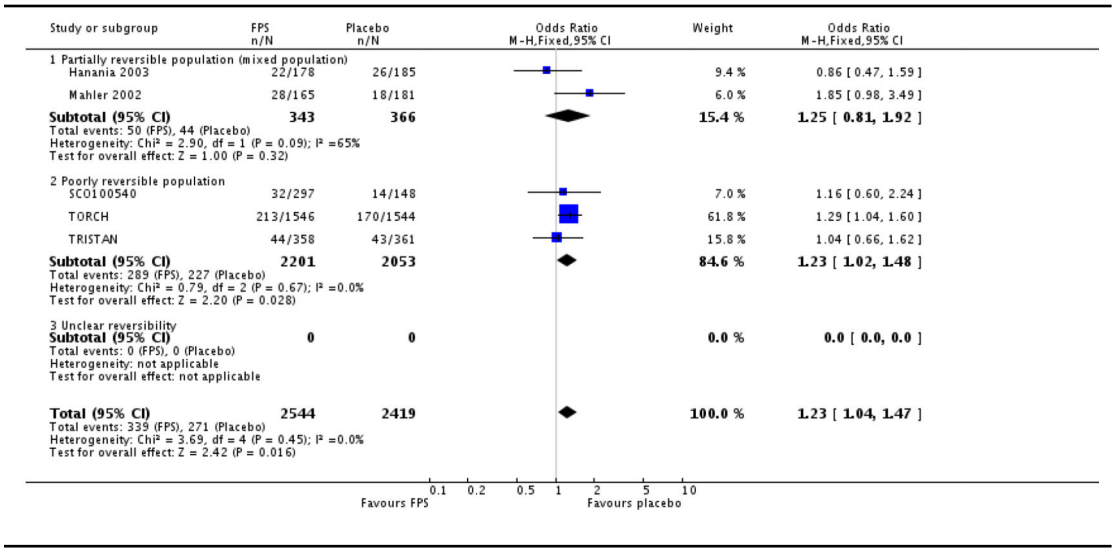
Analysis 2.32

Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 32 Adverse events - upper respiratory tract infection

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

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

Outcome: 32 Adverse events - upper respiratory tract infection



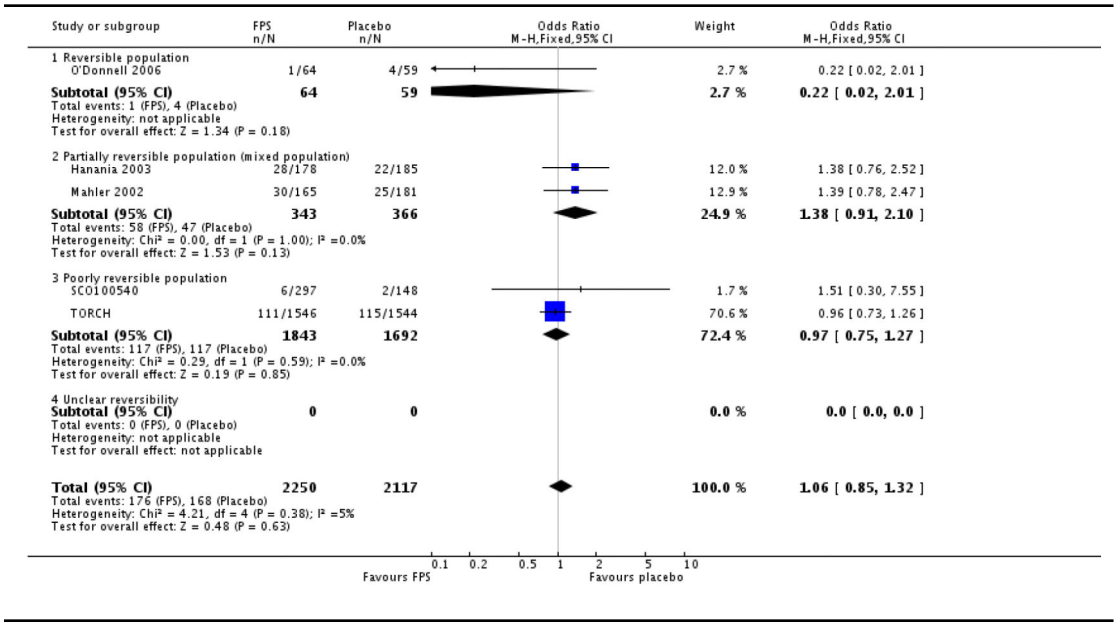
Analysis 2.33

Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 33 Adverse events - headache

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

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

Outcome: 33 Adverse events - headache



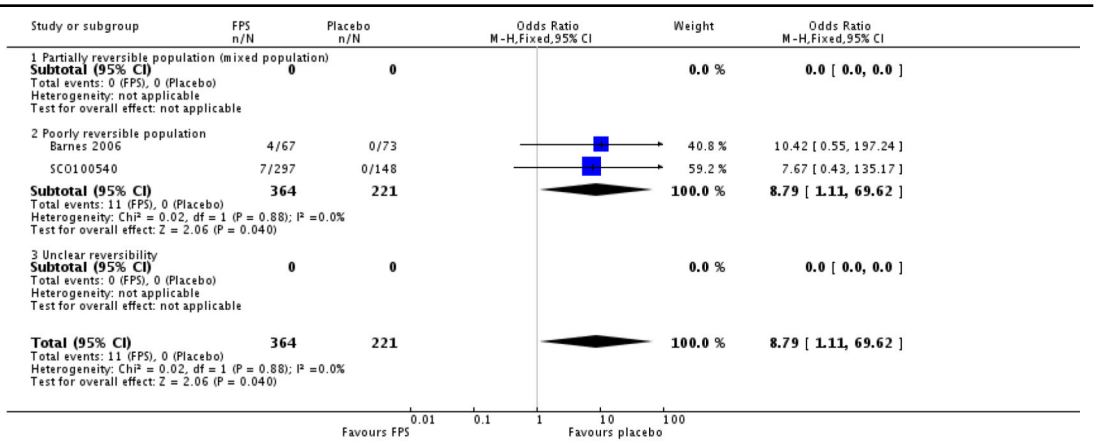
Analysis 2.34

Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 34 Adverse events - hoarseness

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

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

Outcome: 34 Adverse events - hoarseness



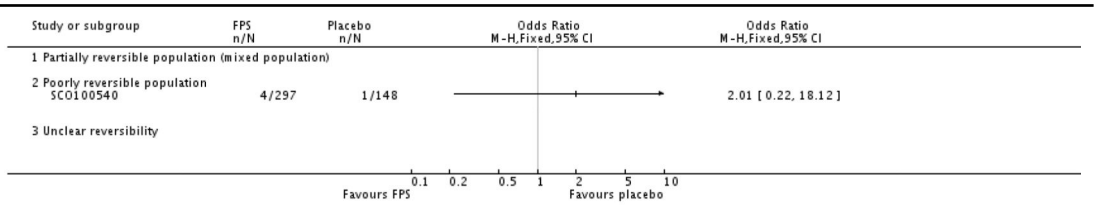
Analysis 2.35

Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 35 Adverse events - pyrexia

Review: Combined corticosteroid and long-acting beta-agonist in one inhaler versus placebo for chronic obstructive pulm onary disease

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

Outcome: 35 Adverse events - pyrexia



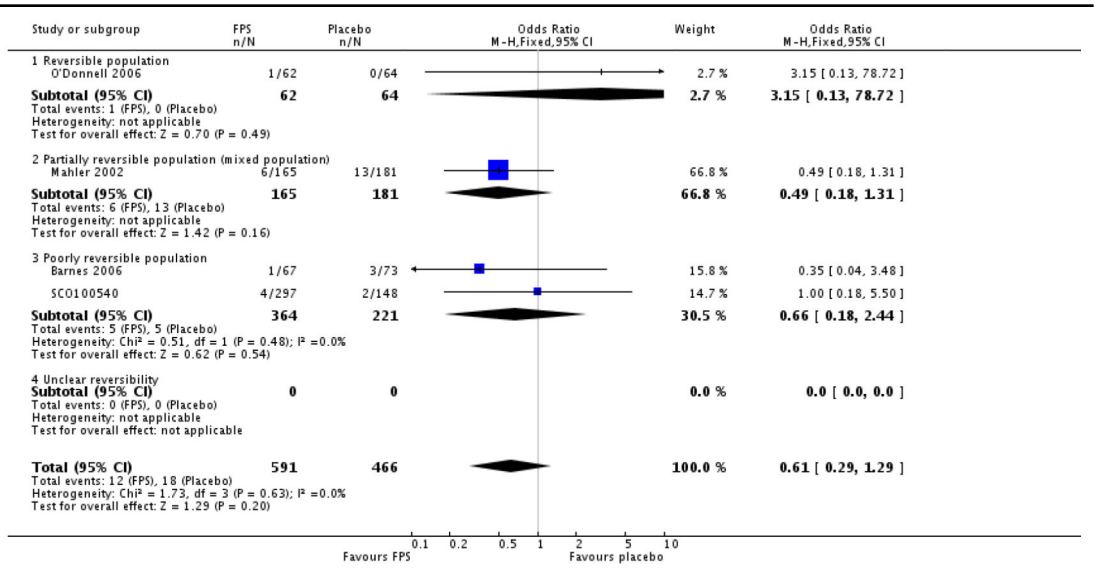
Analysis 2.36

Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 36 Adverse events - cough

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

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

Outcome: 36 Adverse events - cough



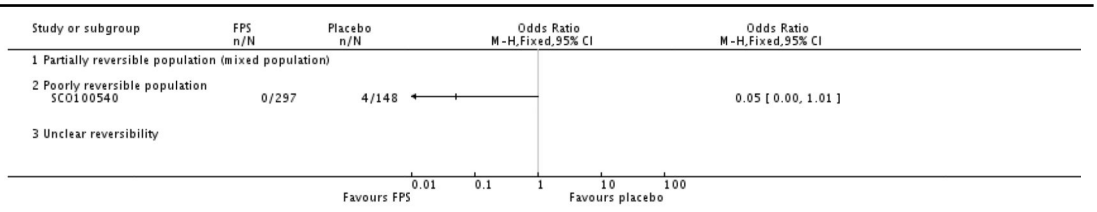
Analysis 2.37

Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 37 Adverse events - palpitations

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

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

Outcome: 37 Adverse events - palpitations



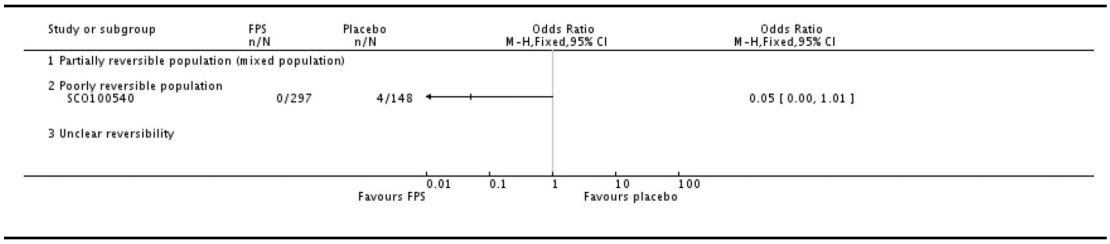
Analysis 2.38

Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 38 Adverse events - mouth ulceration

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

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

Outcome: 38 Adverse events - mouth ulceration



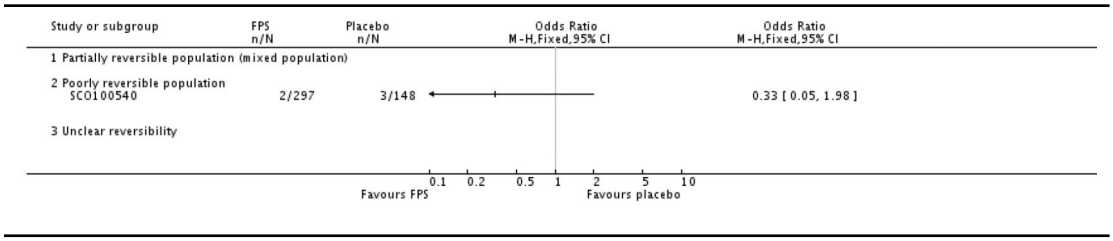
Analysis 2.39

omparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 39 Adverse events - toothache

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

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

Outcome: 39 Adverse events - toothache



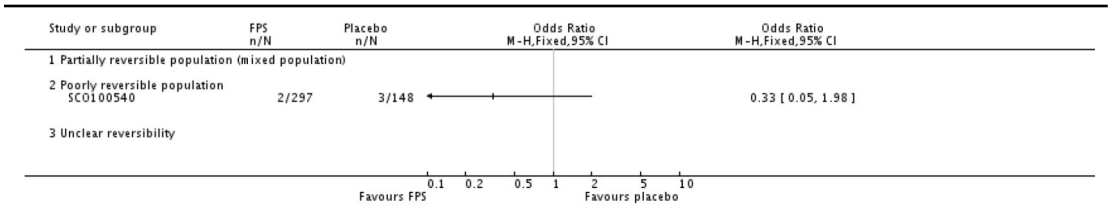
Analysis 2.40

Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 40 Adverse events - urinary tract infection

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

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

Outcome: 40 Adverse events - urinary tract infection



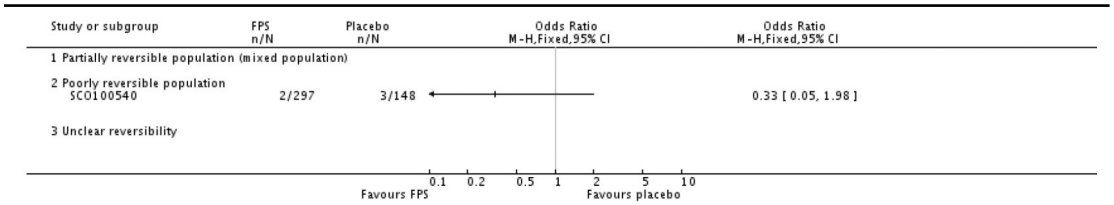
Analysis 2.41

Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 41 Adverse events - dyspnoea

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

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

Outcome: 41 Adverse events - dyspnoea



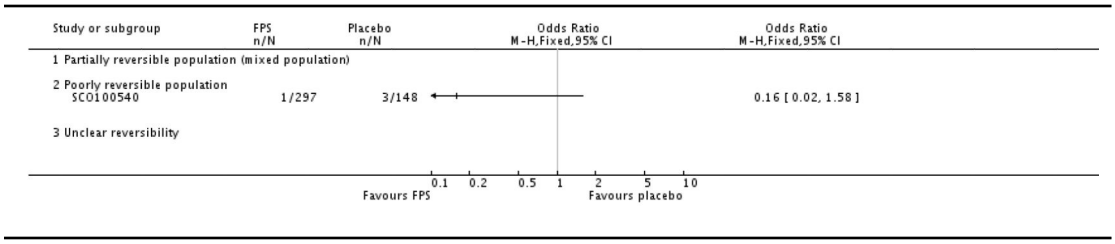
Analysis 2.42

Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 42 Adverse events - blood glucose increased

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

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

Outcome: 42 Adverse events - blood glucose increased



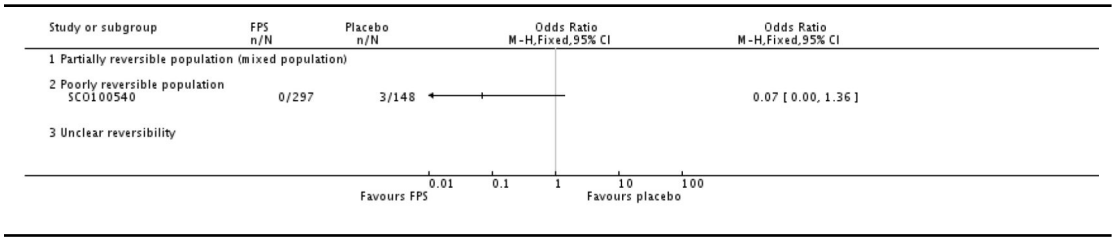
Analysis 2.43

Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 43 Adverse events - insomnia

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

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

Outcome: 43 Adverse events - insomnia



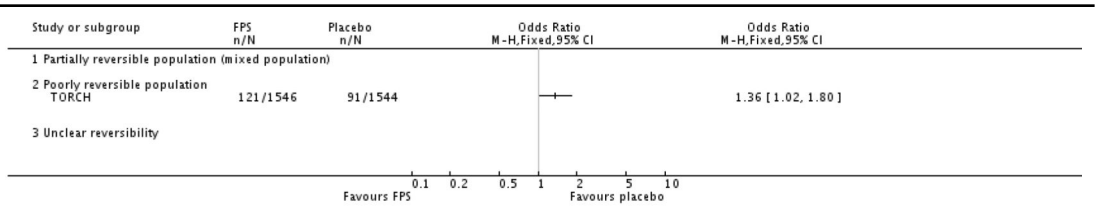
Analysis 2.44

Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 44 Adverse events - bronchitis

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

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

Outcome: 44 Adverse events - bronchitis



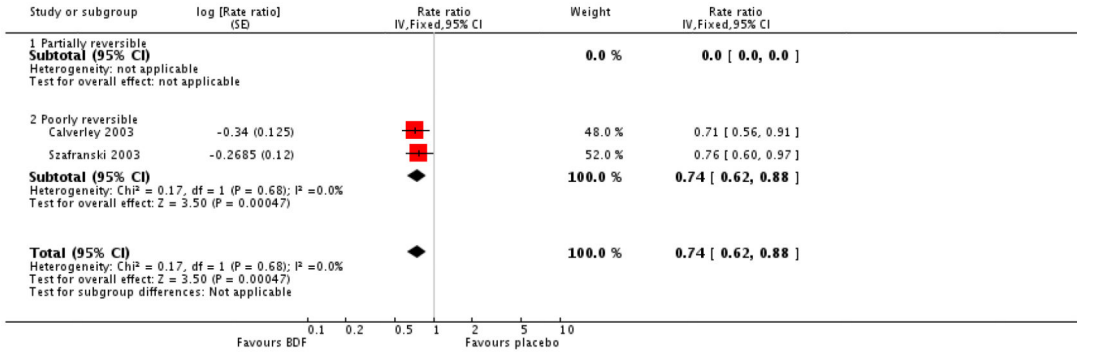
Analysis 3.1

Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 1 Severe Exacerbations

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

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

Outcome: 1 Severe Exacerbations



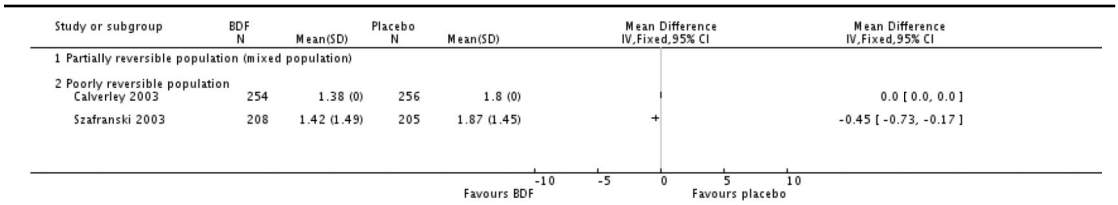
Analysis 3.2

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

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

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

Outcome: 2 Mean severe exacerbation rates per patient per year



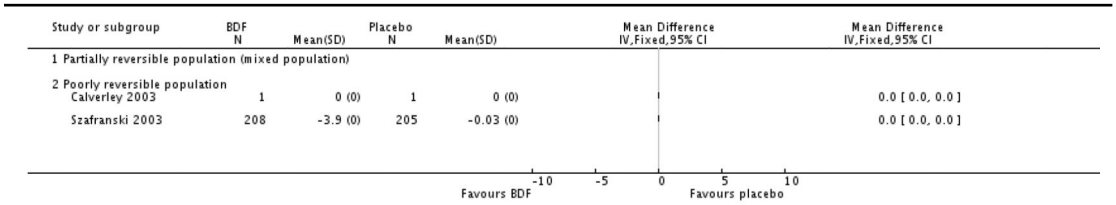
Analysis 3.3

Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 3 Quality of life - SGRQ (change scores)

Review: Combined coitico steroid and long-acting beta-agonist in one inhaler versus placebo for chronic obstructive pulmonary disease

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

Outcome: 3 duality of life - SGRQ (change scores)



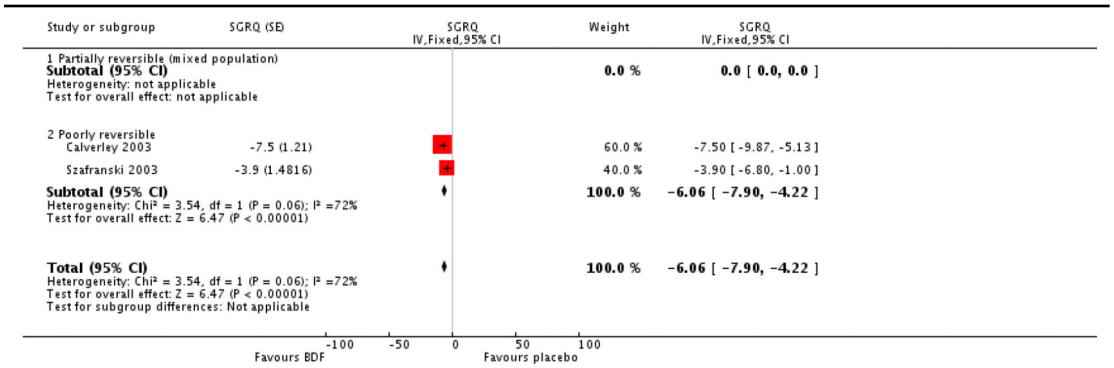
Analysis 3.4

Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 4 Quality of life - change scores

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

Comparison: 3 Budesonide/form oterol (BDF) versus placebo (PLA)

Outcome: 4 Quality of life - change scores



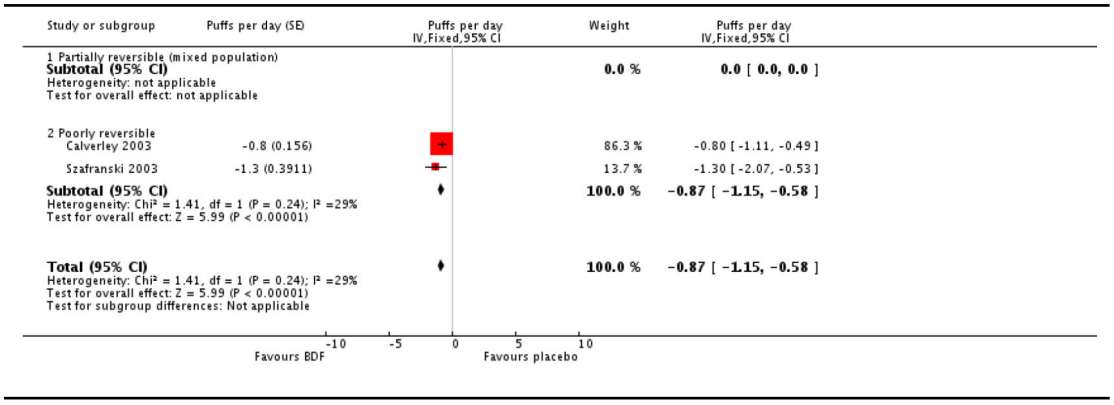
Analysis 3.5

Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 5 Rescue medication usage

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

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

Outcome: 5 Rescue medication usage



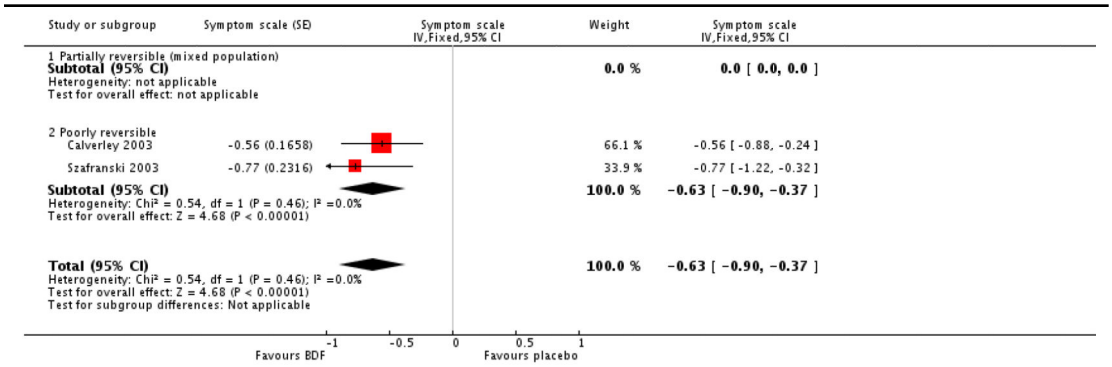
Analysis 3.6

Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 6 Symptoms (change scores)

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

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

Outcome: 6 Symptoms (change scores)



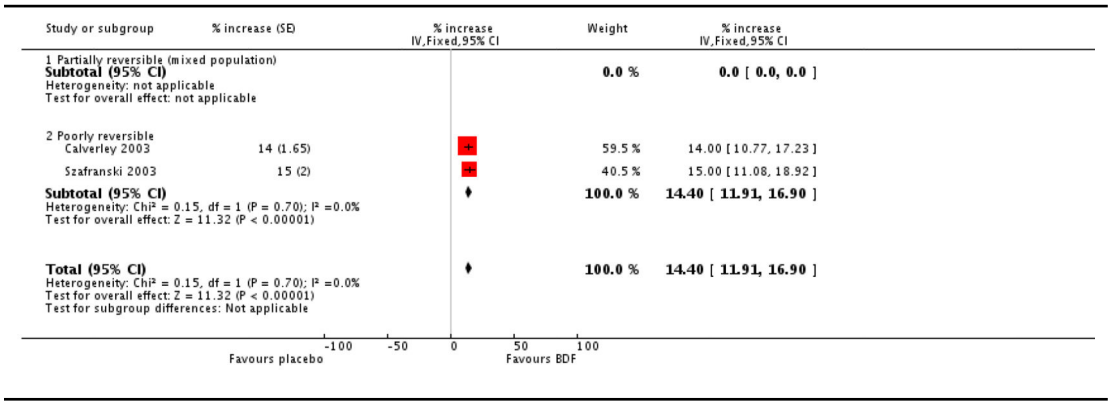
Analysis 3.7

Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 7 Mean FEV1 (% change from baseline)

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

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

Outcome: 7 Mean FEV1 (% change from baseline)



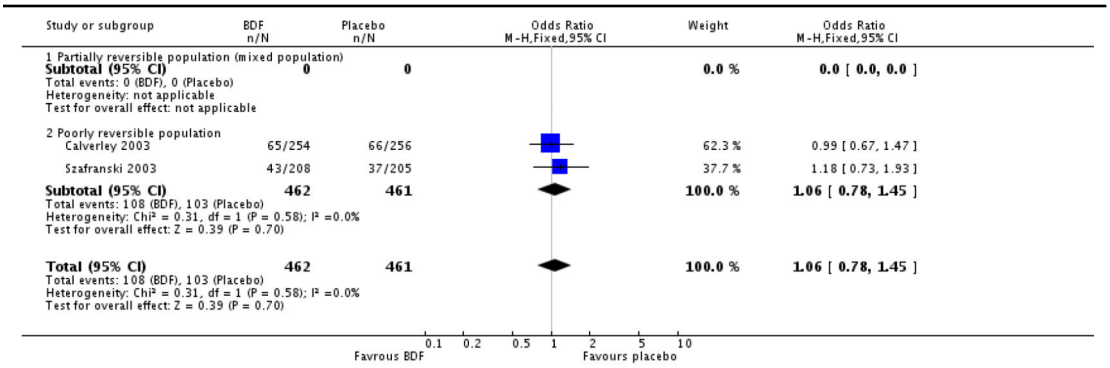
Analysis 3.8

Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 8 Adverse events - 'serious events'

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

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

Outcome: 8 Adverse events - 'serious events'



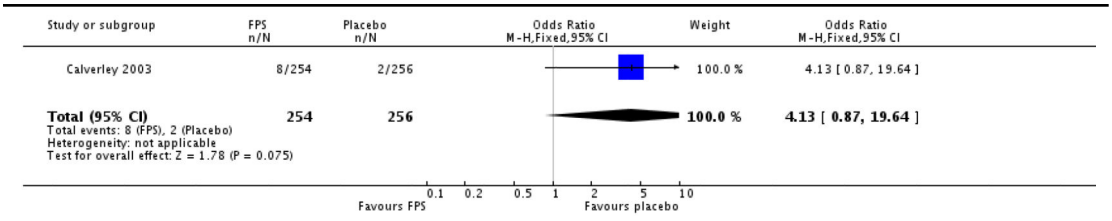
Analysis 3.10

Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 10 Adverse events - pneumonia

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

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

Outcome: 10 Adverse events - pneumonia



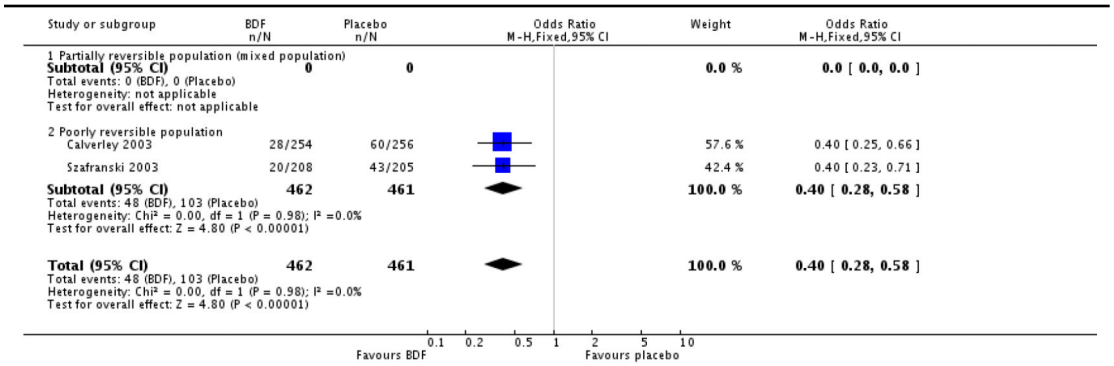
Analysis 3.11

Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 11 Withdrawals due to worsening COPD symptoms

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

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

Outcome: 11 Withdrawals due to worsening COPD symptoms



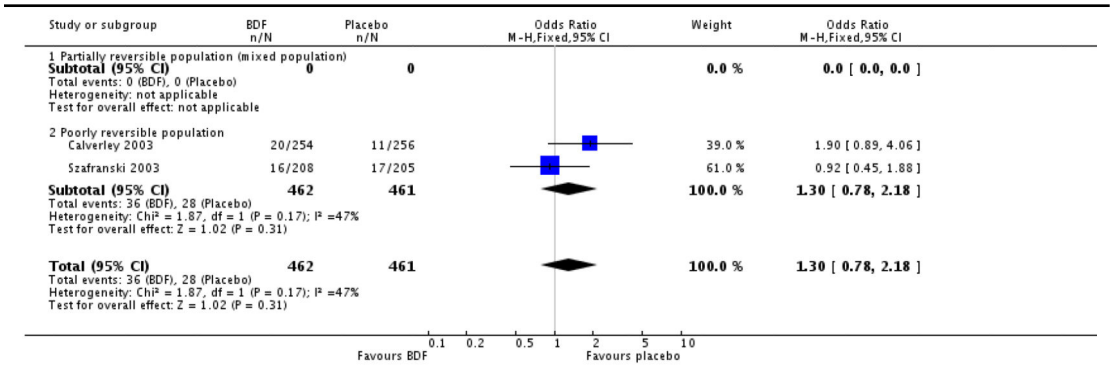
Analysis 3.12

Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 12 Withdrawals due to adverse events

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

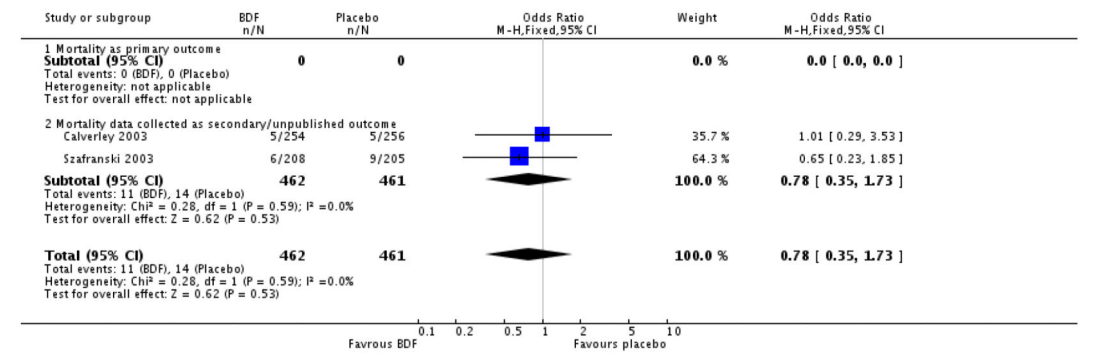
Comparison: 3 Budesonidi/form oterol (BDF) versus placebo (PLA)

Outcome: 12 Withdrawals due to adverse events



Analysis 3.13
Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 13 Mortaity

Review: Combined corticosteroid and long-acting beta-agonist in one inhaler versus placebo for chronic obstructive pulmonary disease
Comparison: 3 Budesonide/form oterol (BDF) versus placebo (PLA)
Outcome: 13 Mortality



WHAT'S NEW

Last assessed as up-to-date: 1 August 2007.

Date	Event	Description
11 November 2009	Amended	Spelling corrections and minor reformatting

HISTORY

Protocol first published: Issue 3, 2002

Review first published: Issue 4, 2003

Date	Event	Description
8 April 2008	Amended	Converted to new review format.
26 February 2008	Amended	Summary of findings table now added to review prepared centrally in GRADEpro by the Summary of Findings table working party (Nancy Santesso)
2 August 2007	New citation required and conclusions have changed	Seven new studies met the entry criteria of the review (Barnes 2006; Kardos 2007; TORCH; SCO100470; SCO40030; SFCT01; SCO10054). New unpublished data have been incorporated for three studies previously included (Hanania 2003; Mahler 2002; TRISTAN). What was known before: Statistically significant findings in favour of combination treatment over placebo. Conflicting findings when combination treatment compared with monocompo-nent therapies. What new data contribute to the review:

Date	Event	Description
		Data on all primary and secondary endpoints. Combined estimates now indicate that combination fluticasone and salmeterol is significantly more effective than fluticasone alone in reducing the rate of exacerbations
30 April 2004	New citation required and conclusions have changed	Two new studies are included in this update (Calverly 2003; Hanania 2003). One study previously reported in abstract form has now been published and baseline and outcome data incorporated in this version of the review (Dal Negro 2003). Data on lung function have been pooled on a WMD rather than a SMD. Pooled SEMs have been calculated from the published p values, and have been used to calculate some exacerbation outcomes, as well as symptoms, quality of life and lung function for some of the comparators. The Discussion and Conclusion reflect the incorporation of the new data, and the data calculated from previously published and included studies

References to studies included in this review

Barnes 2006 {published and unpublished data} . Barnes, NC.; Qiu, Y.; Pavord, I.; Parker, D.; Johnson, M.; Thompson, M., et al. Salmeterol /fluticasone propionate (SFC) anti-inflammatory effects in COPD [Abstract]; American Thoracic Society 2005 International Conference; San Diego, California. May 20-25; 2005. p. B93Poster 320

*Barnes NC, Qiu Y-S, Pavord ID, Parker D, Davis PA, Zhu J, et al. Antiinflammatory effects of salmeterol/fluticasone propionate in chronic obstructive lung disease. American Journal of Respiratory & Critical Care Medicine. 2006; 173(7):736–43. [PubMed: 16424444]

Qiu, Y.; Parker, D.; Barnes, NC.; Johnson, M.; Pavord, L., et al. The effect of salmeterol/fluticasone propionate (SFC) on eosinophils and mast cells in COPD [Abstract]; American Thoracic Society 2005 International Conference; San Diego, California. May 20-25; 2005. p. A43Poster F36

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Qiu YS, Davis P, Zhu J, Peachey L, Barnes NC, Pavord I, et al. Effects of salmeterol/fluticasone propionate (SFC) on airway inflammation in COPD: a placebo-controlled study of endobronchial biopsies. European Respiratory Journal. 2005; 26(Suppl 49):203s.

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Calverley, PMA.; Stahl, E.; Jones, PW. Budesonide/formoterol improves the general health status of patients with COPD [Abstract]; American Thoracic Society 2005 International Conference; San Diego, California. May 20-25; 2005. p. B93Poster 303

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* *Indicates the major publication for the study*

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PLAIN LANGUAGE SUMMARY

Combination therapy with inhaled corticosteroids and long-acting beta-agonists can reduce exacerbations and improve quality of life in people with chronic obstructive pulmonary disease (COPD) when compared to placebo treatment

Combinations of two classes of medication in one inhaler have been developed to treat people with COPD. Two types of combined inhaler exist currently: budesonide/formoterol (BDF - 'Symbicort'), and fluticasone/salmeterol (FPS - 'Advair' or 'Seretide'). The results of the studies showed that combined inhalers were effective and reduced the frequency of exacerbations compared with placebo medication to a level of three quarters of the previous rates. The patients included in these trials had on average 1-2 exacerbations per year which means that treatment with combination therapy would lead to a reduction of one exacerbation every two to four years in these individuals. Combination therapy led to a reduction in mortality over three years, and also led to improvements in lung function and symptoms. However, there was an increased risk of pneumonia associated with combined inhalers, and further monitoring of this outcome in future trials would provide valuable information for consumers and clinicians. Future research is required to show whether there is a difference between combination inhalers with different strengths of inhaled corticosteroids.

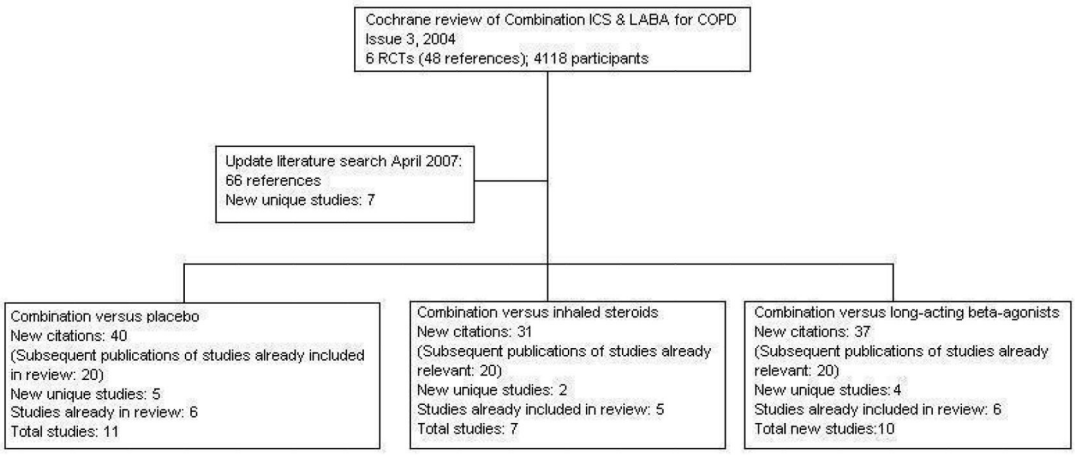

Figure 1. Flow chart to illustrate separation of review between three comparisons. Six RCTs met the original entry criteria of the review. All of these had a placebo and long-acting beta-agonist arm, and five assessed combination against steroids. Seven new studies with one or more control comparisons were identified: five had a placebo arm, three had a long-acting beta-agonist arm, and two had an inhaled steroid treatment arm

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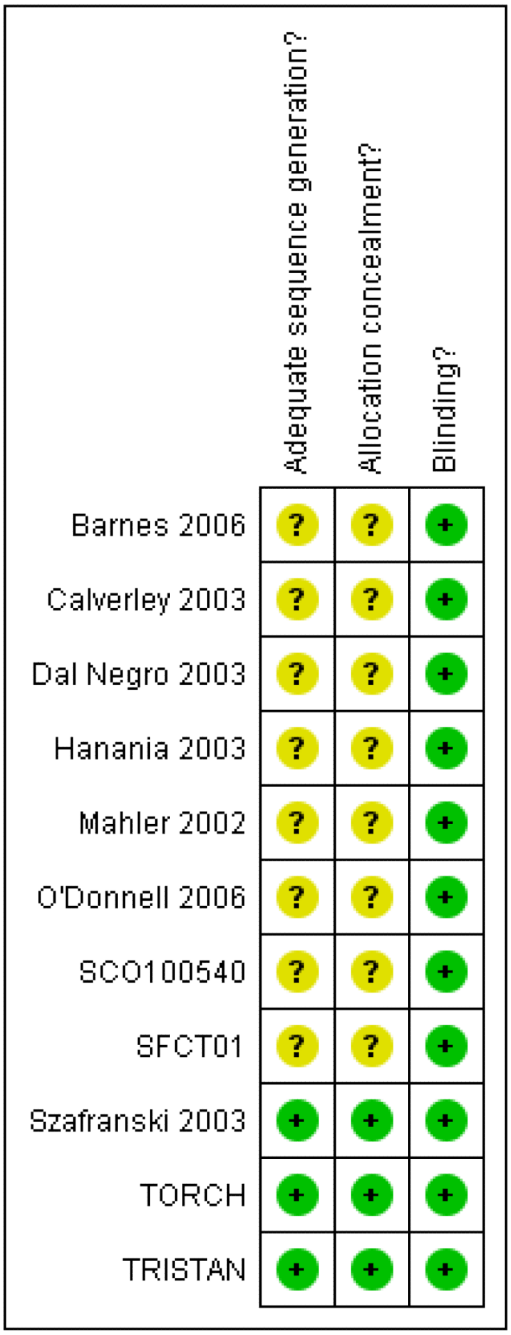

Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study

Combined corticosteroid and long-acting beta-agonist in one inhaler for chronic obstructive pulmonary disease

Patient or population: patients with moderate and severe chronic obstructive pulmonary disease
Settings: outpatient
Intervention: corticosteroid and long-acting beta-agonist in one inhaler[1]
Comparision: no treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk no treatment	Corresponding risk combined inhaler				
Exacerbation rate (follow-up: 3 years)	The mean exacerbation rate in the control groups was **3 exacerbations in 3 years**[2]	The mean exacerbation rate in the intervention groups was **2 exacerbations in 3 years**[2]		4226 (5)	⊕⊕⊕○ **moderate**[3]	Rate Ratio 0.74 (0.69, 0.79)
Hospitalisations	See comment	See comment	Not estimable	0 (0)	See comment	Limited data for hospitalisations was presented in the trials.
Mortality (follow-up: 3 years)	**Medium risk population**[4]		**OR 0.79** (0.65 to 0.96)	5752 (7)	⊕⊕⊕⊕ **high**	
	15 per 100	**12 per 100** (10 to 14)				
Quality of Life St. George's Respiratory Questionnaire. Scale from: 0 to 100. (follow-up: 3 years)	The mean quality of life in the control groups was **48 points**[2]	The mean Quality of Life in the intervention groups was **2.90 lower** (3.61 to 2.18 lower)		3346 (4)	⊕⊕⊕⊕ **high**	Difference did not reach a patient important improvement of 4 points.
Pneumonia (follow-up: 3 years)	**Medium risk population**[4]		**OR 1.83** (1.51 to 2.21)	5739 (8)	⊕⊕⊕⊕ **high**	
	12 per 100	**20 per 100** (17 to 23)				
Any adverse events (follow-up: 3 years)	**Medium risk population**[4]		**OR 1.10** (0.96 to 1.27)	5493 (8)	⊕⊕⊕⊕ **high**	Data from fluticasone/salmeterol studies.
	90 per 100	**91 per 100** (90 to 92)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; OR: Odds ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Both long-acting beta-agonists and inhaled corticosteroids can be used in combination for the treatment of chronic obstructive pulmonary disease. Of the 11 included studies, two evaluated fluticasone/salmeterol at 250 mcg/50 mcg twice daily and seven at 500 mcg/50 mcg twice daily; and two evaluated budesonide/formoterol at 320 mcg/9 mcg twice daily. All studies permitted the use of inhaled short-acting beta-agonists (SABA) on demand.
[2] Assumed risk based on TORCH trial.
[3] Withdrawal of participants with severe frequent exacerbations may have biased results.

Figure 3. Summary of findings table for exacerbations, mortality, quality of life, pneumonia and adverse events

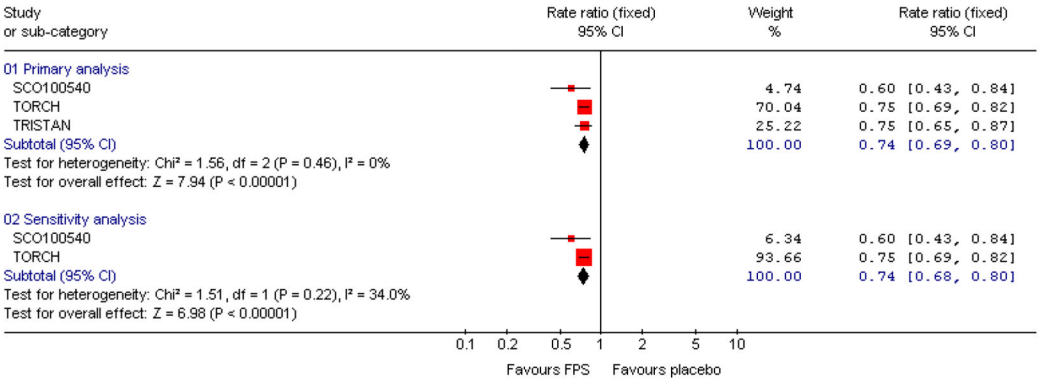

Figure 4. Forest plot of pooled rate ratios for combination fluticasone and salmeterol and placebo, with the summary estimate for TRISTAN included (primary analysis) and removed (sensitivity analysis)

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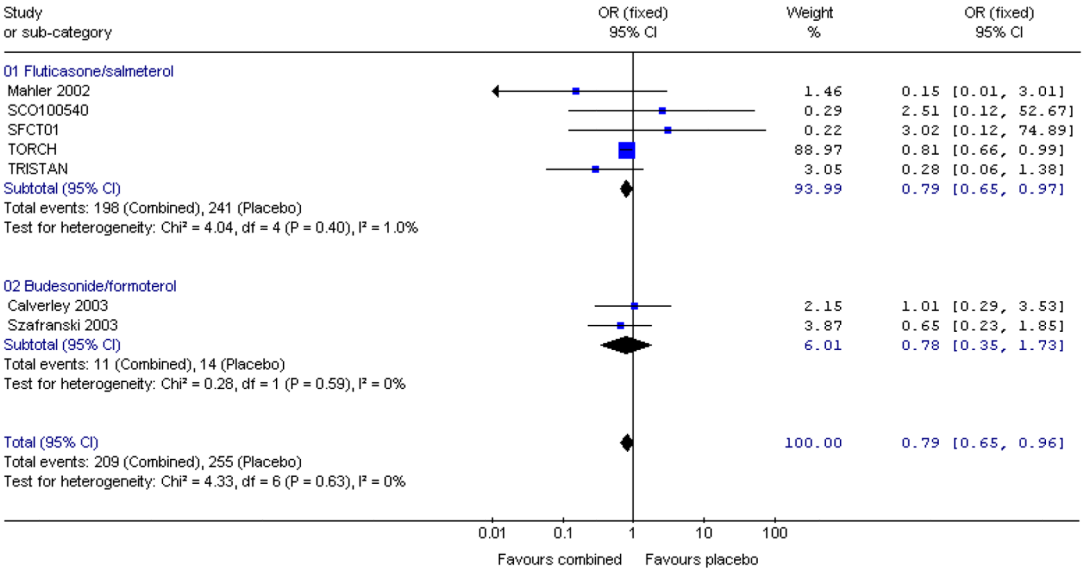

Figure 5. Pooled effect estimate on mortality for all combined inhalers versus placebo

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Table 1

Search history

Version	Detail
1st published version - Issue 4, 2003 (All years to April 2002)	References identified: 34 References retrieved: 7 Studies excluded 3 (Cazzola 2000; Chapman 2002; Soriano 2002) Studies identified from supplementary searching: 4 (Dal Negro 2003; Hanania 2003 - both included; Cazzola 2002a; Cazzola 2004 - both excluded). Studies included: 4
2nd published version - Issue 3, 2004 (April 2003-April 2004)	References identified: 12 References retrieved: 3 (2 papers full publication of a previously included or cited studies study (Dal Negro 2003; Hanania 2003). Hand searching identified two further references to the COSMIC 2003 study. Studies identified from supplementary searching: 1 (TRISTAN 2003) New studies included: 2 Total studies included: 6
3rd published version - Issue 3, 2005 (April 2004-April 2005)	References identified: 52 References retrieved: 46 (references to studies already included/excluded/ongoing: 24) New unique studies identified: 10 (ongoing studies: 2) New studies included: 0 Total studies included: 6
4th published version - April 2005 - April 2007	References identified: 66 References retrieved: 27 (references to studies already included/ excluded/ongoing:) New unique studies identified: 8 (ongoing studies: 0) New studies included: 7 Total studies included: 13

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Table 2

Rates and NNT of mortality

Study ID	Study duration	Placebo rate (%)	NNT
TORCH	156 weeks	15.2	42 (24 to 387)
SCO100540	24 weeks	0	NA
SFCT01	52 weeks	0	NA
TRISTAN	52 weeks	1.94	292 (169 to 2628)
Mahler 2002	24 weeks	1.66	293 (176 to 1540)
Calverley 2003	52 weeks	1.95	249 (149 to 1307)
Szafranski 2003	52 weeks	4.5	110(66 to 581)

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Table 3

Rates and NNT of pneumonia

Study ID	Study duration	Placebo rate (%)	NNT(h)
Hanania 2003	24 weeks	0	NA
Mahler 2002	24 weeks	0	NA
Barnes 2006	13 weeks	0	NA
SCO100540	24 weeks	0	NA
O'Donnell 2006	8 weeks	1.56	83
TORCH	156 weeks	12.3	13
TRISTAN	52 weeks	0.83	153
Calverley 2003	52 weeks	3.6	36