Regular treatment with formoterol and inhaled steroids for chronic asthma: serious adverse events (Review)

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[Intervention Review]

Regular treatment with formoterol and inhaled steroids for chronic asthma: serious adverse events

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ABSTRACT

Background

Epidemiological evidence has suggested a link between beta$_2$-agonists and increases in asthma mortality. There has been much debate about possible causal links for this association, and whether regular (daily) long-acting beta$_2$-agonists are safe when used alone or in conjunction with inhaled corticosteroids.

Objectives

The aim of this review is to assess the risk of fatal and non-fatal serious adverse events in trials that randomised patients with chronic asthma to regular formoterol with inhaled corticosteroids versus the same dose of inhaled corticosteroids alone.

Search methods

Trials were identified using the Cochrane Airways Group Specialised Register of trials. Web sites of clinical trial registers were checked for unpublished trial data and Food and Drug Administration (FDA) submissions in relation to formoterol were also checked. The date of the most recent search was October 2008.

Selection criteria

Controlled parallel design clinical trials on patients of any age and severity of asthma were included if they randomised patients to treatment with regular formoterol and inhaled corticosteroids, and were of at least 12 weeks duration.

Data collection and analysis

Two authors independently selected trials for inclusion in the review. Outcome data were independently extracted by two authors. Unpublished data on mortality and serious adverse events were obtained from the sponsors.

Main results

The review included 14 studies on adults and adolescents (8,028 participants) and seven studies on children and adolescents (2,788 participants). Data on all cause fatal and non-fatal serious adverse events were found for all studies, and the overall risk of bias was low.

Four deaths occurred on regular formoterol with inhaled corticosteroids, and none on regular inhaled corticosteroids alone. All the deaths were in adults, and one was reported to be asthma-related. The difference was not statistically significant.

Non-fatal serious adverse events of any cause were very similar in adults [Peto Odds Ratio 0.99 (95% CI 0.74 to 1.33)], and an increase in events in children on regular formoterol was not statistically significant [Peto Odds Ratio 1.62 (95% CI 0.80 to 3.28)].

Asthma related serious adverse events on formoterol were lower in adults [Peto Odds Ratio 0.53 (95% CI 0.28 to 1.00)] and although they were higher in children [Peto Odds Ratio 1.49 (95% CI 0.48 to 4.61)], this was not statistically significant.

Authors' conclusions

It is not possible, from the data in this review, to reassure people with asthma that inhaled corticosteroids with regular formoterol carries no risk of increasing mortality in comparison to inhaled corticosteroids alone as all four deaths occurred among 6,594 people using inhaled corticosteroids with formoterol. On the other hand, we have found no conclusive evidence of harm and there was only one asthma related death registered during over 3,000 patient year observation on formoterol. In adults, the decrease in asthma-related serious adverse events on regular formoterol with inhaled corticosteroids was not accompanied by a decrease in all cause serious adverse events. In children the number of events was too small, and consequently the results too imprecise, to determine whether the increase in all cause non-fatal serious adverse events found in the previous meta-analysis on regular formoterol alone is abolished by the additional use of inhaled corticosteroids. Clinical decisions and information for patients regarding regular use of formoterol have to take into account the balance between known symptomatic benefits of formoterol and the degree of uncertainty and concern associated with its potential harmful effects.

PLAIN LANGUAGE SUMMARY

Serious adverse events with regular formoterol and inhaled corticosteroids

There has been some concern raised at the possibility of increased serious adverse events following administration of formoterol, a long-acting beta-agonist, to people with asthma. We analysed data from 14 studies in adults and seven in children. Too few deaths occurred in the trials to gain any conclusive reassurance that regular formoterol taken with inhaled corticosteroids either reduces the risk of mortality, or in fact does not increase it (all four deaths that did occur, including one related to asthma, were among 6,594 patients taking formoterol with inhaled corticosteroids). Serious adverse events were very similar in adults with and without formoterol. Although there were more events on formoterol in children, the difference was not big enough to rule out this as being a chance finding. Similarly, decreased risk of asthma-related serious adverse events in adults and increased risk among children taking formoterol could be also be chance findings.

BACKGROUND

When patients with asthma are not controlled by low dose inhaled corticosteroids alone, many asthma guidelines recommend additional long-acting beta$_2$-agonists. Several Cochrane reviews have addressed the efficacy of long-acting beta$_2$-agonists in addition to inhaled corticosteroids (Ni Chroinin 2004; Ni Chroinin 2005), in comparison with placebo (Walters 2007), short-acting beta$_2$-agonists(Walters 2002), leukotriene-receptor antagonists (Ducharme 2006) and assessed them against increased doses of inhaled corticosteroids (Greenstone 2005). The beneficial effects of long-acting beta$_2$-agonists on lung function, symptoms, quality of life and exacerbations requiring oral steroids have been demonstrated.

However, there is also longstanding controversy over the regular use of beta$_2$-agonists in asthma. Sears 1986 suggested that excessive use of short acting beta$_2$-agonists might have contributed directly or indirectly to increases in asthma deaths in New Zealand between 1960 and 1980. The authors comment that "most deaths were associated with poor assessment, underestimation of severity and inappropriate treatment (over-reliance on bronchodilators and under use of systemic corticosteroids), and delays in obtaining help."

Concern remains that the symptomatic benefit from treatment with long-acting beta$_2$-agonists might lead to underestimation of attack severity in acute asthma, and could lead to an increase in asthma-related deaths. Furthermore, regular treatment with beta$_2$-agonists can lead to tolerance to their bronchodilator effects and this phenomenon may be more marked with longer acting as opposed to shorter acting compounds (Lipworth 1997). A number of molecular mechanisms have been proposed to explain the possi-

ble detrimental effect of long-term beta$_2$-agonist use in asthma including receptor down regulation and desensitisation (Giembycz 2006).

There are two currently available long-acting beta$_2$-agonists, salmeterol and formoterol (also known as eformoterol). These two drugs are known to have differences in speed of onset and receptor activity, and are used in different ways (for example salmeterol has a slower onset of action than salbutamol Beach 1992 and is therefore unsuitable for use as a reliever). 'The Fenoterol Story' is a reminder that all beta$_2$-agonists may not carry the same risks (Pearce 2007), so in view of the potential difference in adverse effects between salmeterol and formoterol, we have considered the two drugs separately. Two recent systematic reviews have addressed the impact of long-acting beta$_2$-agonists on all cause mortality and serious adverse events: Cates 2008 (salmeterol) and Cates 2008a (formoterol). Both reviews considered long-acting beta$_2$-agonists which were randomised without additional inhaled corticosteroids and demonstrated increased risks of non-fatal serious adverse events.

There has been much debate about the interaction between inhaled corticosteroids and long-acting beta2-agonists, in relation to serious adverse events, since the publication of SMART 2006. This study did not randomise patients to inhaled corticosteroids, but nevertheless a subgroup analysis of the results was carried out on the basis of inhaled corticosteroid use at baseline. It is tempting to find reassurance from the fact that there was not a statistically significant increase in asthma-related mortality in the subgroup using inhaled corticosteroids, but this is not the correct way to test for interaction (Altman 2003), and no assessment was carried out during the trial in relation to the actual use of inhaled corticosteroids during the course of the study.

Counfounding by severity has been shown by Sears 2008 in data from the RELIEF study, where the rate of asthma-related SAEs was significantly higher in both arms of the study in patients taking ICS in comparison to those not taking ICS. This is a serious threat to any conclusions drawn from observational data when assessing the interaction between ICS and formoterol. Therefore, there is a need to systematically review all the available data from controlled trials that randomised patients to regular formoterol in combination with inhaled corticosteroids, and to consider all serious adverse events (fatal and non-fatal), whether or not these are deemed by the investigators to be related to trial medication.

The focus of this review is therefore on regular formoterol randomised in combination with inhaled corticosteroids, (in a single inhaler or separate inhalers) and compared to inhaled corticosteroids alone. Due to the difficulty in deciding whether adverse events are asthma-related, this review will focus on studies that capture mortality and serious adverse events, and record both all cause outcomes, and those considered by the trial investigators to be asthma-related events.

A review comparing regular salmeterol randomised in combination with inhaled corticosteroids, (in a single inhaler or separate inhalers) and compared to inhaled corticosteroids alone is also currently ongoing.

OBJECTIVES

To assess the risk of mortality and non-fatal serious adverse events in trials which randomise patients with chronic asthma to regular formoterol and inhaled corticosteroid in comparison with the same dose of inhaled corticosteroid.

METHODS

Criteria for considering studies for this review

Types of studies

Controlled parallel design clinical trials, with or without blinding, in which formoterol and inhaled corticosteroid were randomly assigned to patients with chronic asthma in comparison to the same dose of inhaled corticosteroid alone. Studies on acute asthma and exercise induced bronchospasm have not been included.

Types of participants

Patients with a clinical diagnosis of asthma of any age group, unrestricted by disease severity, previous or current treatment.

Types of interventions

Inhaled corticosteroids and formoterol given regularly once or twice daily for a period of at least 12 weeks, at any dose and delivered by any single or separate devices (CFC-MDI, HFA-MDI, DPI). Studies that randomised patients to formoterol and inhaled corticosteroids for intermittent use as a reliever have not been included in this review, and studies that compared different doses of formoterol, or different delivery devices or propellants without a placebo arm were also not be included. Studies in which formoterol was randomised without an inhaled steroid have been considered in a separate review (Cates 2008a). Studies that use comparison groups with the same dose and type of inhaled corticosteroids in the control arm will be included in this review, and co-intervention with leukotriene receptor antagonists, cromones or theophylline will be allowed as long as they are not part of the randomised intervention, and are therefore not systematically different between groups. Studies comparing formoterol to salmeterol will be subject to another review and were not included in this review. We have also excluded in this review studies in which

inhaled corticosteroids were used in all patients as background treatment (rather than randomised intervention).

Types of outcome measures

Primary outcomes

1. All cause mortality
2. All cause non-fatal serious adverse events

Secondary outcomes

1. Asthma-related mortality
2. Asthma-related non-fatal serious adverse events
3. Respiratory-related mortality
4. Respiratory-related non-fatal serious adverse events
5. Cardiovascular-related mortality
6. Cardiovascular-related non-fatal serious adverse events
7. Asthma-related non-fatal life-threatening events (intubation or admission to intensive care)
8. Respiratory-related non-fatal life-threatening events (intubation or admission to intensive care)

Outcomes will not be sub-divided according to whether the trial investigators considered them to be related to trial medication.

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 hand searching of respiratory journals and meeting abstracts. All records in the Specialised Register coded as 'asthma' will be searched using the following terms:

(((beta* and agonist*) and (long-acting or "long acting")) or ((beta* and adrenergic*) and (long-acting or "long acting")) or (bronchodilat* and (long-acting or "long acting")) or (salmeterol or formoterol or eformoterol or advair or symbicort or serevent or seretide or oxis)) AND (serious or safety or surveillance or mortality or death or intubat* or adverse or toxicity or complications or tolerability)

Searching other resources

Reference lists of all primary studies and review articles were checked for additional references. Web sites of clinical trial registers were checked for unpublished trial data and FDA submissions in relation to formoterol were also checked.

Data collection and analysis

Selection of studies

Two review authors independently assessed studies identified in the literature searches by examining titles, abstract and keywords fields. Studies that potentially fulfilled the inclusion criteria were obtained in full text. These were independently assessed by CJC and TL for inclusion. Disagreements were resolved by consensus.

Data extraction and management

Data were extracted using a prepared checklist before being entered into Rev Man 5.0 by one reviewer (CJC), and data extraction and entry were checked by a second reviewer (TL). Outcome data were independently extracted by the third reviewer (RJ) and discrepancies resolved by correspondence with the sponsors. Data included characteristics of included studies (methods, participants, interventions, outcomes) and results of the included studies. Sponsors of included studies were contacted for unpublished adverse event data, and the sponsors's web site was searched for further details of adverse events. All cause serious adverse events (fatal and non-fatal) were recorded, and in view of the difficulty in deciding whether events are asthma related, details of the cause of death and serious adverse events were noted where they are available. The definition of serious adverse events was recorded, and further information was sought if this was not clear (particularly in relation to hospital admissions and serious adverse events).

Assessment of risk of bias in included studies

One review author (CJC) assessed the included studies for bias protection (including sequence generation for randomisation, allocation concealment, blinding of participants and assessors, loss to follow-up, completeness of outcome assessment and other possible bias prevention), with assistance from Susan Hansen.

Unit of analysis issues

We confined our analysis to patients with one or more serious adverse events, rather than the number of events that occurred (as the latter are not independent when one patient suffers multiple events).

Assessment of heterogeneity

Heterogeneity was assessed using I^2 to indicate how much of the total heterogeneity found was between, rather than within studies.

Data synthesis

The outcomes of this review were dichotomous, and we recorded the number of participants with at least one outcome event by allocated treated group. Pooled Odds Ratio (OR) and Risk Difference (RD) were calculated. The Peto Odds Ratio has advantages when events are rare, as no adjustment for zero cells is required. This property was more important than potential problems with unbalanced treatment arms and large effect sizes in view of the high proportion of zero cells, and therefore the results for serious adverse events were calculated in RevMan 5.0 using the Peto method with the Mantel-Haenszel method for sensitivity analysis. Funnel plots were inspected to assess publication bias.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses were conducted on the basis of age (adults versus children), and dose of formoterol (usual dose versus high dose). Subgroups were compared using tests for interaction (Altman 2003).

Sensitivity analysis

Sensitivity analysis was carried out to assess the impact of the method used to combine the study events (Risk Difference, Peto Odds Ratio, and Mantel-Haenszel Odds Ratio). The degree of bias protection in the study designs was also part of sensitivity analysis.

RESULTS

Description of studies

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

Results of the search

523 abstracts were found from the search of the Cochrane Airways Group Specialised Register of trials in October 2008. For this review 59 abstracts were identified as potentially relevant, and of these 48 were subsequently excluded (see Characteristics of excluded studies) and eleven were included in the review. Ten further trials were identified primarily from the AstraZeneca register of controlled trials (Buhl 2003;D5896C00001;Morice 2007; Morice 2008; Peters 2008; SD-039-0714; SD-039-0718; SD-039-0719; SD-039-0725; SD-039-0726). No additional trials were found from the Novartis web site or the FDA web site. A submission from Novartis to the FDA in December 2008 also indicated that there were not trials in the Novartis database in which patients in randomised trials of Foradil had also been randomised to inhaled corticosteroids (Novartis 2008).

Included studies

The 21 trials included in this review are described in detail in Characteristics of included studies. There is also a summary of the daily dose of budesonide and formoterol that was used in each trial in Table 1. To avoid confusion, all delivered doses have been converted to an equivalent metered dose (so Symbicort 320/9 mcg is a delivered dose that is equivalent to a metered dose of budesonide 400 mcg and formoterol 12 mcg).

Table 1 also indicates whether each study randomised patients to once or twice daily formoterol, used combined or separate inhalers and delivered the medication using dry powder inhaler (DPI) or pressurised metered-dose inhalers (pMDI). Some trials had more than two arms so featured more than one option in each of these cases. Since OPTIMA (O'Byrne 2001; O'Byrne 2001a) and FACET (Pauwels 1997; Pauwels 1997a) randomised patients into higher and lower doses of budesonide, each has been considered as two separate comparisons and been given two identifiers. The review therefore lists a total of 23 studies, drawn from the 21 trials which have been conducted.

All the trials have been sponsored or supported by AstraZeneca.

Adults

A total of 8,028 adults and adolescents were randomised in seven trials enrolling participants over the age of 12 years (Corren 2007; Jenkins 2006; Morice 2007; Noonan 2006; D5896C00001; Peters 2008; Price 2002), a further six trials that enrolled adults over the age of 18 years (Buhl 2003; Chuchalin 2002; Kuna 2006; O'Byrne 2001; Pauwels 1997; Zetterstrom 2001) and a single trial enrolling those over 16 years old (SD-039-0726). All these studies had a mean age of greater than 18 years.

The weighted mean duration of the adult and adolescent studies was 31 weeks. The daily metered dose of formoterol used was 12 to 24 mcg, with the exception of Jenkins 2006 and Peters 2008 where 48 mcg daily was used (which remains within the licensed daily dose range). The daily metered dose of budesonide ranged from 200 to 1600 mcg (see Table 1).

Children

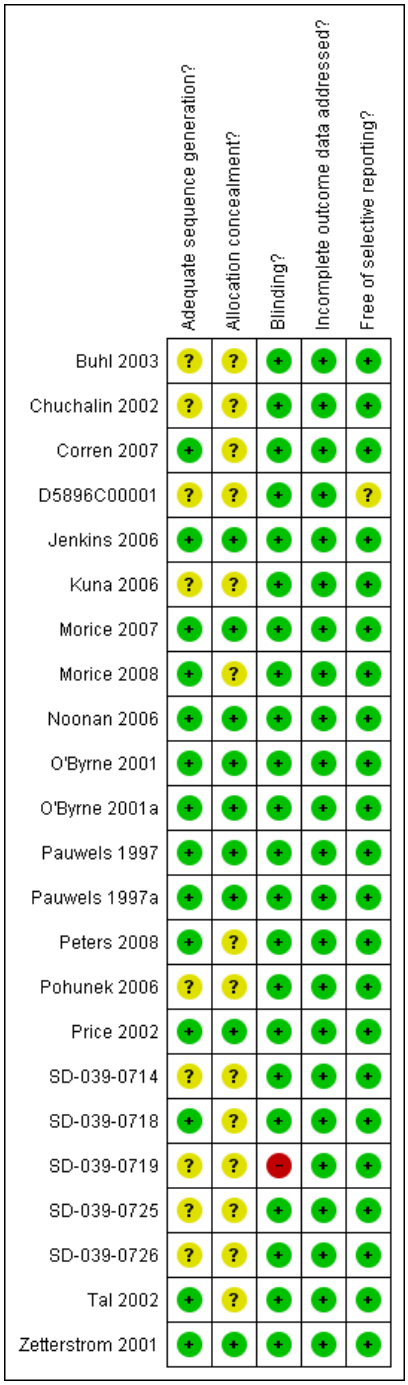
The seven trials in children include 2788 participants in the following age ranges: Morice 2008 (6-11 years old), Pohunek 2006 (4-11), SD-039-0714 (11-17), SD-039-0718 (6-15), SD-039-0719 (6-11), SD-039-0725 (6-15), Tal 2002 (4-17). All these studies had a mean age of participants of less than 18 years.

The weighted mean duration of the children and adolescent studies was 13 weeks. The daily metered dose of formoterol was 12 to 24 mcg. The daily metered dose of budesonide was 200 to 400 mcg (see Table 1).

Risk of bias in included studies

An overview of the risk of bias in individual studies is shown in Figure 1.

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



Allocation

Very little information is available from the paper publications or web reports on sequence generation or allocation concealment, but this is unlikely to be a source of bias in view of the fact that all the studies are sponsored, and standard methodology is likely to have been used to minimise the risk of selection bias.

Blinding

All of the studies were double-blind with the exception of SD-039-0719, which was an open study.

Incomplete outcome data

The rate of withdrawals and dropouts was clearly reported and was generally less than 20% of randomised participants, and similarly in the arms of each study.

Selective reporting

Data have been found or provided from the sponsor for fatal and non-fatal serious adverse events by treatment group and causation for all studies except D5896C00001, which is yet to be published in full and does not include details of asthma-related serious adverse events. With this exception we have therefore obtained data from all trials in relation to the primary outcomes of all cause mortality and all cause serious adverse events.

Other potential sources of bias

All studies were sponsored or supported by AstraZeneca, the manufacturer of combined budesonide/formoterol inhalers.

Effects of interventions

Primary Outcomes

All cause mortality

There were no deaths in the trials on children and adolescents (2,788 participants). In the adult and adolescent studies (8,028 participants), there were four deaths which were all in patients taking formoterol with inhaled corticosteroids. These trials were combined using Peto Odds Ratio (as no continuity correction for zero cells is required). The pooled Peto Odds Ratio was 5.83 (95% confidence interval 0.78 to 43.77) and I^2 was zero Figure 2. When analysed using risk differences with a fixed effects model the RD is 0.001 (95% CI -0.001 to 0.003) for adults and adolescents and the RD is zero (95% CI -0.004 to 0.004) in trials on children and adolescents (in which there were no deaths) Figure 3.

Figure 2. Forest plot of comparison: 1 Formoterol and ICS versus same dose ICS, outcome: 1.1 All-cause Mortality.

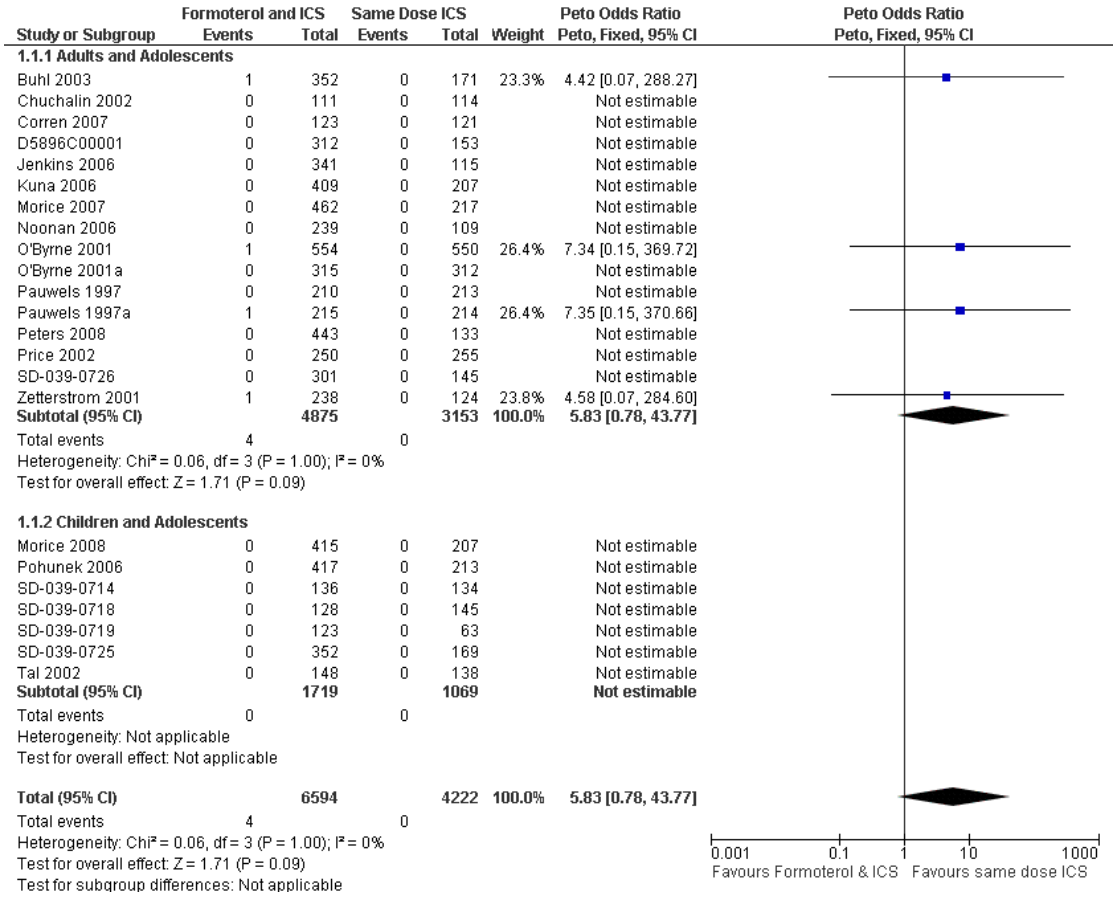
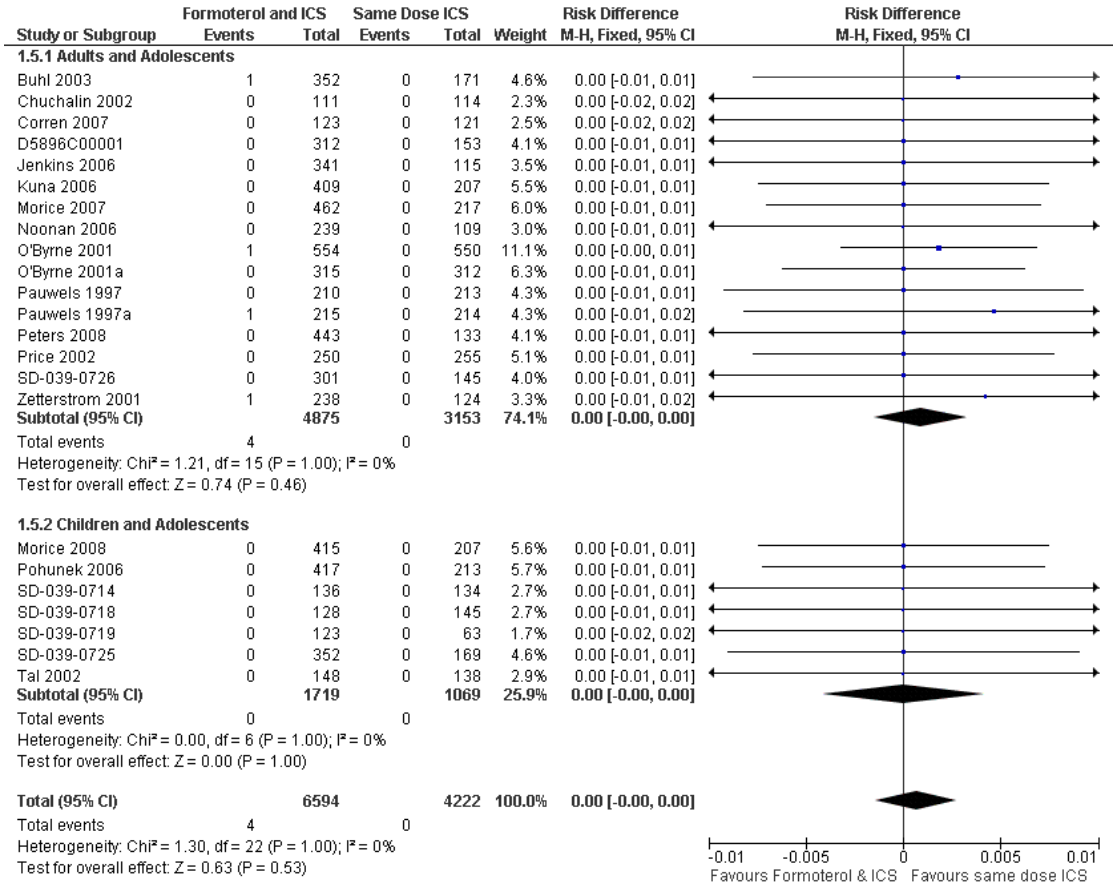


Figure 3. Forest plot of comparison: 1 Formoterol and ICS versus same dose ICS, outcome: 1.5 All-cause Mortality (risk difference)).



The reports of the deaths included one due to cardiac arrest on combined formoterol and budesonide inhaler treatment (Buhl 2003), one due to status asthmaticus with subsequent development of septic shock on separate formoterol and budesonide inhalers (O'Byrne 2001), one due to suicide on separate formoterol and budesonide inhalers (Pauwels 1997a) and one due to suicide on combined formoterol and budesonide inhaler (Zetterstrom 2001). There was one additional death due to pulmonary embolus on combined treatment in Jenkins 2006, but this death occurred after the budesonide only control arm was discontinued and all patients were receiving formoterol, so it has not been included in the meta-analysis.

Serious Adverse Events (non-fatal all cause)

A serious adverse event is defined as an event that falls in any of the following categories:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.

This is further explained in Appendix 3, and the sponsors have confirmed that this definition was used in the included trials (even though this was often not made explicit in the paper reports).

All ages

The combined result in all ages was Peto Odds Ratio of 1.06 (95% CI 0.81 to 1.39) and I^2 was 8% (see Figure 4), and the pooled RD for all ages was 0.001 (95% CI -0.004 to 0.007) Figure 5.

Figure 4. Forest plot of comparison: 1 Formoterol and ICS versus same dose ICS, outcome: 1.2 All-cause non-fatal Serious Adverse Events.

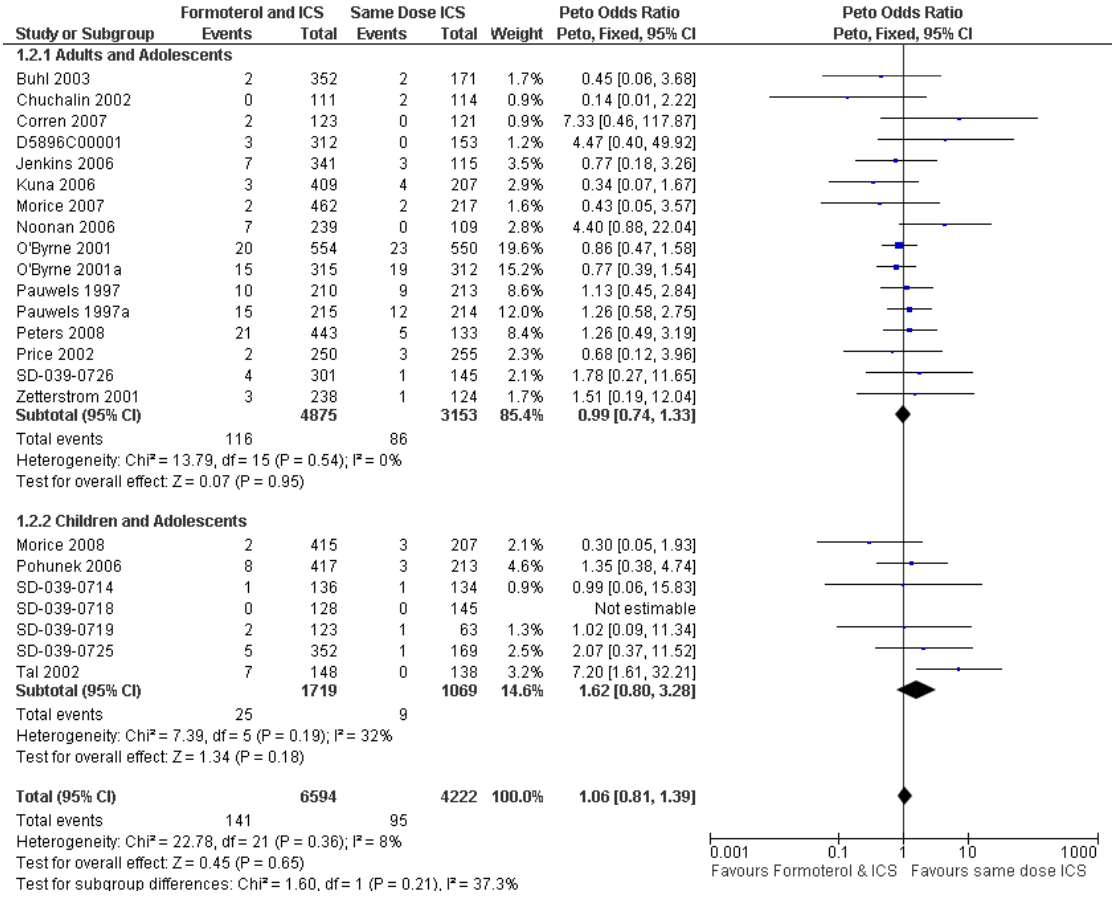
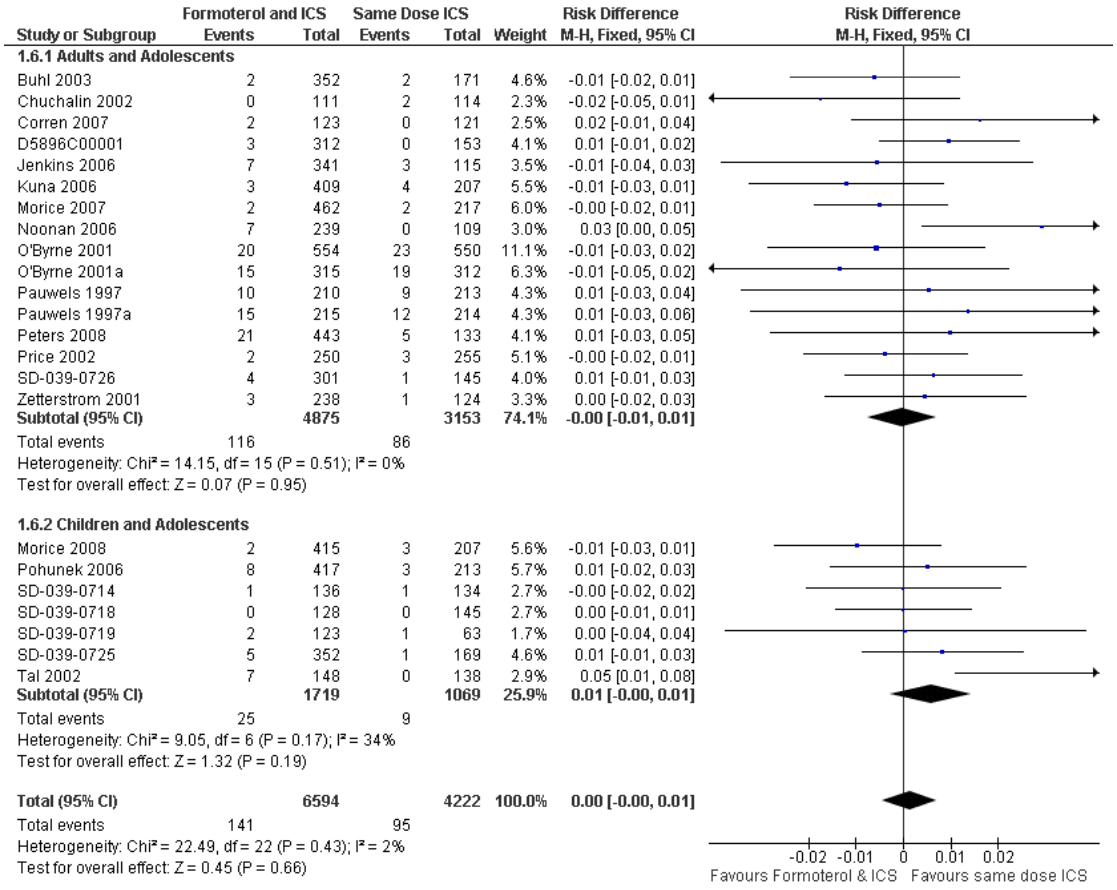


Figure 5. Forest plot of comparison: 1 Formoterol and ICS versus same dose ICS, outcome: 1.6 All-cause non-fatal Serious Adverse Events (risk difference)).



Adults and Adolescents

The number of patients experiencing one or more non-fatal serious adverse events was very similar when formoterol was randomised with inhaled corticosteroids in comparison to inhaled corticosteroids alone. There were 116 out of 4875 (2.4%) participants on regular formoterol with ICS and 86 out of 3153 (2.7%) on ICS alone in whom such events occurred. The Peto Odds Ratio was 0.99 (95% CI 0.74 to 1.33) and I^2 was zero. The pooled RD was -0.0003 (95% CI -0.007 to 0.007).

Children and Adolescents

In the trials in patients who were less than 18 years of age the results were more heterogeneous and more non-fatal serious adverse events occurred with formoterol. There were 25 such events amongst young people out of 1719 (1.5%) on regular formoterol with ICS and nine out of 1069 (0.8%) on ICS alone. The Peto Odds Ratio was 1.62 (95% CI 0.80 to 3.28) and I^2 was 32%, and the pooled RD for children was 0.006 (95% CI -0.003 to 0.01). When Tal 2002 is removed from the analysis, the I^2 measurement is reduced to 0. In this study there were seven children with events on formoterol and none on ICS alone.

The test for interaction between adults and children did not find a significant impact of age on the treatment effect.

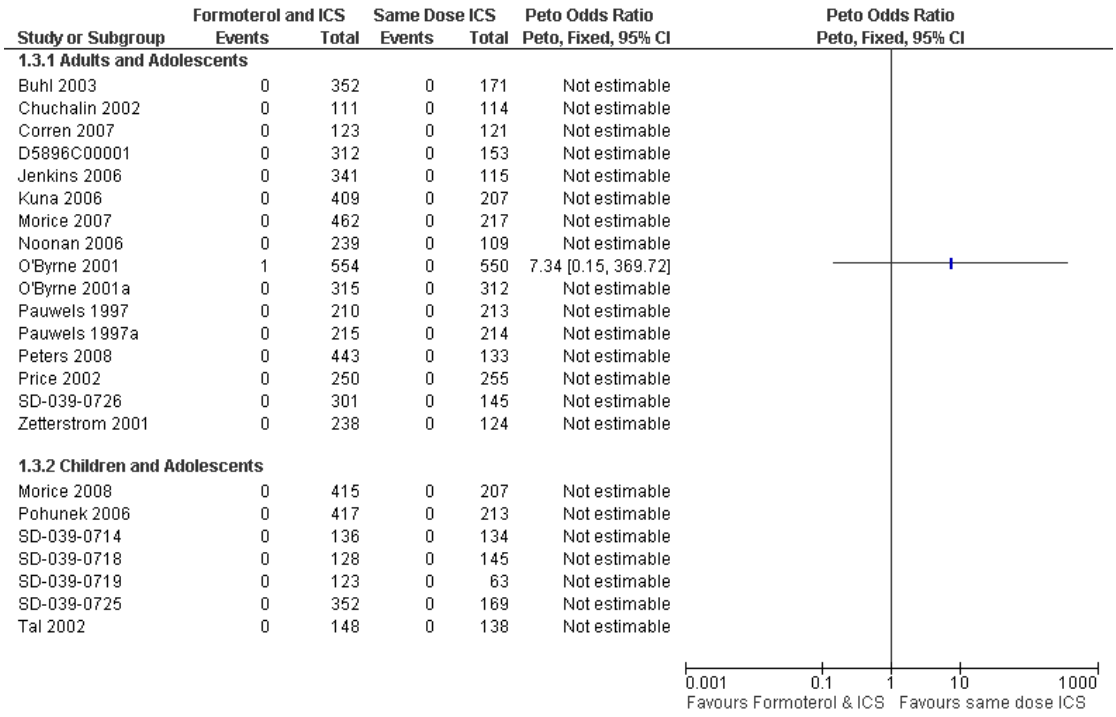
Secondary Outcomes

Mortality by cause of death

None of the four deaths in adults were reported as being due to asthma in the original trial reports, but the death in O'Byrne 2001 (OPTIMA) was subsequently attributed to status asthmaticus and septic shock in a recent meta-analysis (Sears 2008). The full report

of the cause of death from the sponsors was "One of the deaths occurred in a 35 year old female after an 8 day hospitalization for a severe asthma attack leading to intubation, ventilation, and nosocomial pneumonia with septic shock." This is the only death that has been reported as relating to asthma and was in a patient taking budesonide/formoterol Figure 6. Two deaths were reported as due to suicide and one as related to cardiac arrest.

Figure 6. Forest plot of comparison: 1 Formoterol and ICS versus same dose ICS, outcome: 1.3 Asthma Mortality.



Serious Adverse Events related to Asthma

All Ages

The combined result in all ages was Peto Odds Ratio of 0.68 (95% CI 0.39 to 1.18) and I^2 was 21% Figure 7, and the pooled RD for all ages was -0.002 (95% CI -0.005 to 0.001) Figure 8.

Figure 7. Forest plot of comparison: 1 Formoterol and ICS versus same dose ICS, outcome: 1.4 Asthma-related non-fatal Serious Adverse Events.

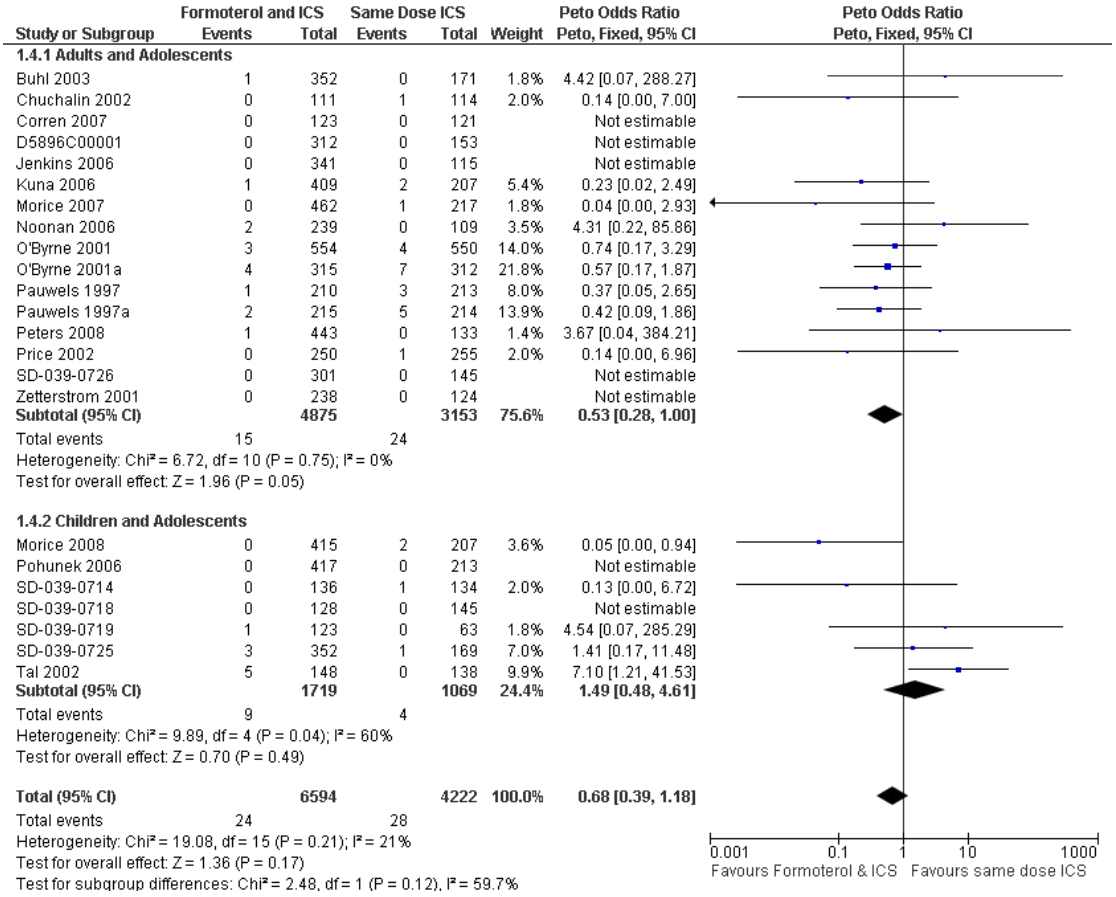
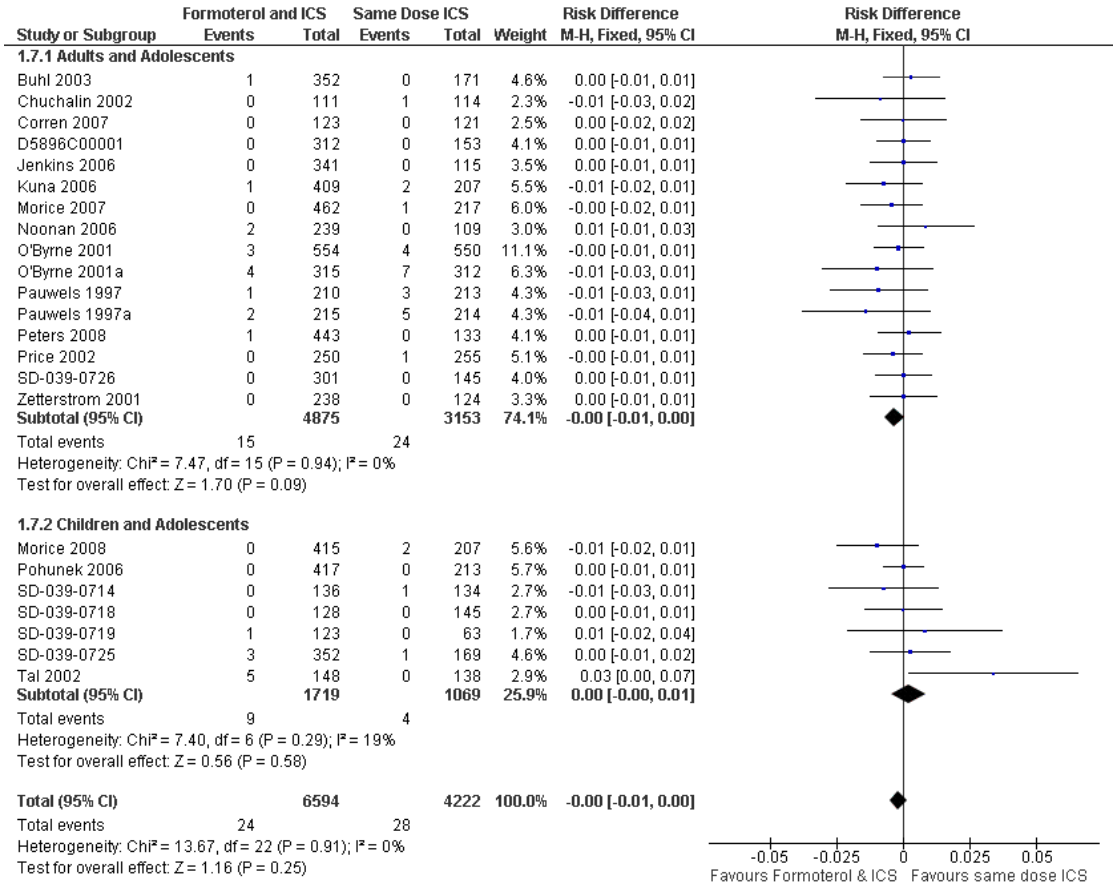


Figure 8. Forest plot of comparison: 1 Formoterol and ICS versus same dose ICS, outcome: 1.7 Asthma-related non-fatal Serious Adverse Events (Risk Difference).



Adults and Adolescents

The number of patients experiencing one or more asthma related non-fatal serious adverse events was lower when formoterol was randomised with inhaled corticosteroids in comparison to inhaled corticosteroids alone, but the result was statistically significant using Peto Odds Ratio but not Risk Difference. There were 15 out of 4875 (0.3%) participants on regular formoterol with ICS and 24 out of 3153 (0.8%) on ICS alone. The Peto Odds Ratio was 0.53 (95% CI 0.28 to 1.00) and I^2 was zero. The pooled RD was -0.003 (95% CI -0.007 to 0.0005).

Children and Adolescents

In the trials in patients who were less than 18 years of age the results were again more heterogeneous. There were 9 young people out of 1719 (0.5%) on regular formoterol with ICS and four out of 1069 (0.4%) on ICS alone. The Peto Odds Ratio showed a non-significant increase at 1.49 (95% CI 0.48 to 4.61) and I^2 was 60%. The pooled RD was 0.002 (95% CI -0.005 to 0.009). The difference between children and adults was again not statistically significant. We did not find sufficient data to assess the other proposed secondary outcomes (such as ITU admission and intubation). There was one intubation (inhaled corticosteroid only group, O'Byrne 2001).

Sensitivity Analyses

Risk of bias

No deaths occurred in the unblinded study in children (SD-039-0719) so exclusion of this study made no difference to mortality outcomes. When this study was excluded for non fatal serious adverse events, the Peto Odds Ratio for children was 1.69 (95%

CI 0.81 to 3.54) and I^2 was 45% Figure 9. A funnel plot did not suggest obvious publication bias Figure 10.

Figure 9. Forest plot of comparison: 1 Formoterol and ICS versus same dose ICS, outcome: 1.10 All-cause non-fatal Serious Adverse Events (sensitivity analysis without unblinded study).

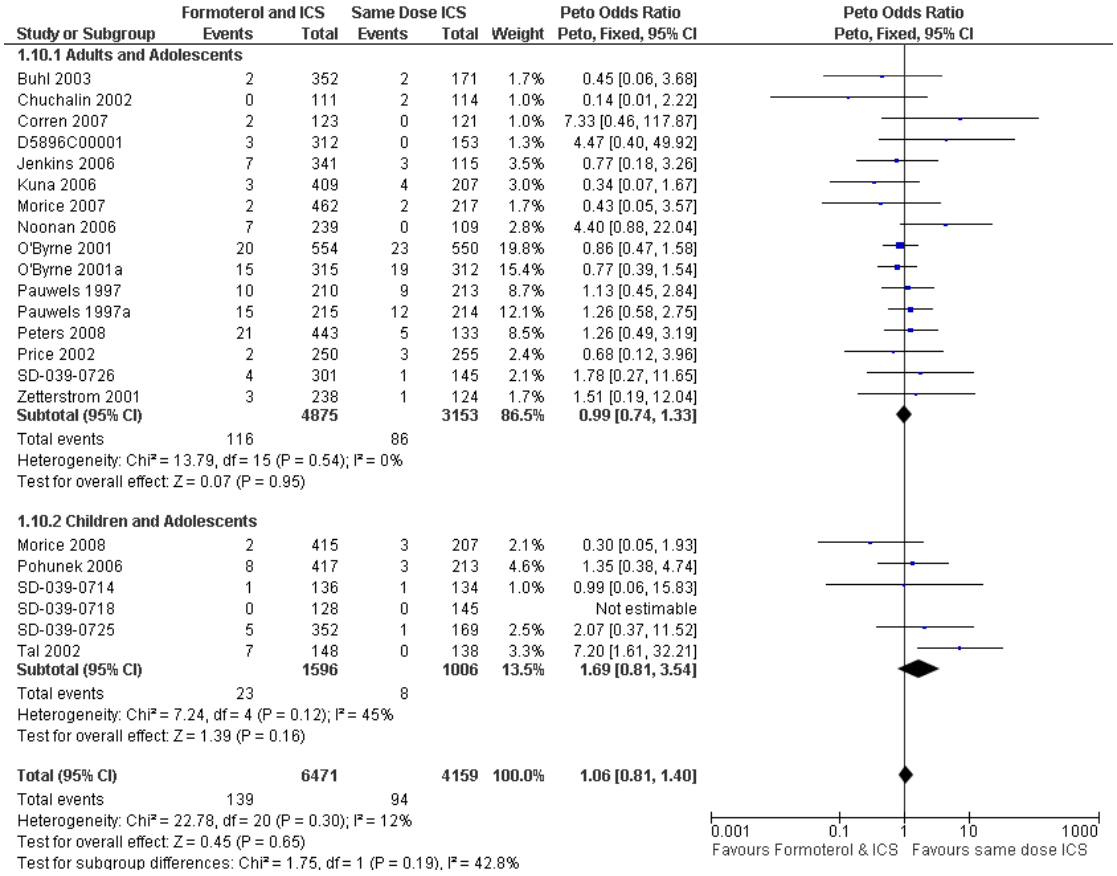
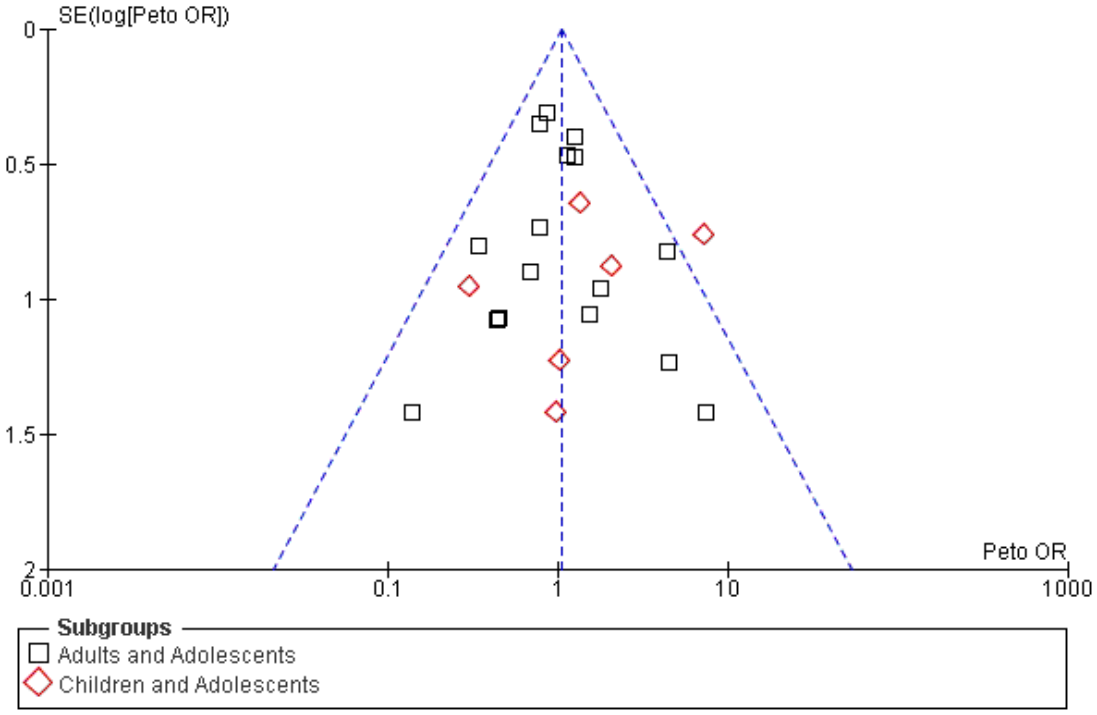


Figure 10. Funnel plot of comparison: 1 Formoterol and ICS versus same dose ICS, outcome: 1.2 All-cause non-fatal Serious Adverse Events.



Methods of analysis

The primary outcomes were also analysed using Mantel-Haenszel fixed and random effects models. The results of the fixed effects model for mortality are shown in Figure 11. This method uses a correction for zero cells which means that the pooled OR is smaller than the Peto OR, since the addition of 0.5 to all cells when the arms have similar numbers randomised will generate an OR of 3 when there is only one event. When there are very sparse outcomes (such as for mortality), the results are entirely dependent on the size of the zero cell adjustment, and whether the treatment arms are balanced. For serious adverse events the Mantel-Haenszel fixed and random effects models gave almost identical results to the Peto method Figure 12.

Figure 11. Forest plot of comparison: 1 Formoterol and ICS versus same dose ICS, outcome: 1.8 All-cause Mortality.

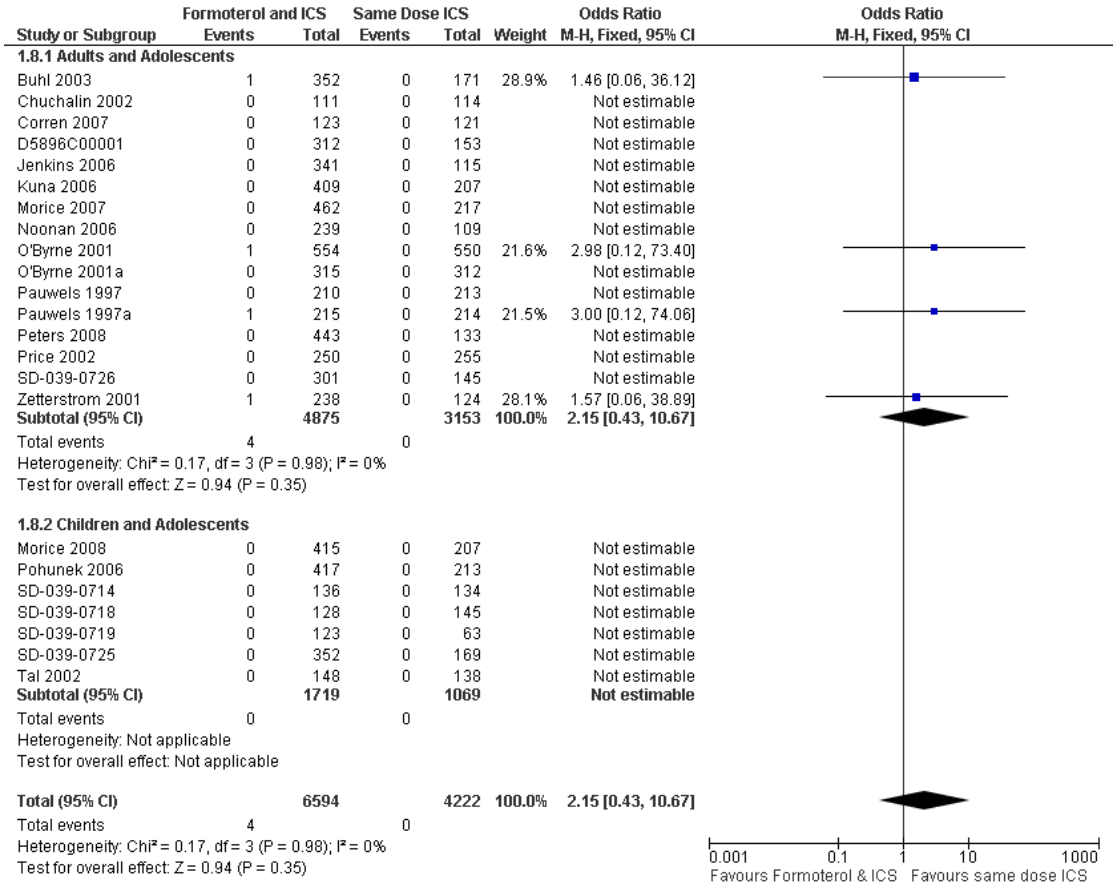
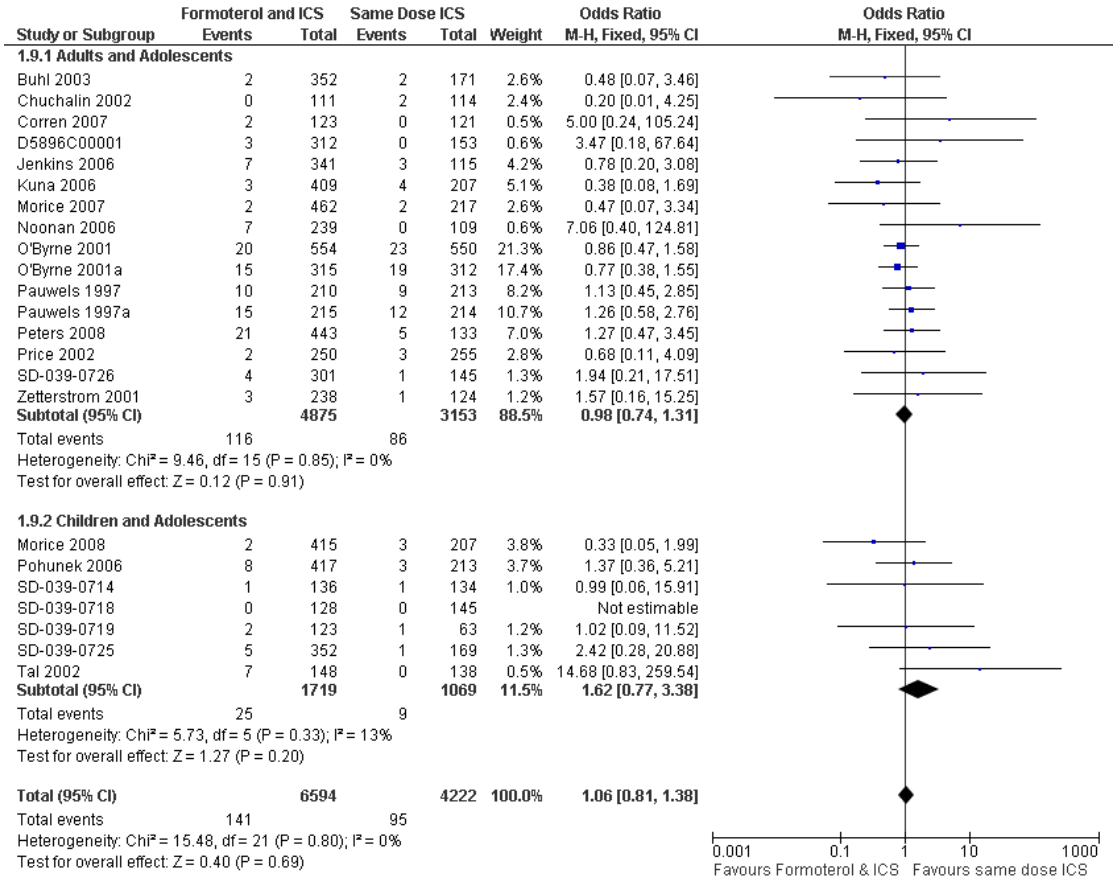


Figure 12. Forest plot of comparison: 1 Formoterol and ICS versus same dose ICS, outcome: 1.9 All-cause non-fatal Serious Adverse Events.



Dose of formoterol

The dose of formoterol used in all studies was within the licensed daily dose, so no sensitivity analysis was required to exclude unlicensed doses.

Subgroup Analyses

Mortality data were too sparse to carry out any sub-group analysis. Although the results for adults and children showed trends in opposite directions for non fatal serious adverse events (both all-cause and asthma-related), the test for interaction did not show a significant interaction of treatment effect and age.

DISCUSSION

Summary of main results

All cause mortality

The confidence intervals for all cause mortality in adults indicate that for every thousand patients treated with regular formoterol and inhaled corticosteroids in comparison to inhaled corticosteroids alone we can expect something between three additional deaths and one less death in adults over 31 weeks of treatment, and at most four additional deaths to four less deaths in children over 13 weeks of treatment (the average duration of treatment in the respective trials). The pooled Peto Odds Ratio for adults was 5.83 (95% confidence interval 0.78 to 43.77), and could not be calculated for children as there were no deaths in children.

All cause non fatal serious adverse events

For non-fatal serious adverse events the limits of the pooled confidence interval are seven more to seven fewer adults and ten more to three fewer children for every thousand treated over the period of time represented in the trials. The Peto Odds Ratio was 0.99 (95% CI 0.74 to 1.33) for adults, and 1.62 (95% CI 0.80 to 3.28) for children with heterogeneity present for the results of the studies in children.

Overall completeness and applicability of evidence

Two large studies have been carried out on the use of regular salmeterol (SMART 2006, SNS 1993), but the only large surveillance study on formoterol Pauwels 2003 (RELIEF) investigated its use as a reliever rather than as maintenance therapy and has therefore not been included in this review. This means that there is less data in this review to investigate the impact of formoterol on serious adverse events in comparison to our previous review on salmeterol (Cates 2008).

The small numbers of events in this review results in low precision of the estimates of relative risk between formoterol and control. However, outcome data were obtained from all the included studies and a funnel plot did not suggest publication bias.

Quality of the evidence

Risks of bias in the studies included in this review are thought to be low, as almost all the studies were double blind, and although allocation concealment was not well reported, it is likely to have been adequate as all the trials were sponsored or supported by AstraZeneca. Since the trials were carried out for regulatory purposes the collection of serious adverse event data will have been assessed using uniform definitions across the studies.

The level of heterogeneity within the subgroup of paediatric trials is significant (I^2 = 60%), and cannot be explained easily. The confidence intervals from two studies do not overlap (Morice 2008; Tal 2002), with the observed results indicating protection (Morice 2008), and harm (Tal 2002).

Potential biases in the review process

The selection of the best method to combine studies with rare events is contentious when event rates are low, not least because of the corrections required to calculate Odds Ratios with zero events (Sweeting 2004). Since it became apparent in the course of the review that the pooled odds ratios were heavily dependent on the zero adjustment used in the Mantel-Haenszel and Inverse variance methods, we used the Peto Odds Ratio and risk differences to report results of this review. Since the imbalance between the trial arms is never more than two to one the likely bias in using the Peto Odds Ratio is small (Sweeting 2004).

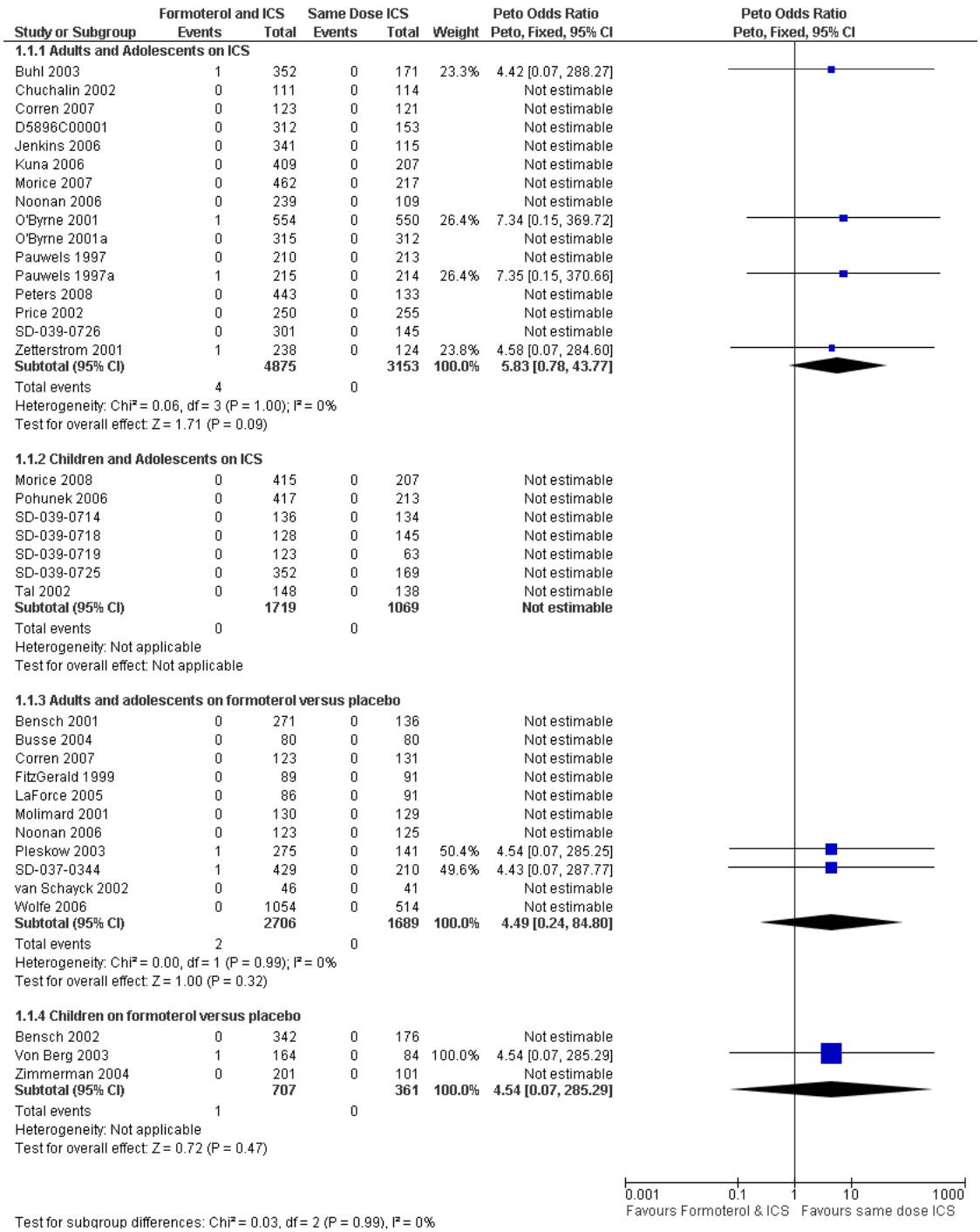
Similarly the included studies were influenced by the decision to restrict the review to trials that randomised participants to formoterol and inhaled corticosteroids, but this decision reduces the risk of bias arising from patients discontinuing their usual inhaled steroid medication if they feel better on the randomised treatment. This presupposes a similar risk of SAEs when formoterol and budesonide are delivered via one inhaler, and when formoterol is introduced to ICS therapy via a separate inhaler, when both are randomised treatments in a controlled trial.

Agreements and disagreements with other studies or reviews

Mortality

Comparing the results from this review and the review on regular formoterol without randomised inhaled corticosteroids (Cates 2008a) indicates that all 7 deaths in the trials comparing formoterol to placebo or comparing formoterol with ICS to the same dose of ICS were in patients who were randomised to formoterol (with or without ICS), see Figure 13. This is a cause for concern, because although it may seem that many of the deaths were not related to asthma, it is often hard to be sure of the exact cause of death, and the classification of cause of death is not straightforward. For example the patient who died in OPTIMA (O'Byrne 2001) was recorded in the paper as dying from septic shock, but listed in Sears 2008 as status asthmaticus and septic shock, whereas the 13 year old boy who died in Von Berg 2003 is listed in Sears 2008 as dying of respiratory failure but the paper has reported that the cause of death was subarachnoid haemorrhage. Sears 2008 does not report all-cause mortality in the sub-group of trials in patients on regular formoterol and maintenance ICS; the primary analysis on all-cause mortality include the RELIEF study which allowed regular long-acting $beta_2$-agonists in both arms and therefore was not included in this review. The adjusted all-cause mortality in Sears 2008 is RR 1.79 (95% CI 0.80, 4.00) when studies with any baseline ICS are considered; the conditional logistic regression was adjusted for trial effect (data on file provided by AstraZeneca).

Figure 13. All cause mortality in trials of regular formoterol with or without ICS



Only one asthma related death was reported in this review, but the overview of Sears 2008 identified two further asthma-related deaths from the AstraZeneca database of trials in which participants were on maintenance ICS; all three deaths were in participants randomised to regular formoterol.

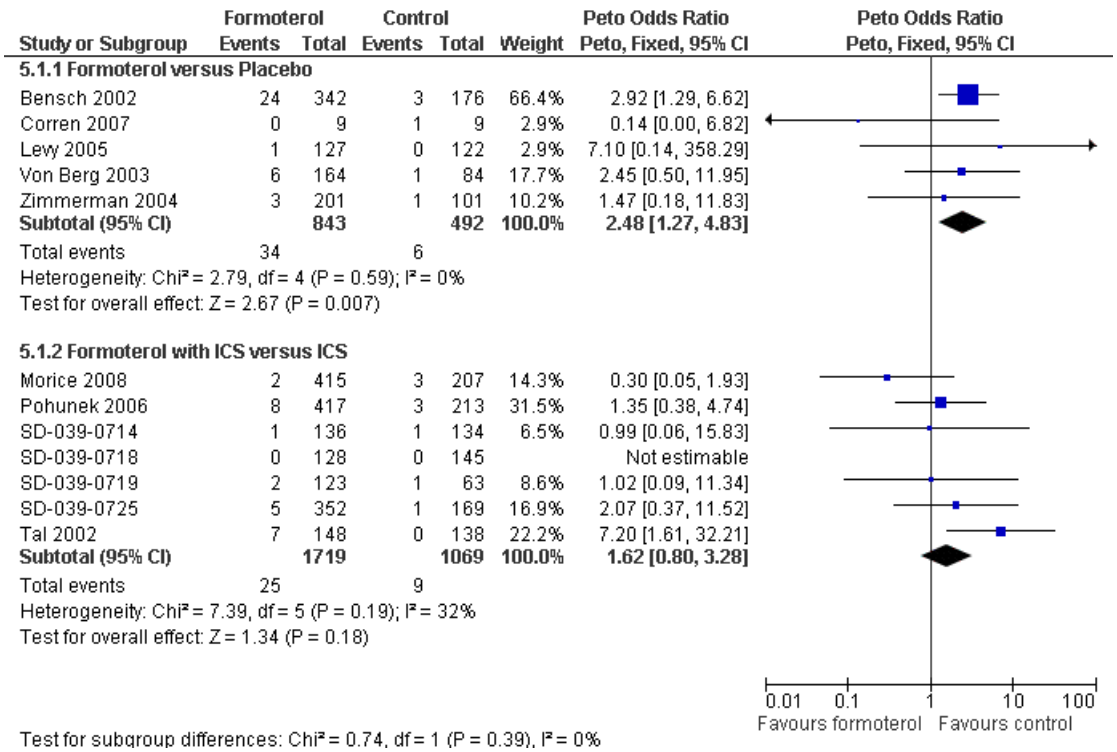
There were 6 additional death when formoterol and inhaled corticosteroids were compared to higher dose of inhaled corticosteroids - three deaths in each arm (Jaeschke 2008).

We agree with the conclusion of Sears 2008 that "the power is insufficient to conclude no increased mortality with formoterol" when regular formoterol is used in conjunction with ICS.

All-cause non fatal serious adverse events

Sears 2008 does not present data on all-cause serious adverse events, but Jaeschke 2008 has also found that the reduction in asthma-related serious adverse events and hospitalisations do not seem to translate into similar reductions in all-cause serious adverse events (which are about four times more common). Jaeschke 2008 and Jaeschke 2008a did not include trials in children. There is insufficient information from the trials in children in this review to determine whether the increased risk of non-fatal serious adverse events found on formoterol alone found in Cates 2008a (Peto OR 2.48; 95% CI 1.27 to 4.83), is abolished by the addition of randomised inhaled corticosteroids (Peto OR 1.62; 95% CI 0.80 to 3.28), as there is a large degree of overlap in the confidence intervals leading to a negative test for interaction, see Figure 14.

Figure 14. All cause serious adverse events in children on regular formoterol (with or without ICS)



AUTHORS' CONCLUSIONS

Implications for practice

It is not possible, from the data in this review, to reassure people with asthma that regular use of inhaled corticosteroids with formoterol carries no risk of increasing mortality in comparison to

inhaled corticosteroids alone as all four deaths occurred among 6,594 people using both drugs. On the other hand we have found no conclusive evidence of harm and there was only one asthma related death registered during over 3,000 patient years observation on formoterol. In adults, the decrease in asthma-related serious adverse events on regular formoterol with inhaled corticosteroids was not accompanied by a similar decrease in all cause serious adverse events. In children the number of events was too small to determine whether the increase in all cause non-fatal serious adverse events previously found on regular formoterol alone is abolished by the additional use of inhaled corticosteroids. Clinical decisions and information for patients regarding regular use of formoterol have to take into account the balance between known symptomatic benefits of formoterol and the degree of uncertainty and concern associated with its potential harmful effects.

Implications for research

Future research should clearly specify the number of patients with fatal and non-fatal serious adverse events by treatment group and cause. Any new surveillance study to investigate the impact of regular formoterol and inhaled corticosteroids on all-cause mortality would need to be very large.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Buhl 2003

Methods	**Study Design**: A randomised, double-blind, double-dummy, active-controlled, Multicentre, parallel-group study over 12 weeks from October 1999 to June 2000 at 56 centres in 9 countries. (Argentina (5), Belgium (5), the Czech Republic (14), Germany (6), Mexico (4), Russia (6), Spain (5), the Netherlands (7) and United Kingdom (4)) Run-in 2 weeks (budesonide 200 mcg twice daily)
Participants	**Population**: 523 adults (18-78) years with moderate persistent asthma. **Baseline Characteristics**: Mean age 44 years. FEV_1 77% predicted. Concomitant inhaled corticosteroids used by 100% of participants (400-1000 mcg/day) and patients not fully controlled on this dose **Inclusion Criteria**:Out-patients aged 18 years and older with perennial asthma (ATS) with a minimum duration of 6 months. Used any inhaled corticosteroid at a constant daily dose of 400-1000 µg for at least 30 days before entry and still had sub-optimal asthma control. FEV_1 % predicted between 60% to 90%, bronchodilator reversibility by an increase of at least 12% in FEV_1 over baseline at 15 minutes after inhalation of a short-acting beta2-agonist **Exclusion Criteria**: Use of oral, parental or rectal GCS within 30 days prior to visit 1, seasonal asthma, significant respiratory infection within 30 days of visit 1, severe cardiovascular disorder or any other significant disease or disorder, pregnant or planning a pregnancy, breast-feeding, not using acceptable contraceptives, not surgically sterile, hypersensitivity to study drugs, tobacco smokers or previous smokers if greater than 10 pack-years
Interventions	1. Budesonide/Formoterol 320/9 µg daily 2. Budesonide/Formoterol 160/4.5 µg twice daily 3. Budesonide 400 µg daily (equivalent daily dose of budesonide) Delivery was DPI
Outcomes	The primary efficacy variable was morning peak expiratory flow (am PEF, L/min) Paper reports five SAEs: one in the once daily BDF group and two each in the other groups. They included one death due to cardiac arrest and four other events. (No details given by treatment group in paper or on web report) Jaeschke 2008 reports one death on combined treatment and two participants with non-fatal SAE on combined treatment and two on budesonide. One SAE on BDF was asthma-related
Notes	Sponsored by AstraZeneca

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not reported

Buhl 2003 (*Continued*)

Allocation concealment?	Unclear	Not reported
Blinding? All outcomes	Yes	Double-blind
Incomplete outcome data addressed? All outcomes	Yes	480/523 (92%) completed the study
Free of selective reporting?	Yes	SAE data not attributable to treatment groups in paper but obtained from Jaeschke 2008

Chuchalin 2002

Methods	**Study Design**: A randomised, double-blind, parallel-group study over 12 weeks in Russia. Run-in 2 weeks
Participants	**Population**: 338adults (18- 66) years with mild to moderate asthma. **Baseline Characteristics**: Mean age 45 years. FEV_1 unknown% predicted. Concomitant inhaled corticosteroids used by 0% of participants. **Inclusion Criteria**:Diagnosed at least 6 months. FEV_1 % predicted between 50% and 85%, bronchodilator reversibility at least 15% in FEV_1 over baseline after inhalation of terbutaline. Female patients to be postmenopausal, surgically sterile or using medically approved contraceptive measures. **Exclusion Criteria**: smoking history of greater than 10 pack-years, current or recent users of inhaled, oral or parenteral corticosteroids, oral leukotriene antagonists, nedocromil sodium or sodium cromoglycate, beta-blockers (including eye drops)
Interventions	1. Budesonide and Formoterol 200 and 9 µg BD 2. Budesonide 200 µg BD Delivery was DPI
Outcomes	The primary efficacy variable was the change in peak expiratory flow (PEF) in the morning before any study medication was taken Paper reports no deaths and two serious adverse events (aggravated asthma and hypertension) that required hospitalisation in the budesonide only group
Notes	Supported by AstraZeneca

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Not reported
Allocation concealment?	Unclear	"Allocated a randomised number (identifying which of the three treatments they would receive) in consecutive order, per

Chuchalin 2002 (*Continued*)

		centre, at the second visit"
Blinding? All outcomes	Yes	Double-blind
Incomplete outcome data addressed? All outcomes	Yes	316/338 (93%) completed the study.
Free of selective reporting?	Yes	SAE data reported in the paper

Corren 2007

Methods	Randomized, double-blind, double-dummy, multicenter, placebo-controlled study over 12 weeks at 56 US centres from July 2002 to September 2003. Run-in 7-21 days in which usual asthma therapy was withdrawn
Participants	**Population**: 480 adolescents and adults (12- 78) years with mild to moderate persistent asthma. 123 randomised to BDF and 121 to Budesonide. The web report also includes a further 13 children in these treatment groups aged 6-11 years, but they are not separately analysed **Baseline Characteristics**: Mean age 36 years. FEV_1 75% predicted. Concomitant inhaled corticosteroids used by 100% of participants at baseline but withdrawn for the formoterol and placebo arms of this study **Inclusion Criteria**: Mild to moderate persistent asthma for at least 6 months, treated with inhaled corticosteroids for at least 4 weeks before screening, FEV_1 between 60% and 90% predicted on ICS at screening and between 50% and 85% predicted after discontinuation of ICS during run-in period. Bronchodilator reversibility of at least 12% and 0.20 L in FEV_1 over baseline within 15 to 30 minutes after administration of albuterol pMDI (2-4 inhalations [90 µg per inhalation]) **Exclusion Criteria**: Reasons for exclusion from the study included severe asthma (as judged by the investigator), asthma requiring hospitalization once or emergency treatment more than once within the 6 months before the study or requiring treatment with systemic corticosteroids within the 4 weeks before screening, and/or a >10-pack-year smoking history at screening. Pregnant or breastfeeding
Interventions	**1.** Budesonide/Formoterol 160/9 µg (DPI) twice daily **2.** Budesonide 160 µg (DPI) twice daily The Symbicort and Budesonide arms of this study are included in this review
Outcomes	The co-primary efficacy variables were changes from baseline in morning predose FEV_1 and 12-hour mean FEV_1 (from serial spirometry) after administration of the morning dose of study medication Two serious adverse events in the BDF group (lobar pneumonia and facial bone fracture) reported in the paper. No cardiac related serious adverse events were reported in any group. No deaths occurred in any group (web site data) Jaeschke 2008 reports no asthma related SAE events.
Notes	Study sponsored by AstraZeneca.

Corren 2007 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	By study site, computer-generated allocation schedule using balanced blocks of 4
Allocation concealment?	Unclear	No information
Blinding? All outcomes	Yes	Double dummy. Patients received both a pMDI and DPI containing either active treatment or placebo of the alternative active treatment as appropriate
Incomplete outcome data addressed? All outcomes	Yes	18/123 discontinued on BDF and 18/121 Budesonide
Free of selective reporting?	Yes	Serious Adverse Events reported in paper publication

D5896C00001

Methods	**Study Design**:A randomised, double-blind, single-dummy, active-controlled, multicenter, parallel-group study over 12 weeks from October 2003 to February 2005 at 143 centres in the United States. Run-in 4-5 weeks
Participants	**Population**: 619 adolescents and adults (12- 79) years with asthma. **Baseline Characteristics**: Mean age 35 years. FEV_1 76% predicted. Concomitant inhaled corticosteroids used by 100% of participants. **Inclusion Criteria**: 12 years of age and older, had a documented clinical diagnosis of asthma for at least 6 months prior to screening, and who were in stable condition. Should have received maintenance asthma treatment with inhaled corticosteroids (ICS) for at least 4 weeks prior to the screening visit. FEV_1 % predicted between 60% and 90% measured at least 24 hours after the last dose of long-acting B_2-agonist and 6 hours after the last dose of short-acting B_2-agonist.
Interventions	1. Budesonide/Formoterol 160/4.5 µg 2x QD pMDI 2. Budesonide/Formoterol 80/4.5 µg 2x QD pMDI (data not used from this arm) 3. Budesonide/Formoterol 80/4.5 µg 2x BD pMDI 4. Budesonide 160 µg 2x QD pMDI
Outcomes	Primary variable: evening predose FEV1. No full paper publication for this study. Web report indicated 2 SAE on BDF 160/4.5 twice daily with a further patient who had a myocardial infarction on the day after the treatment was discontinued. No deaths occurred. No data on asthma SAEs found
Notes	Sponsored by AstraZeneca

D5896C00001 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Not reported
Allocation concealment?	Unclear	Not reported
Blinding? All outcomes	Yes	Double-blind. To maintain blinding with the twice-daily dosing regimen, all subjects randomised to receive once-daily dosing were to take the active treatment in the evening and a matched placebo device in the morning
Incomplete outcome data addressed? All outcomes	Yes	12% drop out in each arm
Free of selective reporting?	Unclear	No asthma-related SAE data found

Jenkins 2006

Methods	Study Design: A randomised, double-blind, double-dummy, reference -controlled, Multicentre, parallel-group study over 24 weeks from July 2001 to June 2002 at 54 centres in 6 countries. (Australia (11), Austria (6) Czech Republic (15), France(9), Poland (8) Spain (5)) Run-in 2 weeks (on usual ICS)
Participants	**Population**: 456 adolescents and adults (12-79) years with persistent symptomatic asthma. **Baseline Characteristics**: Mean age 46 years. FEV_1 66% predicted.Concomitant inhaled corticosteroids used by 100% of participants. **Inclusion Criteria**:Out-patients aged 12 years and older with a diagnosis of asthma (minimum duration 6 months) FEV_1 % predicted between 40?85%, bronchodilator reversibility by an increase of at least 15% in FEV_1 over baseline after inhalation of a bronchodilator. For patients aged 18 years and older, an increase in baseline FEV1 of at least 200 mL 15 to 30 min post bronchodilator was required at study entry (visit 1). All patients had used ICS for at least 4 months at a constant daily dose of at least 750 mcg for at least 4 weeks before study entry. **Exclusion Criteria**:If asthma deteriorated, resulting in a change of asthma therapy. Total asthma symptom score had to be >1 on a scale of 0?6 for at least 4 of the last 7 days of run-in. The total asthma symptom score was the sum of daytime and night-time asthma symptom scores, each measured on a scale of 0-3 (where 0 = no symptoms and 3 = unable to perform usual activities (or to sleep) because of asthma)
Interventions	1. Budesonide/Formoterol 320/9 µg two inhalations BD + Placebo BD 2. Budesonide 400 µg two inhalations BD + Formoterol 9 µg two inhalations BD + Placebo BD

Jenkins 2006 (*Continued*)

	3. Budesonide 400 µg two inhalations BD + Placebo BD This was the treatment for the first twelve weeks, then group three was split between the first two treatments. DPI delivery
Outcomes	The primary efficacy variable was morning PeakExpiratory Flow (PEF) as registered daily in diary cards Paper reports 5 patients with SAE on BDF and two on Budesonide. One death occurred in the BDF group from Pulmonary Embolism, but as this was after 17 weeks when there was no budesonide control arm, this has not been included in the meta-analysis Data from AstraZeneca shows 7 patients with SAE on BDF and 3 on Budesonide in the first 12 weeks of the study. This has been used in the meta-analysis. It is not clear why the paper reports different numbers
Notes	Sponsored by AstraZeneca

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Individual treatment codes were computer generated in balanced blocks of 8 at AstraZeneca R&D, Lund, Sweden
Allocation concealment?	Yes	codes were then assigned to patients and kept in sealed envelopes until data analysis
Blinding? All outcomes	Yes	Double-blind
Incomplete outcome data addressed? All outcomes	Yes	400/456 (88%) completed the study
Free of selective reporting?	Yes	SAE data in paper, but this did not match final data from sponsors

Kuna 2006

Methods	**Study design:** A randomised, double-blind, double-dummy, active-controlled, Multicentre, parallel-group study over 12 weeks from November 1999 to July 2000 at 60 centres in 8 countries. (Finland (5), Germany (17), Mexico (4), New Zealand (3) Norway (6), Poland (7), Russia (5), Sweden (13) Run-in 2 weeks in which all patients received budesonide 200 mcg daily (half the previous average dose)
Participants	**Population**: 616 adults (18-80) years with mild to moderate persistent asthma. **Baseline Characteristics**: Mean age 45 years. FEV_1 78.5% predicted. Concomitant inhaled corticosteroids used by 100% of participants. **Inclusion Criteria**: 18 years of age and older, a diagnosis of asthma (minimum duration: 6 months) that was not optimally controlled despite a daily ICS dose of 200 to 500 mg

	for at least 30 days before study entry. FEV_1 % predicted of 60 to 90%, bronchodilator reversibility by an increase of at least 12% in FEV_1 over baseline after inhalation of either 1mg of terbutaline or salbutamol 0.4 mg. **Exclusion Criteria**: used any systemic corticosteroids within the previous 30 days; seasonal asthma (defined as asthma exacerbated by seasonal increases in aero allergens); a respiratory infection in the 4 weeks before study entry; a severe cardiovascular disorder or any other significant disease; used ß-blocker therapy (including eye drops) or had a history of heavy smoking (X10 pack-years), women of child-bearing potential who were pregnant or who failed to use acceptable contraceptive measures,
Interventions	1. Budesonide/Formoterol 80/4.5 µg 2x QD 2. Budesonide/Formoterol 80/4.5 µg BD 3. Budesonide 200 µg QD Delivery was DPI and all arms received equivalent delivered dose of 160 mcg budesonide daily
Outcomes	The primary variable was morning PEF. "Seven serious adverse events were reported:two in the once daily BDF group, one in the twice daily BDF group and four in the budesonide group." Although the three asthma SAEs were not described by treatment group in the paper or the web report, Jaeschke 2008 indicates one on BDF and two events on budesonide, with one hospitalisation for asthma in each group. No mortality
Notes	Sponsored by AstraZeneca

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Not described
Allocation concealment?	Unclear	Not described
Blinding? All outcomes	Yes	To ensure treatment blinding, a double-dummy design was used so that patients received four successively numbered Turbuhalers, with the corresponding placebo inhalers being identical in appearance to those containing active medication
Incomplete outcome data addressed? All outcomes	Yes	555/616 (90%) completed the study
Free of selective reporting?	Yes	SAE reported in paper by treatment group

Morice 2007

Methods	**Study Design**: A randomised, double-blind, double-dummy, parallel-group study over 12 weeks from April 2002 to February 2003 at 62 centres in Brazil (7), Bulgaria (5), Canada (9), Hungary (9), Mexico (7), the Philippines (6), Thailand (5), UK (14)). Run-in 2 weeks on pre-study ICS but LABA was withdrawn from the 15% previously treated with LABA and ICS
Participants	**Population**: 680 adolescents and adults (12 - 79) years with asthma. **Baseline Characteristics**: Mean age 40 years. FEV_1 70% predicted. Concomitant inhaled corticosteroids used previously by 100% of participants (mean dose 770 mcg/day) . **Inclusion Criteria**: 12 years of age and older with asthma for at least 6 months, who were inadequately controlled on ICS alone, FEV1 % predicted between 50% and 90%, bronchodilator reversibility by an increase of at least 12% in FEV_1 after inhalation of terbutaline 1 mg, a history of daily ICS use (stable dose of 500?1600 mcg/day within 30 days prior to enrolment) for at least 3 months. Symptoms must have been present on at least 4 of the last 7 days of run-in **Exclusion Criteria**: not defined
Interventions	1. Budesonide 200 µg 2x BD pMDI (CFC propellant) 2. Budesonide/Formoterol 160/4.5 µg 2x BD DPI 3. Budesonide/Formoterol 160/4.5 µg 2x BD pMDI (HFA propellant) All delivered the same daily dose of budesonide
Outcomes	The primary efficacy end-point was the change in morning peak expiratory flow (PEF) from baseline (mean of the last 10 days of run-in) to the mean value over the 12-week treatment period Paper report: "No deaths occurred. Four subjects experienced serious adverse events, two in the budesonide group (joint dislocation, asthma) and two in BDF pMDI (menorrhagia, increased liver enzymes)."
Notes	Sponsored by AstraZeneca.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Patients were randomised sequentially in blocks of six using a computer-generated randomisation schedule
Allocation concealment?	Yes	Eligible patients were consecutively allocated the lowest available randomisation code. In view of double-dummy design this is considered satisfactory
Blinding? All outcomes	Yes	Double-blind, double-dummy. To maintain blinding, each patient also received a placebo device

Incomplete outcome data addressed? All outcomes	Yes	600/680 (88%) completed the study
Free of selective reporting?	Yes	Full SAE data available from paper by treatment group and cause

Morice 2008

Methods	**Study Design**: A randomised, double-blind, double-dummy, parallel-group study over 12 weeks from June 2002 to May 2003 at 53 centres in Argentina (4), Brazil (6), Denmark (14), Hong Kong (1), Mexico (6), Poland (4), Slovakia (12), and Taiwan (6)) Run-in 2 weeks on previous ICS dose (but previous LABA may have been withdrawn ? not made clear in the paper)
Participants	**Population**: 622 children (6- 11) years with symptomatic asthma. **Baseline Characteristics**: Mean age 8 years. FEV_1 82% predicted. Concomitant inhaled corticosteroids used by 100% of participants (375 to 100 mcg daily). **Inclusion Criteria**: Paediatric out-patients (6-11 years) with asthma and a history of clinically important exercise-induced bronchoconstriction, daily using 375-1000 µg of inhaled glucocorticosteroids (GCSs), peak expiratory flow (PEF) at least 50% of predicted normal value (pre bronchodilator). Had to have a total asthma-symptom score (night-time plus daytime) of at least 1 on at least 4 of the last 7 days of the run-in period and a mean morning PEF (mPEF) during the last 7 days of the run-in period of 50-85% of post bronchodilatory PEF, measured at Visit 1 (enrolment). **Exclusion Criteria**: inability to use DPI and Peak Flow meter.
Interventions	1. Budesonide 100 µg 2x BD pMDI 2. Budesonide/Formoterol 80/4.5 µg 2x BD DPI 3. Budesonide/Formoterol 80/4.5 µg 2x BD pMDI Dose of budesonide was equivalent in each arm (100 metered dose equivalent to 160 delivered dose)
Outcomes	The primary efficacy end-point was the change in morning peak expiratory flow (PEF) from baseline (mean of the last 10 days of run-in) to the mean value over the 12-week treatment period Paper reports: "Five patients reported serious adverse events: 3 in budesonide group (asthma aggravation (2), nervousness), 2 BDF DPI (acute sinusitis, migraine). No deaths were reported."
Notes	Sponsored by AstraZeneca

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Patients were randomised sequentially in blocks of six using a computer-generated randomisation schedule

Morice 2008 (*Continued*)

Allocation concealment?	Unclear	No details
Blinding? All outcomes	Yes	Double blind (all patients used a placebo inhaler and an active inhaler)
Incomplete outcome data addressed? All outcomes	Yes	583/622 (94%) completed the study
Free of selective reporting?	Yes	SAE reported by treatment group and cause in paper

Noonan 2006

Methods	Randomized, double-blind, double-dummy, multicenter, placebo-controlled study over 12 weeks from July 2002 to January 2004 at 84 US centres (respiratory or allergy speciality clinical practice) Run-in 2 weeks
Participants	**Population**: 596 adolescents and adults (12-87) years with moderate to severe persistent asthma. BDF 124 patients, BD + F 115 patients, Budesonide 109 patients **Baseline Characteristics**: Mean age 41 years. FEV_1 67% predicted. Concomitant inhaled corticosteroids used by 100% of participants. **Inclusion Criteria**: Moderate to severe persistent asthma chronically treated with a medium to high dose of ICS, FEV_1 %predicted within the entrance range of 45% to 85%, bronchodilator reversibility of FEV_1 of at least 12% and 0.20 L from the pre-albuterol baseline value within 15 to 30 minutes after administration of a standard dose of salbutamol. **Exclusion Criteria**: Requiring hospitalisation once or emergency treatment more than once in the preceding 6 months, greater than 10-pack-per-year smoking history
Interventions	1. Budesonide 160 mcg twice daily 2. Budesonide/Formoterol 160/9 mcg pMDI twice daily 3. Budesonide pMDI and Formoterol DPI 160/9 mcg twice daily
Outcomes	The co-primary efficacy variables were baseline adjusted average 12-hour FEV $_1$ and predose FEV $_1$. "Nine subjects had SAEs during double-blind treatment: 4 on BDF pMDI (asthma -2, urti and ECG T wave inversion), 2 in the formoterol group and 3 in the budesonide + formoterol group (small intestine obstruction, abdominal injury, pneumonia)." Web data found on AZ clinical trials web site SD-039-0717
Notes	Sponsored by AstraZeneca. Jaeschke 2008 excluded this study as there were more than 20% dropouts.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer generated allocation schedule

Noonan 2006 (*Continued*)

Allocation concealment?	Yes	Identical packages shipped to centres
Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Yes	23% withdrawals in combined arms and 28% in budesonide arm
Free of selective reporting?	Yes	Full SAE data on web site

O'Byrne 2001

Methods	**Study design:** A randomised, double-blind, parallel-group study over 12 months from January 1998 to February 2000 at 198 centres in 17 countries. Run-in 1 month
Participants	**Population**: 1970 adults (18-76) years with mild asthma, (Group A - 698) and mild-to-moderate asthma (Group B - 1,272) **Baseline Characteristics**: (Group A) Mean age 31 years. FEV_1 90% predicted. Concomitant inhaled corticosteroids used by 0% of participants. (Group B) Mean age 37 years. FEV_1 87% predicted. Concomitant inhaled corticosteroids used by 100% of participants. **Inclusion Criteria**: 12 years of age and older. Diagnosis of stable asthma, according to the American Thoracic Society (ATS). (Group A) had used no inhaled corticosteroid for at least 3 months, pre-bronchodilator FEV_1 % predicted at least 70% at visit 1. 15 min post bronchodilator FEV_1 % predicted at least 80% at visit 1 (2x0.5 mg Bricanyl Turbuhaler). (Group B) taking no more than 400 µg of inhaled budesonide or its equivalent for at least 3 months, pre-bronchodilator FEV_1 % predicted at least 50% at visit 1. 15 min post bronchodilator FEV_1 % predicted at least 70% at visit 1 (2x0.5 mg Bricanyl Turbuhaler). **Exclusion Criteria**: use of oral GCS within 3 months prior to visit 1, beta-blocker therapy (eyedrops included).pregnant and/or lactating women or women not using acceptable contraceptives as judged by the investigator, patients with a history of smoking more than 15 pack-years
Interventions	THIS REPORT RELATES TO PATIENTS GIVEN **200 mcg Budesonide twice daily** (Group A) **1. Budesonide 200 µg** **2. Budesonide and Formoterol 200 and 4.5 µg** Placebo arm from Group A was not included in this review (Group B) **1. Budesonide 200 µg** **2. Budesonide and Formoterol 200 and 4.5 µg** 3. Budesonide 400 µg 4. Budesonide and Formoterol 400 and 4.5 µg

O'Byrne 2001 (*Continued*)

Outcomes	Primary variable was time to first severe asthma exacerbation, expressed as the risk for a first severe exacerbation, and rate (proportion) of poorly controlled days Serious Adverse Events are not mentioned at all in the paper publication and the web report (SD-037-0345) only gives total numbers of patients with SAEs for Group A and B (with no indication of treatment group) AstraZeneca have provided a breakdown of all-cause SAE and asthma-related SAE (AstraZeneca Data on file 2008) There was one death that was not reported in the paper, but mentioned in the web report as probably due to 'septic shock' in group A. Sears 2008 indicates that the death was also related to status asthmaticus and was in a patient taking budesonide/formoterol combination treatment. The full report of the death from the sponsors is: "One of the deaths occurred in a 35 year old female after an 8 day hospitalization for a severe asthma attack leading to intubation, ventilation, and nosocomial pneumonia with septic shock. "
Notes	Sponsored by AstraZeneca

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer generated random numbers
Allocation concealment?	Yes	Opaque consecutive numbered envelopes containing assignment
Blinding? All outcomes	Yes	Double-blind. Identical placebo
Incomplete outcome data addressed? All outcomes	Yes	81% in Group A and 87% in Group B completed the study
Free of selective reporting?	Yes	SAE data provided by sponsors and found from other sources

O'Byrne 2001a

Methods	**Study design:** A randomised, double-blind, parallel-group study over 12 months from January 1998 to February 2000 at 198 centres in 17 countries. Run-in 1 month
Participants	**Population**: 1970adults (18-76) years with mild asthma, (Group A - 698) and mild-to-moderate asthma (Group B - 1,272) **Baseline Characteristics**: (Group A) Mean age 31 years. FEV_1 90% predicted. Concomitant inhaled corticosteroids used by 0% of participants. (Group B) Mean age 37 years. FEV_1 87% predicted. Concomitant inhaled corticosteroids used by 100% of participants. **Inclusion Criteria**: 12 years of age and older. Diagnosis of stable asthma, according to

O'Byrne 2001a (*Continued*)

	the American Thoracic Society (ATS). (Group A) had used no inhaled corticosteroid for at least 3 months, pre-bronchodilator FEV_1 % predicted at least 70% at visit 1. 15 min post bronchodilator FEV_1 % predicted at least 80% at visit 1 (2x0.5 mg Bricanyl Turbuhaler). (Group B) taking no more than 400 µg of inhaled budesonide or its equivalent for at least 3 months, pre-bronchodilator FEV_1 % predicted at least 50% at visit 1. 15 min post bronchodilator FEV_1 % predicted at least 70% at visit 1 (2x0.5 mg Bricanyl Turbuhaler). **Exclusion Criteria**: use of oral GCS within 3 months prior to visit 1, beta-blocker therapy (eyedrops included).pregnant and/or lactating women or women not using acceptable contraceptives as judged by the investigator, patients with a history of smoking more than 15 pack-years
Interventions	THIS REPORT RELATES TO PATIENTS GIVEN 400 mcg Budesonide twice daily (Group A) 1. Budesonide 200 µg 2. Budesonide and Formoterol 200 and 4.5 µg Placebo arm from Group A was not included in this review (Group B) 1. Budesonide 200 µg 2. Budesonide and Formoterol 200 and 4.5 µg **3. Budesonide 400 µg** **4. Budesonide and Formoterol 400 and 4.5 µg**
Outcomes	The primary variable was time to first severe asthma exacerbation, expressed as the risk for a first severe exacerbation, and rate (proportion) of poorly controlled days Serious Adverse Events are not mentioned at all in the paper publication and the web report (SD-037-0345) only gives total numbers of patients with SAEs for Group A and B (with no indication of treatment group) AstraZeneca have provided a breakdown of all-cause SAE and asthma-related SAE which has been used in the meta-analysis. (AstraZeneca Data on file 2008)
Notes	Sponsored by AstraZeneca

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer generated random numbers
Allocation concealment?	Yes	Opaque consecutive numbered envelopes containing assignment
Blinding? All outcomes	Yes	Double-blind. Identical placebo
Incomplete outcome data addressed? All outcomes	Yes	81% in Group A and 87% in Group B completed the study

Free of selective reporting?	Yes	SAE data provided by sponsors

Pauwels 1997

Methods	**Study Design**:A randomised, double-blind, Multicentre, parallel-group study over 12 months at 71 centres in 9 countries. (Belgium, Canada, the Netherlands, Israel, Italy, Luxembourg, Norway, Spain and the United Kingdom). Run-in 4 weeks on 800 mcg twice daily
Participants	**Study Design**: A randomised, double-blind, Multicentre, parallel-group study over 12 months at 71 centres in 9 countries. (Belgium, Canada, the Netherlands, Israel, Italy, Luxembourg, Norway, Spain and the United Kingdom) Run-in 4 weeks on 800 mcg twice daily. **Population**: 852 adults (18-70) years with persistent symptomatic asthma. **Baseline Characteristics**: Mean age 42 years. FEV_1 76% predicted. Concomitant inhaled corticosteroids used by 100% of participants (mean dose 820 mcg/day). **Inclusion Criteria**: 18 to 70 years old, who had had asthma for at least six months and had been treated with an inhaled glucocorticoid for at least three months. FEV_1 % predicted at least 50 %, bronchodilator reversibility by an increase of at least 15% in FEV_1 over baseline after inhalation of 1mg of terbutaline. Stable asthma during run-in and compliant with treatment. **Exclusion Criteria**: Three or more courses of oral glucocorticoids or had been hospitalized for asthma during the previous six months. Taking more than 2000 mcg of beclomethasone or 1600 mcg of budesonide daily by pressurized metered dose inhaler, 800 mcg of budesonide daily by Turbuhaler dry-powder inhaler or 800 mcg of fluticasone daily
Interventions	**Budesonide 100 µg BD + Placebo** **Budesonide100 µg + Formoterol 12 µg BD (9 µg delivered dose)** Budesonide 400 µg BD + Placebo Budesonide 400 µg + Formoterol 12 µg BD (9 µg delivered dose) Delivery was DPI
Outcomes	Two primary outcome variables, the rate of severe exacerbations and the rate of mild exacerbations, according to treatment group SAE data (all-cause and asthma related) provided by AstraZeneca from Data on file 2008 No SAE data given in the paper publication, except asthma admissions but the sponsors have provided data on file for the number of patients with all-cause and asthma-related SAEs
Notes	Sponsored by AstraZeneca

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer generated randomisation schedule (Ni Chroinin 2005)

Pauwels 1997 (*Continued*)

Allocation concealment?	Yes	The patients were randomly assigned to treatment groups in balanced blocks of four at each centre
Blinding? All outcomes	Yes	Double-blind
Incomplete outcome data addressed? All outcomes	Yes	694/852 (81%) completed the study
Free of selective reporting?	Yes	SAE data provided from sponsors

Pauwels 1997a

Methods	**Study Design**:A randomised, double-blind, Multicentre, parallel-group study over 12 months at 71 centres in 9 countries. (Belgium, Canada, the Netherlands, Israel, Italy, Luxembourg, Norway, Spain and the United Kingdom). Run-in 4 weeks on 800 mcg twice daily
Participants	**Study Design**: A randomised, double-blind, Multicentre, parallel-group study over 12 months at 71 centres in 9 countries. (Belgium, Canada, the Netherlands, Israel, Italy, Luxembourg, Norway, Spain and the United Kingdom) Run-in 4 weeks on 800 mcg twice daily. **Population**: 852 adults (18-70) years with persistent symptomatic asthma. **Baseline Characteristics**: Mean age 42 years. FEV_1 76% predicted. Concomitant inhaled corticosteroids used by 100% of participants (mean dose 820 mcg/day). **Inclusion Criteria**: 18 to 70 years old, who had asthma for at least six months and had been treated with an inhaled glucocorticoid for at least three months. FEV_1 % predicted at least 50 %, bronchodilator reversibility by an increase of at least 15% in FEV_1 over baseline after inhalation of 1mg of terbutaline. Stable asthma during run-in and compliant with treatment. **Exclusion Criteria**: Three or more courses of oral glucocorticoids or had been hospitalized for asthma during the previous six months. Taking more than 2000 mcg of beclomethasone or 1600 mcg of budesonide daily by pressurized metered dose inhaler, 800 mcg of budesonide daily by Turbuhaler dry-powder inhaler or 800 mcg of fluticasone daily
Interventions	This report deals with patients on 800 mcg budesonide daily Budesonide 100 µg BD + Placebo Budesonide100 µg + Formoterol 12 µg BD (9 µg delivered dose) **Budesonide 400 µg BD + Placebo** **Budesonide 400 µg + Formoterol 12 µg BD (9 µg delivered dose)** Delivery was DPI
Outcomes	Two primary outcome variables, the rate of severe exacerbations and the rate of mild exacerbations, according to treatment group SAE data (all-cause and asthma related) provided by AstraZeneca from Data on file 2008 No SAE data given in the paper publication, except asthma admissions but the sponsors

Pauwels 1997a (*Continued*)

	have provided data on file for the number of patients with all-cause and asthma-related SAEs. There was one death (unrelated to asthma) in a participant on Budesonide 400 and Formoterol 12 twice daily
Notes	Sponsored by AstraZeneca

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer generated randomisation schedule (Ni Chroinin 2005)
Allocation concealment?	Yes	The patients were randomly assigned to treatment groups in balanced blocks of four at each centre
Blinding? All outcomes	Yes	Double-blind
Incomplete outcome data addressed? All outcomes	Yes	694/852 (81%) completed the study
Free of selective reporting?	Yes	SAE data provided from sponsors

Peters 2008

Methods	**Study Design**: A randomised, double-blind, single-dummy, Multicentre, Phase III,parallel-group study over 52 weeks from August 2003 to February 2005 at 77 centres in the United States Run-in 2 weeks on budesonide 320 mcg bd (LABA discontinued).
Participants	**Population**: 708 adults and adolescents (12 - 81) years with moderate to severe persistent asthma **Baseline Characteristics**: Mean age 40 years. FEV_1 72% predicted. Concomitant inhaled corticosteroids used by 100% of participants (mean daily dose around 500 mcg) **Inclusion Criteria**: 12 years of age and older with a documented clinical diagnosis of moderate-to-severe asthma for at least 6 months prior to screening, received maintenance asthma treatment with a stable dose of inhaled corticosteroids (ICS) for at least 4 weeks prior to the screening visit. FEV_1 % predicted of at least 45%, bronchodilator reversibility by an increase of at least 12% in FEV_1 and at least 0.20 L from baseline within 15?30 minutes after administration of a fast-acting beta2-agonist or have a documented history of this level of reversibility after administration of a fast-acting beta2-agonist while using ICS within 1 year of screening. To require two asthma controller medications or to have had a history of at least two asthma-related nighttime awakenings or at least three uses of rescue medication within the week before screening. Required to be nonsmokers, with a less than 20 pack-year smoking history. **Exclusion Criteria**: had a significant disease or disorder (*e.g.* cardiovascular, pulmonary

	[other than asthma], hepatic, renal) that, in the opinion of the investigator, may put the patient at risk or influence the results of the study. In addition, treated with systemic corticosteroids within 30 days before screening or during the period between screening and randomisation were excluded
Interventions	1. Budesonide/Formoterol 640/18 µg BD 2. Budesonide/ Formoterol 320/9 µg BD (this arm was not used in the analysis for this review) 3. Budesonide 640 µg BD Delivery was pMDI
Outcomes	Because this study was a safety study, no single variable was considered primary. However, spirometry (predose and 2-hour post dose FEV_1) was conducted at each study visit to detect any untoward decreases in lung function over the 52-week period Web report indicates 21 patients with SAE on BDF 640/18 bd and 5 on budesonide 640 bd. No deaths in the study Paper reports one asthma SAE in the BDF 640/18 bd group.
Notes	Sponsored by AstraZeneca (SD-039-0728)

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	randomised using a 3:1:1 overall randomisation scheme and a computer-generated allocation schedule
Allocation concealment?	Unclear	Not reported
Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Yes	579/708 (82%) completed the study
Free of selective reporting?	Yes	SAE data available from paper and web report.

Pohunek 2006

Methods	**Study Design**:A randomised, double-blind, double-dummy, active-controlled, Multi-centre, parallel-group study over 12 weeks from March, 2002 to March, 2003 at 80 centres in 8 countries (Austria (5), Belgium (11), Czech Republic (14), France (11), Hungary (12), Poland (17), Spain (8) and Switzerland (2)) Run-in 2 weeks on previous dose of ICS but LABA appears to have been withdrawn from the 40% previously taking LABA?
Participants	**Population**: 630 children (4-11) years with asthma. **Baseline Characteristics**: Mean age 8 years. FEV_1 92% predicted. Concomitant inhaled corticosteroids used by 100% of participants (mean 450 mcg/day), and around 40% had previously being taking LABA. **Inclusion Criteria**: Outpatients aged 4 to 11 yr who had been diagnosed with asthma [as defined by the American Thoracic Society] for a minimum period of 6 months, to have a pre-bronchodilator PEF at least 50% of predicted normal and received treatment with an ICS (any brand) for at least 3 months before entry into the study, with the dose remaining constant (375 to1000 µg day) during the 30 days immediately prior to enrolment, had to have a history of an average of more than 1 clinically important exercise-induced bronchoconstriction per week during the 3 months leading up to the study. **Exclusion Criteria**: used oral, parenteral or rectal corticosteroids within 30 days of inclusion in the study; any respiratory infection affecting asthma control within the 30 days before enrolment; any significant disease or concomitant disorder; known or suspected hypersensitivity to the study medication or inhaled lactose. The use of inhaled anticholinergics, beta-blockers (including eye drops), xanthines and other anti-asthma products was not permitted during the study
Interventions	1. Budesonide/Formoterol 80/4.5 µg 2x BD 2. Budesonide 100 µg 2x BD 3. Budesonide 100 µg 2x BD + Formoterol 4.5 µg 2x BD (separate inhalers) Equivalent budesonide in each arm (400 mcg metered dose). DPI delivery
Outcomes	The primary efficacy variable was the change from baseline to treatment (average of the 12-wk treatment period) in morning peak expiratory flow (PEF) Paper reports: " Serious adverse events were experienced by a total of 11 patients: 3 BDF (fracture, laryngitis, torticollis), 5 with budesonide and formoterol in separate inhalers (appendicitis (2), vomiting, laryngitis, pneumonia) and 3 with budesonide (gastroenteritis (2) and fracture). There were no deaths
Notes	Sponsored by AstraZeneca

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not reported
Allocation concealment?	Unclear	Not reported

Pohunek 2006 (*Continued*)

Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Yes	592/630 (94%) completed the study
Free of selective reporting?	Yes	SAE reported by treatment group and event type in paper

Price 2002

Methods	**Study Design**: A randomised, double-blind, Multicentre, parallel-group study in 152 general practices in the UK and Republic of Ireland and comprising two parts (4 weeks and 24 weeks) Run-in 7 to 14 days
Participants	**Population**: 663 adolescents and adults (12+) years with mild to moderate asthma (part 1), **505 continued to part 2** **Baseline Characteristics**: Mean age 38 years. Concomitant inhaled corticosteroids used by 67% of participants. **Inclusion Criteria**: 12 years and older with a diagnosis of asthma confirmed in the clinical record for at least 3 months. Current treatment had to include a short acting b2 agonist alone or with an inhaled corticosteroid (< 400 mg/day beclomethasone dipropionate or budesonide via pressurised metered dose inhaler, or < 200 mg/day fluticasone or budesonide via Turbohaler) at a constant dose for > 4 weeks. Were required to have experienced asthma symptoms (chest tightness, cough, wheeze, or shortness of breath) on a minimum of 3 days in the week before enrolment into the study. Either reversibility of peak expiratory flow (PEF)/forced expiratory volume in 1 second (FEV1) of > 12% (or > 9% of predicted normal), or a diurnal variation of > 20% on at least one day during the run in period **Exclusion Criteria**: more severe or recently unstable asthma, PEF <50% predicted; currently receiving (during 4 weeks before enrolment) nebulised therapy, oral corticosteroids, leukotriene antagonist, or long acting b2 agonist; a clinically relevant upper respiratory tract infection in the 4 weeks leading up to enrolment, irreversible chronic airways disease
Interventions	1. Budesonide 400 µg BD + eformoterol 9 µg BD 2. Budesonide 400 µg BD + placebo Data from Part 2 used following 4 weeks stabilisation of patients on the same treatments in part 1. DPI delivery
Outcomes	In part II the primary outcome measure was time to the first mild asthma exacerbation SAE data not reported in paper but obtained from Jaeschke 2008.
Notes	Supported by grant from AstraZeneca

Risk of bias

Item	Authors' judgement	Description

Price 2002 (*Continued*)

Adequate sequence generation?	Yes	Computer generated random numbers (Ni Chroinin 2005)
Allocation concealment?	Yes	Numbered coded solutions supplied by pharmacy (Ni Chroinin 2005)
Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Yes	400/505 (79%) completed part 2
Free of selective reporting?	Yes	Data on SAEs from Jaeschke 2008

SD-039-0714

Methods	A randomized, double-blind, multicentre, parallel-group study over 12 weeks from August 2001 to September 2002 at 122 centres in the United Kingdom. (119 general practice centres and 3 hospital centres) Run-in 2 weeks on budesonide 200 mcg twice daily Efficacy and safety of budesonide/formoterol Turbuhaler® (160/4.5 mg b.i.d. delivered dose) compared to budesonide Turbuhaler® (200 mg b.i.d. metered dose) in steroid-using asthmatic adolescent patients. A double-blind, double dummy, randomised, parallel group, phase III, multicentre study. (ATTAIN STUDY)
Participants	**Population**: 271 steroid-using asthmatic adolescents(11 to 17) years. **Baseline Characteristics**: Mean age 14 years. FEV_1 75% predicted. Concomitant inhaled corticosteroids used by 100% of participants (. **Inclusion Criteria**: 12-17 years old, . FEV_1 % predicted 40-90%, bronchodilator reversibility of at least 12% in FEV_1 and experiencing asthma symptoms. Receiving an iGCS for perennial asthma, dose of iGCS within or equal to 375-1000 mg daily dose within the licensed dose for the patients' age, **Exclusion Criteria**: not obvious
Interventions	1. Budesonide/Formoterol 160/4.5 µg BD 2. Budesonide 200 µg BD Delivery was DPI
Outcomes	am PEF as recorded daily by patients in diary. Web report indicates no deaths and one SAE in each group (overdose on BDF and bronchospasm on budesonide)
Notes	Sponsored by AstraZeneca

Risk of bias

Item	Authors' judgement	Description

SD-039-0714 (*Continued*)

Adequate sequence generation?	Unclear	Not reported
Allocation concealment?	Unclear	Not reported
Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Yes	219/271 (81%) completed the study
Free of selective reporting?	Yes	SAE data in web report

SD-039-0718

Methods	**Study Design**: A randomized, double-blind, double-dummy, active-controlled study over 12 weeks from July 2002 to October 2003 at 52 centers in the United States. Run-in 2 weeks on 100 mcg budesonide twice daily
Participants	**Population**: 411 children (6 -15) with mild to moderate asthma. **Baseline Characteristics**: Mean age 10 years. FEV_1 82% predicted. Concomitant inhaled corticosteroids used by 100% of participants (mean 235 mcg/day). **Inclusion Criteria**: 6 to 15 years of age, chronically treated with a low to medium dose of inhaled corticosteroid (ICS), FEV_1 % predicted at least 50% on ICS therapy, older than 12 years, bronchodilator reversibility of at least 12% in FEV_1 and at least 0.20 L from the pre-albuterol value within 15-30 minutes after administration of a standard dose of a fast-acting beta2-agonist (albuterol pMDI, 2 to 4 actuations [90 µg per actuation], with or without a spacer, or after administration of up to 2.5 mg nebulized albuterol). Younger than 12 years needed to show only reversibility of at least 12%. Alternatively, reversibility of PEF of at least 15%, but not more than 50%, could be used by any subject to meet the reversibility criterion. **Exclusion Criteria**: not obvious
Interventions	1. Budesonide/Formoterol 40/4.5 µg 2x BD pMDI delivery 2. Budesonide 40 µg 2x BD pMDI delivery 3. Formoterol 4.5 µg 2x BD DPI delivery Arm three not used in this review
Outcomes	Primary efficacy variable: morning peak expiratory flow (PEF) Web report lists no deaths and no patients with SAE in groups one or two
Notes	Sponsored by AstraZeneca

Risk of bias

Item	**Authors' judgement**	**Description**

SD-039-0718 (*Continued*)

Adequate sequence generation?	Yes	Randomization was stratified by age group (children under 8 years of age versus children 8 years and older) Subjects were randomly assigned to 1 of the 3 treatment groups
Allocation concealment?	Unclear	No details
Blinding? All outcomes	Yes	Double-blind. Treatments were given in double-dummy fashion because of the difference in devices
Incomplete outcome data addressed? All outcomes	Yes	28% dropout on BDF and 35% on budesonide (all randomised patients in safety analysis and no events reported!)
Free of selective reporting?	Yes	SAE data on web report

SD-039-0719

Methods	**Study Design** : A randomized, open-label, safety study over 26 weeks from July 2002 to October 2003 at 29 centers in the United States. Run-in 1 week
Participants	**Population**: 187 children (6 -11) years with ICS-dependent asthma. **Baseline Characteristics**: Mean age 9 years. FEV_1 84% predicted. Concomitant inhaled corticosteroids used by 100% of participants. **Inclusion Criteria**: 6 to under 12 years of age with ICS-dependent asthma. FEV_1 % predicted at least 50%, documented historic peak expiratory flow (PEF) or FEV1 reversibility at least 12% from a pre-albuterol value within 15 to 30 minutes after administration of a standard dose of fast-acting B_2-agonist. Subjects without a documented history of reversibility must have demonstrated FEV_1 reversibility as above at any time before Visit 2. **Exclusion Criteria**: not obvious
Interventions	1. Budesonide/Formoterol 160/4.5 µg 2x BD pMDI delivery 2. Budesonide 160 µg 2x BD TBH delivery
Outcomes	Outcome: No single variable was considered to be primary. The primary objective of the study was to assess long-term safety Web report indicates no deaths. Two SAEs in BDF group (asthma and pneumonia) and one on budesonide (sickle cell anaemia)
Notes	Sponsored by AstraZeneca

Risk of bias

Item	**Authors' judgement**	**Description**

SD-039-0719 (*Continued*)

Adequate sequence generation?	Unclear	Not reported
Allocation concealment?	Unclear	Not reported
Blinding? All outcomes	No	Open
Incomplete outcome data addressed? All outcomes	Yes	87% completed the study
Free of selective reporting?	Yes	SAE reported fully

SD-039-0725

Methods	**Study Design**: A randomized, double-blind, double-dummy, multicenter, active-controlled, parallel group, study over 12 weeks from January 2003 to August 2004 at 128 centers in the United States. Run-in 4-5 week single-blind (in which participants had to be stable on budesonide/formoterol 40/4.5 mcg two puffs twice daily) A Twelve-Week, Randomized, Double-blind, Double-Dummy, Active-Controlled Study of SYMBICORT® pMDI Administered Once Daily in Children and Adolescents 6 to 15 Years of Age with Asthma
Participants	**Population**: 522 children and adolescents (6 -15) years with asthma. **Baseline Characteristics**: Mean age 10 years. FEV_1 78% predicted. Concomitant inhaled corticosteroids previously used by 100% of participants (mean 245 mcg/day) **Inclusion Criteria**: 6 to 15 years with a documented clinical diagnosis of asthma for at least 6 months prior to screening, and in stable condition. Should have received maintenance asthma treatment with inhaled corticosteroids (ICS) for at least 4 weeks prior to the screening visit. FEV_1 % predicted of between 60%-90%, measured approximately 24 hours after the last dose of long-acting B_2- agonist and 6 hours after the last dose of short-acting B_2-agonist. Subjects with an FEV_1 predicted between 90-95% predicted could be included if they had an FEV_1/FVC ratio measured on screening spirometry of less than 80%. Bronchodilator reversibility of at least 12% in FEV_1 and at least 0.20 L from baseline within 15 to 30 minutes after administration of a standard dose of fast-acting ?2-agonist, except for subjects under 11 years of age, who were required to show reversibility of at least 12%, but not also a change of at least 0.20 L. **Exclusion Criteria**: not stated
Interventions	1. Budesonide/Formoterol 80/4.5 µg 2x QD 2. Budesonide/Formoterol 40/4.5 µg 2x BD 3. Budesonide 80 µg 2x QD Delivery was pMDI. All groups had 160 mcg budesonide daily.
Outcomes	Primary variable: evening PEF (from daily diary) "There were no deaths at any time during the study." "6 subjects had an SAE during the double blind treatment period: 2 on BDF 40 bd (abdominal pain, asthma), 3 in BDF 80 qd group (influenza, asthma -2), and one in the budesonide group (asthma)."

SD-039-0725 (*Continued*)

Notes	Sponsored by AstraZeneca	
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Randomization was stratified by age (6 to 11 years of age versus 12 to 15 years of age) at the time of screening, to ensure an approximately uniform distribution of subjects across treatment groups within each of these 2 strata
Allocation concealment?	Unclear	No details
Blinding? All outcomes	Yes	Double-blind. In order to maintain blinding with the twice-daily dosing regimen, all subjects randomized to receive once-daily dosing were to receive the active treatment in the evening and placebo treatment with a matched device in the morning
Incomplete outcome data addressed? All outcomes	Yes	499/521 (96%) completed the study
Free of selective reporting?	Yes	SAEs reported by treatment group and cause

SD-039-0726

Methods	**Study Design**: A randomized, double-blind, double-dummy, multicenter, parallel group, placebo- and active-controlled study over 12 weeks from April 2003 to June 2004 at 151 centers in the United States. Run-in 4-5 week single-blind A Twelve-Week, Randomized, Double-Blind, Double-Dummy, Placebo- and Active-Controlled Study of SYMBICORT® pMDI Administered Once Daily in Adults and Adolescents with Asthma
Participants	**Population**: 752 adolescents and adults (16 -79) years with asthma. **Baseline Characteristics**: Mean age 38 years. FEV_1 75% predicted. Concomitant inhaled corticosteroids used by 100% of participants. **Inclusion Criteria**: 16-years of age and older, with a documented clinical diagnosis of asthma for at least 6 months prior to screening, and in stable condition. Received maintenance asthma treatment with a low to medium dose of inhaled corticosteroids (ICS) for at least 4 weeks prior to the screening visit FEV_1 % predicted of between 60%-90%, measured at least 24 hours after the last dose of long-acting B_2- agonist and 6 hours after the last dose of short-acting B_2-agonist. **Exclusion Criteria**: not obvious

SD-039-0726 (*Continued*)

Interventions	1. Budesonide/Formoterol 160/4.5 µg 2x QD 2. Budesonide/Formoterol 80/4.5 µg 2x QD 3. Budesonide/Formoterol 80/4.5 µg 2x BD 4. Budesonide 160 µg 2x QD Placebo arm and arm two not used in this analysis. MDI delivery
Outcomes	Primary variable: evening PEF (from daily diary) SAE data obtained from web report. Five patients suffered an SAE: Three on BDF 80 bd (breast cancer in situ, road traffic accident, musculoskeletal chest pain), one on BDF 160 daily (prostate cancer), and one on budesonide (tension headache). There were no deaths
Notes	Sponsored by AstraZeneca

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Not reported
Allocation concealment?	Unclear	Not reported
Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Yes	707/751 (94%) completed the study
Free of selective reporting?	Yes	SAE data on web report

Tal 2002

Methods	**Study Design**: A randomized, double-blind, double-dummy, active-controlled, multicentre, parallel-group study over 12 weeks from November 1998 to June 1999 at 48 centres in 7 countries Hungary (6), the Czech Republic (7), the United Kingdom (11), Spain (7), Belgium (4), Israel (4) and South Africa (4) Run-in 2-4 weeks on budesonide 400 mcg daily (unclear if previous LABA withdrawn)
Participants	**Population**: 286 children (4-17) years with asthma. **Baseline Characteristics**: Mean age 11 years. FEV_1 75% predicted. Concomitant inhaled corticosteroids used by 100% of participants (mean 548 mcg/day), previous LABA use not reported **Inclusion Criteria**: Between 4 to 17 years of age with a diagnosis of asthma (minimum duration, 6 months), FEV_1 % predicted of 40 to 90%, bronchodilator reversibility by an increase of at least 15% in FEV_1 over baseline within 15 min of inhalation of a short-acting b2-agonist. **Exclusion Criteria**: unstable asthma (defined as the use of oral, parenteral, or rectal corticosteroids within 30 days of study commencement), any respiratory infection af-

Tal 2002 (*Continued*)

	fecting disease control within the previous 4 weeks, and known hypersensitivity to study medication or inhaled lactose
Interventions	1. Budesonide/Formoterol 80/4.5 µg 2x BD 2. Budesonide 100 µg 2x BD Delivery was DPI
Outcomes	The primary efficacy variable was the change in morning PEF from baseline to end of treatment "A total of 7 patients in the budesonide/formoterol group had a serious adverse event requiring admission to hospital (asthma (5), larynx edema (1), pneumonia (1)." Deaths are not mentioned nor are any events in the budesonide group. Further clarification was sought from the sponsors, who have confirmed no serious adverse events in the budesonide group
Notes	Sponsored by AstraZeneca

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	computer-generated block-randomization list
Allocation concealment?	Unclear	individual treatment code envelopes provided for each subject
Blinding? All outcomes	Yes	Double-blind, double-dummy technique
Incomplete outcome data addressed? All outcomes	Yes	268/286 (94%) completed the study
Free of selective reporting?	Yes	SAEs appear to be fully reported in the paper.

Zetterstrom 2001

Methods	**Study Design**: A randomized, double-blind, double-dummy, active-controlled, parallel-group study over 12 weeks at 63 centres in 6 countries (Finland (7), Germany (12), Ireland (6), Norway (12), Spain (11) and Sweden (15)) Run-in 2 weeks on usual inhaled corticosteroid (no mention of continuing previous LABA)
Participants	**Population**: 362adults (18 - 78) years with asthma not controlled with inhaled corticosteroids alone **Baseline Characteristics**: Mean age 47 years. FEV_1 74% predicted. Concomitant inhaled corticosteroids used by 100% of participants (mean dose 960 mcg/day). **Inclusion Criteria**: 18 years and older, using inhaled glucocorticosteroids at a constant

Zetterstrom 2001 (*Continued*)

	daily dose of at least 500 µg for at least 30 days before entry, FEV_1 % predicted of 50? 90%, bronchodilator reversibility by an increase of at least 15% in FEV_1 over baseline after inhalation of terbutaline sulphate 1 mg (Bricanyl Turbuhaler) or salbutamol 0.4 mg. **Exclusion Criteria**: use of oral, parenteral or rectal glucocorticosteroids within 30 days before study entry; respiratory infection; seasonal asthma; severe cardiovascular disorder; beta-blocker therapy; a history of heavy smoking (greater than10 pack-yrs); pregnancy or failure to use acceptable contraceptives in women of childbearing potential
Interventions	1. Budesonide/Formoterol 160/4.5 µg 2x BD 2. Budesonide 200 µg + Formoterol 4.5 µg 2x BD 3. Budesonide 200 µg 2x BD Delivery was DPI, equivalent to budesonide 400 mcg bd metered dose in all arms
Outcomes	The primary efficacy variable was change in average morning PEF from baseline to study end Paper reports: "There were five serious adverse events in the single inhaler therapy group and one in the budesonide alone group. There was one death by suicide and four hospital admissions (due to pneumonia, liver cysts, ischaemic stroke and intervertebral disc prolapse)." The sponsors have confirmed that the death was on a combined budesonide/formoterol inhaler
Notes	Sponsored by AstraZeneca

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computerized randomization occurred on a per country basis.
Allocation concealment?	Yes	individual treatment codes were kept in sealed envelopes until data analysis
Blinding? All outcomes	Yes	Double-blind, patients successively used three numbered inhalers (identical in appearance to the corresponding placebo) each morning and evening
Incomplete outcome data addressed? All outcomes	Yes	309/362 (85%) completed the study
Free of selective reporting?	Yes	SAE by treatment group in paper.

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

Study	Reason for exclusion
Ankerst 2003	Short term crossover study
AstraZeneca 2005	Comparison with Budesonide and Theophylline
AstraZeneca 2005a	Ongoing study
AstraZeneca 2005b	Comparison of Single Inhaler Therapy with Current Best Practice
AstraZeneca 2005c	Comparison of Single Inhaler Therapy with Current Best Practice
AstraZeneca 2005d	Comparison of Single Inhaler Therapy with Current Best Practice
AstraZeneca 2006	Comparison of Single Inhaler Therapy with ICS and terbutaline
AstraZeneca 2006a	Comparison of Single Inhaler Therapy with Current Best Practice
AstraZeneca 2006b	Comparison of Single Inhaler Therapy with Current Best Practice
Balanag 2006	Comparison to salbutamol in acute asthma
Bateman 2003	BDF compared to higher dose Fluticasone
Bateman 2006	Acute asthma
Bouros 1999	Formoterol and beclometasone compared to higher dose beclometasone
Buhl 2004	Adjustable versus fixed dose BDF
Burgess 1998	Short term cross-over study
Canonica 2004	Adjustable versus fixed dose BDF
Ceylan 2004	Formoterol in comparison with montelukast in addition to low dose ICS
Dhillon 2006	Review of beclometasone/formoterol treatment
FitzGerald 1999	No randomisation to ICS
FitzGerald 2003	Adjustable versus fixed dose BDF
Haahtela 2006	Formoterol used as needed (with or without budesonide)
Ind 2004	Adjustable versus fixed dose BDF

(*Continued*)

Kozlik-Feldmann 1996	No randomisation to ICS
Lalloo 2003	BDF compared to higher dose ICS
Leuppi 2003	Adjustable versus fixed dose BDF
Lotvall	Short term comparison of bronchodilation following FPS and BDF
Lundborg 2006	Cost effectiveness of Single inhaler therapy
Mitchell 2003	Comparison with higher dose ICS
Molimard 2001	Not randomised to ICS
Novartis 2005	No randomisation to ICS
O'Byrne 2005	BDF as single inhaler therapy or fixed dose compared to higher dose budesonide
Overbeek 2005	Duration of less than 12 weeks on each dose of budesonide
Papi 2007	Delivery device comparison for beclometasone/formoterol combination inhalers
Pauwels 2003	Comparison of formoterol with salbutamol as relief medication
Pleskow 2003	Not randomised to ICS
Pohl 2006	Adjustable Maintenance Dosing study
Rabe 2006	BDF single inhaler therapy compared to higher dose budesonide
Rosenhall 2002	Combined BDF inhaler compared to both medications given together in separate inhalers
Rosenhall 2003	Combined BDF inhaler compared to both medications given together in separate inhalers
Rosenhall 2003a	Combined BDF inhaler compared to both medications given together in separate inhalers
Scicchitano 2004	BDF single inhaler therapy compared to higher dose budesonide
Stelmach 2007	4 week study
van der Molen 1997	No randomisation to inhaled corticosteroids
Villa, 2002	Formoterol as needed compared to terbutaline as needed
Von Berg 2003	No randomisation to ICS
Worth 2005	Single inhaler therapy compared to current best practice

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Zetterstrom 2001a	Single inhaler therapy
Zetterström 2000	Single inhaler therapy

DATA AND ANALYSES

Comparison 1. Formoterol and ICS versus same dose ICS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause Mortality	23	10816	Peto Odds Ratio (Peto, Fixed, 95% CI)	5.83 [0.78, 43.77]
1.1 Adults and Adolescents	16	8028	Peto Odds Ratio (Peto, Fixed, 95% CI)	5.83 [0.78, 43.77]
1.2 Children and Adolescents	7	2788	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2 All-cause non-fatal Serious Adverse Events	23	10816	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.06 [0.81, 1.39]
2.1 Adults and Adolescents	16	8028	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.99 [0.74, 1.33]
2.2 Children and Adolescents	7	2788	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.62 [0.80, 3.28]
3 Asthma Mortality	23		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
3.1 Adults and Adolescents	16		Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
3.2 Children and Adolescents	7		Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
4 Asthma-related non-fatal Serious Adverse Events	23	10816	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.68 [0.39, 1.18]
4.1 Adults and Adolescents	16	8028	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.53 [0.28, 1.00]
4.2 Children and Adolescents	7	2788	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.49 [0.48, 4.61]
5 All-cause Mortality (risk difference)	23	10816	Risk Difference (M-H, Fixed, 95% CI)	Not estimable
5.1 Adults and Adolescents	16	8028	Risk Difference (M-H, Fixed, 95% CI)	Not estimable
5.2 Children and Adolescents	7	2788	Risk Difference (M-H, Fixed, 95% CI)	Not estimable
6 All-cause non-fatal Serious Adverse Events (risk difference)	23	10816	Risk Difference (M-H, Fixed, 95% CI)	0.00 [-0.00, 0.01]
6.1 Adults and Adolescents	16	8028	Risk Difference (M-H, Fixed, 95% CI)	Not estimable
6.2 Children and Adolescents	7	2788	Risk Difference (M-H, Fixed, 95% CI)	0.01 [-0.00, 0.01]
7 Asthma-related non-fatal Serious Adverse Events (risk difference)	23	10816	Risk Difference (M-H, Fixed, 95% CI)	-0.00 [-0.01, 0.00]
7.1 Adults and Adolescents	16	8028	Risk Difference (M-H, Fixed, 95% CI)	Not estimable
7.2 Children and Adolescents	7	2788	Risk Difference (M-H, Fixed, 95% CI)	0.00 [-0.00, 0.01]
8 All-cause Mortality (Mantel-Haenszel fixed)	23	10816	Odds Ratio (M-H, Fixed, 95% CI)	2.15 [0.43, 10.67]
8.1 Adults and Adolescents	16	8028	Odds Ratio (M-H, Fixed, 95% CI)	2.15 [0.43, 10.67]
8.2 Children and Adolescents	7	2788	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
9 All-cause non-fatal Serious Adverse Events (Mantel-Haenszel fixed)	23	10816	Odds Ratio (M-H, Fixed, 95% CI)	1.06 [0.81, 1.38]
9.1 Adults and Adolescents	16	8028	Odds Ratio (M-H, Fixed, 95% CI)	0.98 [0.74, 1.31]
9.2 Children and Adolescents	7	2788	Odds Ratio (M-H, Fixed, 95% CI)	1.62 [0.77, 3.38]
10 All-cause non-fatal Serious Adverse Events (sensitivity analysis without unblinded study)	22	10630	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.06 [0.81, 1.40]
10.1 Adults and Adolescents	16	8028	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.99 [0.74, 1.33]
10.2 Children and Adolescents	6	2602	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.69 [0.81, 3.54]

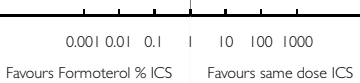
Analysis 1.1. Comparison 1 Formoterol and ICS versus same dose ICS, Outcome 1 All-cause Mortality.

Review: Regular treatment with formoterol and inhaled steroids for chronic asthma: serious adverse events

Comparison: 1 Formoterol and ICS versus same dose ICS

Outcome: 1 All-cause Mortality

Study or subgroup	Formoterol and ICS n/N	Same Dose ICS n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
1 Adults and Adolescents				
Buhl 2003	1/352	0/171		4.42 [0.07, 288.27]
Chuchalin 2002	0/111	0/114		0.0 [0.0, 0.0]
Corren 2007	0/123	0/121		0.0 [0.0, 0.0]
D5896C00001	0/312	0/153		0.0 [0.0, 0.0]
Jenkins 2006	0/341	0/115		0.0 [0.0, 0.0]
Kuna 2006	0/409	0/207		0.0 [0.0, 0.0]
Morice 2007	0/462	0/217		0.0 [0.0, 0.0]
Noonan 2006	0/239	0/109		0.0 [0.0, 0.0]
O'Byrne 2001	1/554	0/550		7.34 [0.15, 369.72]
O'Byrne 2001a	0/315	0/312		0.0 [0.0, 0.0]
Pauwels 1997	0/210	0/213		0.0 [0.0, 0.0]
Pauwels 1997a	1/215	0/214		7.35 [0.15, 370.66]
Peters 2008	0/443	0/133		0.0 [0.0, 0.0]
Price 2002	0/250	0/255		0.0 [0.0, 0.0]
SD-039-0726	0/301	0/145		0.0 [0.0, 0.0]
Zetterstrom 2001	1/238	0/124		4.58 [0.07, 284.60]
Subtotal (95% CI)	**4875**	**3153**		**5.83 [0.78, 43.77]**
Total events: 4 (Formoterol and ICS), 0 (Same Dose ICS)				
Heterogeneity: Chi^2 = 0.06, df = 3 (P = 1.00); I^2 =0.0%				
Test for overall effect: Z = 1.71 (P = 0.087)				
2 Children and Adolescents				
Morice 2008	0/415	0/207		0.0 [0.0, 0.0]
Pohunek 2006	0/417	0/213		0.0 [0.0, 0.0]
SD-039-0714	0/136	0/134		0.0 [0.0, 0.0]
SD-039-0718	0/128	0/145		0.0 [0.0, 0.0]
SD-039-0719	0/123	0/63		0.0 [0.0, 0.0]



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Study or subgroup	Formoterol and ICS n/N	Same Dose ICS n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
SD-039-0725	0/352	0/169		0.0 [0.0, 0.0]
Tal 2002	0/148	0/138		0.0 [0.0, 0.0]
Subtotal (95% CI)	**1719**	**1069**		**0.0 [0.0, 0.0]**
Total events: 0 (Formoterol and ICS), 0 (Same Dose ICS)				
Heterogeneity: Chi² = 0.0, df = 0 (P<0.00001); I² =0.0%				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Total (95% CI)	**6594**	**4222**		**5.83 [0.78, 43.77]**
Total events: 4 (Formoterol and ICS), 0 (Same Dose ICS)				
Heterogeneity: Chi² = 0.06, df = 3 (P = 1.00); I² =0.0%				
Test for overall effect: Z = 1.71 (P = 0.087)				
Test for subgroup differences: Not applicable				

Analysis 1.2. Comparison 1 Formoterol and ICS versus same dose ICS, Outcome 2 All-cause non-fatal Serious Adverse Events.

Review: Regular treatment with formoterol and inhaled steroids for chronic asthma: serious adverse events

Comparison: 1 Formoterol and ICS versus same dose ICS

Outcome: 2 All-cause non-fatal Serious Adverse Events

Study or subgroup	Formoterol and ICS n/N	Same Dose ICS n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
1 Adults and Adolescents				
Buhl 2003	2/352	2/171		0.45 [0.06, 3.68]
Chuchalin 2002	0/111	2/114		0.14 [0.01, 2.22]
Corren 2007	2/123	0/121		7.33 [0.46, 117.87]
D5896C00001	3/312	0/153		4.47 [0.40, 49.92]
Jenkins 2006	7/341	3/115		0.77 [0.18, 3.26]
Kuna 2006	3/409	4/207		0.34 [0.07, 1.67]
Morice 2007	2/462	2/217		0.43 [0.05, 3.57]

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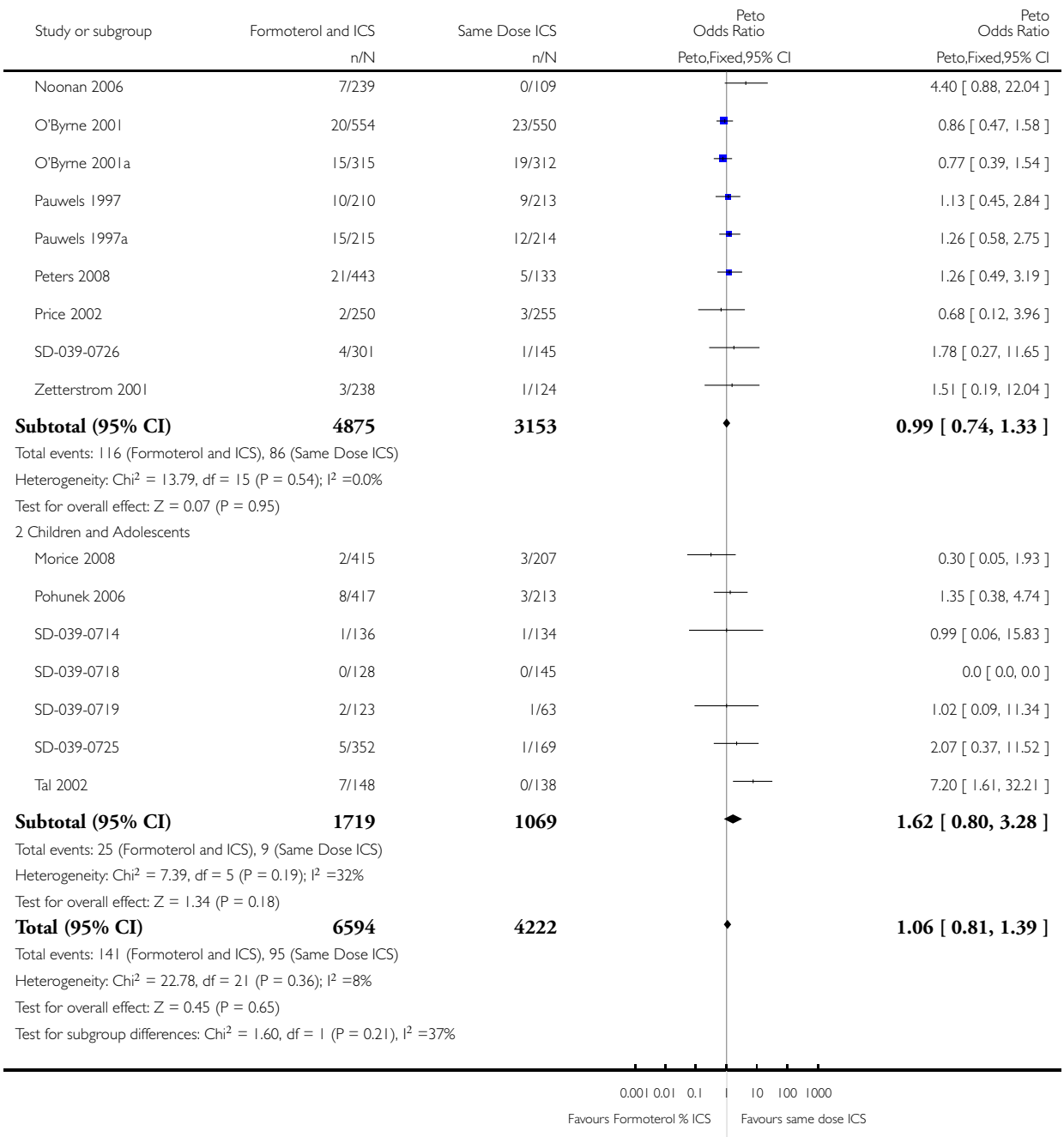

Analysis 1.3. Comparison 1 Formoterol and ICS versus same dose ICS, Outcome 3 Asthma Mortality.

Review: Regular treatment with formoterol and inhaled steroids for chronic asthma: serious adverse events

Comparison: 1 Formoterol and ICS versus same dose ICS

Outcome: 3 Asthma Mortality

Study or subgroup	Formoterol and ICS n/N	Same Dose ICS n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
1 Adults and Adolescents				
Buhl 2003	0/352	0/171		0.0 [0.0, 0.0]
Chuchalin 2002	0/111	0/114		0.0 [0.0, 0.0]
Corren 2007	0/123	0/121		0.0 [0.0, 0.0]
D5896C00001	0/312	0/153		0.0 [0.0, 0.0]
Jenkins 2006	0/341	0/115		0.0 [0.0, 0.0]
Kuna 2006	0/409	0/207		0.0 [0.0, 0.0]
Morice 2007	0/462	0/217		0.0 [0.0, 0.0]
Noonan 2006	0/239	0/109		0.0 [0.0, 0.0]
O'Byrne 2001	1/554	0/550		7.34 [0.15, 369.72]
O'Byrne 2001a	0/315	0/312		0.0 [0.0, 0.0]
Pauwels 1997	0/210	0/213		0.0 [0.0, 0.0]
Pauwels 1997a	0/215	0/214		0.0 [0.0, 0.0]
Peters 2008	0/443	0/133		0.0 [0.0, 0.0]
Price 2002	0/250	0/255		0.0 [0.0, 0.0]
SD-039-0726	0/301	0/145		0.0 [0.0, 0.0]
Zetterstrom 2001	0/238	0/124		0.0 [0.0, 0.0]
2 Children and Adolescents				
Morice 2008	0/415	0/207		0.0 [0.0, 0.0]
Pohunek 2006	0/417	0/213		0.0 [0.0, 0.0]
SD-039-0714	0/136	0/134		0.0 [0.0, 0.0]
SD-039-0718	0/128	0/145		0.0 [0.0, 0.0]
SD-039-0719	0/123	0/63		0.0 [0.0, 0.0]
SD-039-0725	0/352	0/169		0.0 [0.0, 0.0]
Tal 2002	0/148	0/138		0.0 [0.0, 0.0]

Analysis 1.4. Comparison 1 Formoterol and ICS versus same dose ICS, Outcome 4 Asthma-related non-fatal Serious Adverse Events.

Review: Regular treatment with formoterol and inhaled steroids for chronic asthma: serious adverse events

Comparison: 1 Formoterol and ICS versus same dose ICS

Outcome: 4 Asthma-related non-fatal Serious Adverse Events

Study or subgroup	Formoterol and ICS n/N	Same Dose ICS n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
1 Adults and Adolescents				
Buhl 2003	1/352	0/171		4.42 [0.07, 288.27]
Chuchalin 2002	0/111	1/114		0.14 [0.00, 7.00]
Corren 2007	0/123	0/121		0.0 [0.0, 0.0]
D5896C00001	0/312	0/153		0.0 [0.0, 0.0]
Jenkins 2006	0/341	0/115		0.0 [0.0, 0.0]
Kuna 2006	1/409	2/207		0.23 [0.02, 2.49]
Morice 2007	0/462	1/217		0.04 [0.00, 2.93]
Noonan 2006	2/239	0/109		4.31 [0.22, 85.86]
O'Byrne 2001	3/554	4/550		0.74 [0.17, 3.29]
O'Byrne 2001a	4/315	7/312		0.57 [0.17, 1.87]
Pauwels 1997	1/210	3/213		0.37 [0.05, 2.65]
Pauwels 1997a	2/215	5/214		0.42 [0.09, 1.86]
Peters 2008	1/443	0/133		3.67 [0.04, 384.21]
Price 2002	0/250	1/255		0.14 [0.00, 6.96]
SD-039-0726	0/301	0/145		0.0 [0.0, 0.0]
Zetterstrom 2001	0/238	0/124		0.0 [0.0, 0.0]
Subtotal (95% CI)	**4875**	**3153**		**0.53 [0.28, 1.00]**
Total events: 15 (Formoterol and ICS), 24 (Same Dose ICS)				
Heterogeneity: Chi^2 = 6.72, df = 10 (P = 0.75); I^2 =0.0%				
Test for overall effect: Z = 1.96 (P = 0.050)				
2 Children and Adolescents				
Morice 2008	0/415	2/207		0.05 [0.00, 0.94]
Pohunek 2006	0/417	0/213		0.0 [0.0, 0.0]
SD-039-0714	0/136	1/134		0.13 [0.00, 6.72]
SD-039-0718	0/128	0/145		0.0 [0.0, 0.0]

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Study or subgroup	Formoterol and ICS n/N	Same Dose ICS n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
SD-039-0719	1/123	0/63		4.54 [0.07, 285.29]
SD-039-0725	3/352	1/169		1.41 [0.17, 11.48]
Tal 2002	5/148	0/138		7.10 [1.21, 41.53]
Subtotal (95% CI)	**1719**	**1069**		**1.49 [0.48, 4.61]**
Total events: 9 (Formoterol and ICS), 4 (Same Dose ICS)				
Heterogeneity: Chi^2 = 9.89, df = 4 (P = 0.04); I^2 =60%				
Test for overall effect: Z = 0.70 (P = 0.49)				
Total (95% CI)	**6594**	**4222**		**0.68 [0.39, 1.18]**
Total events: 24 (Formoterol and ICS), 28 (Same Dose ICS)				
Heterogeneity: Chi^2 = 19.08, df = 15 (P = 0.21); I^2 =21%				
Test for overall effect: Z = 1.36 (P = 0.17)				
Test for subgroup differences: Chi^2 = 2.48, df = 1 (P = 0.12), I^2 =60%				

Analysis 1.5. Comparison 1 Formoterol and ICS versus same dose ICS, Outcome 5 All-cause Mortality (risk difference).

Review: Regular treatment with formoterol and inhaled steroids for chronic asthma: serious adverse events

Comparison: 1 Formoterol and ICS versus same dose ICS

Outcome: 5 All-cause Mortality (risk difference)

Study or subgroup	Formoterol and ICS n/N	Same Dose ICS n/N	Risk Difference M-H,Fixed,95% CI	Weight	Risk Difference M-H,Fixed,95% CI
1 Adults and Adolescents					
Buhl 2003	1/352	0/171		4.6 %	0.00 [-0.01, 0.01]
Chuchalin 2002	0/111	0/114		2.3 %	0.0 [-0.02, 0.02]
Corren 2007	0/123	0/121		2.5 %	0.0 [-0.02, 0.02]
D5896C00001	0/312	0/153		4.1 %	0.0 [-0.01, 0.01]
Jenkins 2006	0/341	0/115		3.5 %	0.0 [-0.01, 0.01]
Kuna 2006	0/409	0/207		5.5 %	0.0 [-0.01, 0.01]
Morice 2007	0/462	0/217		6.0 %	0.0 [-0.01, 0.01]
Noonan 2006	0/239	0/109		3.0 %	0.0 [-0.01, 0.01]
O'Byrne 2001	1/554	0/550		11.1 %	0.00 [0.00, 0.01]
O'Byrne 2001a	0/315	0/312		6.3 %	0.0 [-0.01, 0.01]
Pauwels 1997	0/210	0/213		4.3 %	0.0 [-0.01, 0.01]
Pauwels 1997a	1/215	0/214		4.3 %	0.00 [-0.01, 0.02]
Peters 2008	0/443	0/133		4.1 %	0.0 [-0.01, 0.01]
Price 2002	0/250	0/255		5.1 %	0.0 [-0.01, 0.01]
SD-039-0726	0/301	0/145		4.0 %	0.0 [-0.01, 0.01]
Zetterstrom 2001	1/238	0/124		3.3 %	0.00 [-0.01, 0.02]
Subtotal (95% CI)	**4875**	**3153**		**74.1 %**	**0.00 [0.00, 0.00]**
Total events: 4 (Formoterol and ICS), 0 (Same Dose ICS)					
Heterogeneity: Chi^2 = 1.21, df = 15 (P = 1.00); I^2 =0.0%					
Test for overall effect: Z = 0.74 (P = 0.46)					
2 Children and Adolescents					
Morice 2008	0/415	0/207		5.6 %	0.0 [-0.01, 0.01]
Pohunek 2006	0/417	0/213		5.7 %	0.0 [-0.01, 0.01]
SD-039-0714	0/136	0/134		2.7 %	0.0 [-0.01, 0.01]
SD-039-0718	0/128	0/145		2.7 %	0.0 [-0.01, 0.01]

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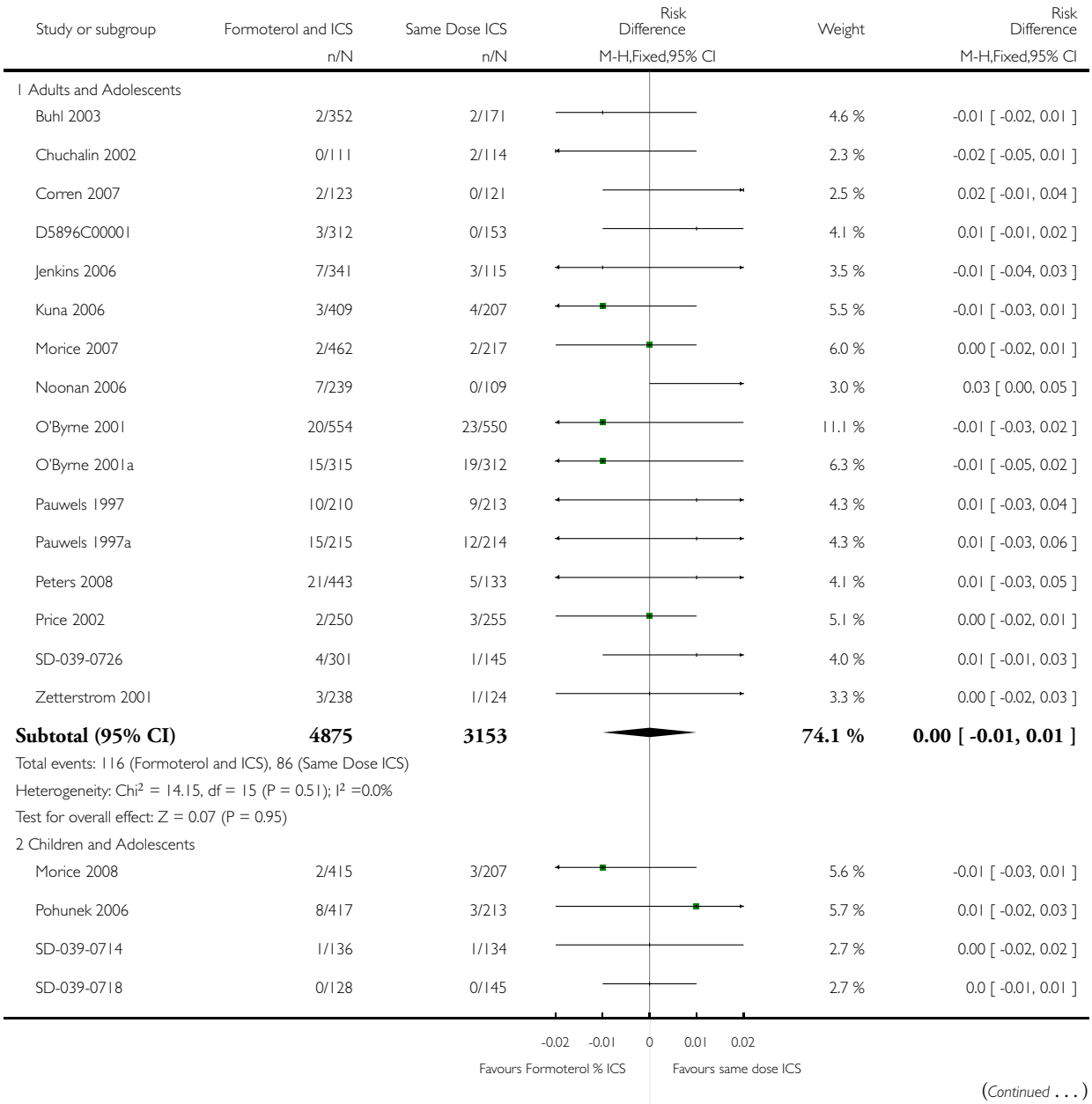
Study or subgroup	Formoterol and ICS n/N	Same Dose ICS n/N	Risk Difference M-H,Fixed,95% CI	Weight	Risk Difference M-H,Fixed,95% CI
SD-039-0719	0/123	0/63		1.7 %	0.0 [-0.02, 0.02]
SD-039-0725	0/352	0/169		4.6 %	0.0 [-0.01, 0.01]
Tal 2002	0/148	0/138		2.9 %	0.0 [-0.01, 0.01]
Subtotal (95% CI)	**1719**	**1069**		**25.9 %**	**0.0 [0.00, 0.00]**
Total events: 0 (Formoterol and ICS), 0 (Same Dose ICS)					
Heterogeneity: Chi^2 = 0.0, df = 6 (P = 1.00); I^2 =0.0%					
Test for overall effect: Z = 0.0 (P = 1.0)					
Total (95% CI)	**6594**	**4222**		**100.0 %**	**0.00 [0.00, 0.00]**
Total events: 4 (Formoterol and ICS), 0 (Same Dose ICS)					
Heterogeneity: Chi^2 = 1.30, df = 22 (P = 1.00); I^2 =0.0%					
Test for overall effect: Z = 0.63 (P = 0.53)					

Analysis 1.6. Comparison 1 Formoterol and ICS versus same dose ICS, Outcome 6 All-cause non-fatal Serious Adverse Events (risk difference).

Review: Regular treatment with formoterol and inhaled steroids for chronic asthma: serious adverse events

Comparison: 1 Formoterol and ICS versus same dose ICS

Outcome: 6 All-cause non-fatal Serious Adverse Events (risk difference)



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Study or subgroup	Formoterol and ICS n/N	Same Dose ICS n/N	Risk Difference M-H,Fixed,95% CI	Weight	Risk Difference M-H,Fixed,95% CI
SD-039-0719	2/123	1/63		1.7 %	0.00 [-0.04, 0.04]
SD-039-0725	5/352	1/169		4.6 %	0.01 [-0.01, 0.03]
Tal 2002	7/148	0/138		2.9 %	0.05 [0.01, 0.08]
Subtotal (95% CI)	**1719**	**1069**		**25.9 %**	**0.01 [0.00, 0.01]**
Total events: 25 (Formoterol and ICS), 9 (Same Dose ICS)					
Heterogeneity: Chi^2 = 9.05, df = 6 (P = 0.17); I^2 =34%					
Test for overall effect: Z = 1.32 (P = 0.19)					
Total (95% CI)	**6594**	**4222**		**100.0 %**	**0.00 [0.00, 0.01]**
Total events: 141 (Formoterol and ICS), 95 (Same Dose ICS)					
Heterogeneity: Chi^2 = 22.49, df = 22 (P = 0.43); I^2 =2%					
Test for overall effect: Z = 0.45 (P = 0.66)					

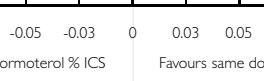
Analysis 1.7. Comparison 1 Formoterol and ICS versus same dose ICS, Outcome 7 Asthma-related non-fatal Serious Adverse Events (risk difference).

Review: Regular treatment with formoterol and inhaled steroids for chronic asthma: serious adverse events

Comparison: 1 Formoterol and ICS versus same dose ICS

Outcome: 7 Asthma-related non-fatal Serious Adverse Events (risk difference)

Study or subgroup	Formoterol and ICS n/N	Same Dose ICS n/N	Risk Difference M-H,Fixed,95% CI	Weight	Risk Difference M-H,Fixed,95% CI
1 Adults and Adolescents					
Buhl 2003	1/352	0/171		4.6 %	0.00 [-0.01, 0.01]
Chuchalin 2002	0/111	1/114		2.3 %	-0.01 [-0.03, 0.02]
Corren 2007	0/123	0/121		2.5 %	0.0 [-0.02, 0.02]
D5896C00001	0/312	0/153		4.1 %	0.0 [-0.01, 0.01]
Jenkins 2006	0/341	0/115		3.5 %	0.0 [-0.01, 0.01]
Kuna 2006	1/409	2/207		5.5 %	-0.01 [-0.02, 0.01]
Morice 2007	0/462	1/217		6.0 %	0.00 [-0.02, 0.01]
Noonan 2006	2/239	0/109		3.0 %	0.01 [-0.01, 0.03]
O'Byrne 2001	3/554	4/550		11.1 %	0.00 [-0.01, 0.01]
O'Byrne 2001a	4/315	7/312		6.3 %	-0.01 [-0.03, 0.01]
Pauwels 1997	1/210	3/213		4.3 %	-0.01 [-0.03, 0.01]
Pauwels 1997a	2/215	5/214		4.3 %	-0.01 [-0.04, 0.01]
Peters 2008	1/443	0/133		4.1 %	0.00 [-0.01, 0.01]
Price 2002	0/250	1/255		5.1 %	0.00 [-0.01, 0.01]
SD-039-0726	0/301	0/145		4.0 %	0.0 [-0.01, 0.01]
Zetterstrom 2001	0/238	0/124		3.3 %	0.0 [-0.01, 0.01]
Subtotal (95% CI)	**4875**	**3153**		**74.1 %**	**0.00 [-0.01, 0.00]**
Total events: 15 (Formoterol and ICS), 24 (Same Dose ICS)					
Heterogeneity: Chi^2 = 7.47, df = 15 (P = 0.94); I^2 =0.0%					
Test for overall effect: Z = 1.70 (P = 0.089)					
2 Children and Adolescents					
Morice 2008	0/415	2/207		5.6 %	-0.01 [-0.02, 0.01]
Pohunek 2006	0/417	0/213		5.7 %	0.0 [-0.01, 0.01]
SD-039-0714	0/136	1/134		2.7 %	-0.01 [-0.03, 0.01]
SD-039-0718	0/128	0/145		2.7 %	0.0 [-0.01, 0.01]



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Study or subgroup	Formoterol and ICS n/N	Same Dose ICS n/N	Risk Difference M-H,Fixed,95% CI	Weight	Risk Difference M-H,Fixed,95% CI
SD-039-0719	1/123	0/63		1.7 %	0.01 [-0.02, 0.04]
SD-039-0725	3/352	1/169		4.6 %	0.00 [-0.01, 0.02]
Tal 2002	5/148	0/138		2.9 %	0.03 [0.00, 0.07]
Subtotal (95% CI)	**1719**	**1069**		**25.9 %**	**0.00 [0.00, 0.01]**
Total events: 9 (Formoterol and ICS), 4 (Same Dose ICS)					
Heterogeneity: Chi^2 = 7.40, df = 6 (P = 0.29); I^2 =19%					
Test for overall effect: Z = 0.56 (P = 0.58)					
Total (95% CI)	**6594**	**4222**		**100.0 %**	**0.00 [-0.01, 0.00]**
Total events: 24 (Formoterol and ICS), 28 (Same Dose ICS)					
Heterogeneity: Chi^2 = 13.67, df = 22 (P = 0.91); I^2 =0.0%					
Test for overall effect: Z = 1.16 (P = 0.25)					

Analysis 1.8. Comparison 1 Formoterol and ICS versus same dose ICS, Outcome 8 All-cause Mortality (Mantel-Haenszel fixed).

Review: Regular treatment with formoterol and inhaled steroids for chronic asthma: serious adverse events

Comparison: 1 Formoterol and ICS versus same dose ICS

Outcome: 8 All-cause Mortality (Mantel-Haenszel fixed)

Study or subgroup	Formoterol and ICS n/N	Same Dose ICS n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 Adults and Adolescents				
Buhl 2003	1/352	0/171		1.46 [0.06, 36.12]
Chuchalin 2002	0/111	0/114		0.0 [0.0, 0.0]
Corren 2007	0/123	0/121		0.0 [0.0, 0.0]
D5896C00001	0/312	0/153		0.0 [0.0, 0.0]
Jenkins 2006	0/341	0/115		0.0 [0.0, 0.0]
Kuna 2006	0/409	0/207		0.0 [0.0, 0.0]
Morice 2007	0/462	0/217		0.0 [0.0, 0.0]

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Study or subgroup	Formoterol and ICS n/N	Same Dose ICS n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Noonan 2006	0/239	0/109		0.0 [0.0, 0.0]
O'Byrne 2001	1/554	0/550		2.98 [0.12, 73.40]
O'Byrne 2001a	0/315	0/312		0.0 [0.0, 0.0]
Pauwels 1997	0/210	0/213		0.0 [0.0, 0.0]
Pauwels 1997a	1/215	0/214		3.00 [0.12, 74.06]
Peters 2008	0/443	0/133		0.0 [0.0, 0.0]
Price 2002	0/250	0/255		0.0 [0.0, 0.0]
SD-039-0726	0/301	0/145		0.0 [0.0, 0.0]
Zetterstrom 2001	1/238	0/124		1.57 [0.06, 38.89]
Subtotal (95% CI)	**4875**	**3153**		**2.15 [0.43, 10.67]**
Total events: 4 (Formoterol and ICS), 0 (Same Dose ICS)				
Heterogeneity: Chi^2 = 0.17, df = 3 (P = 0.98); I^2 =0.0%				
Test for overall effect: Z = 0.94 (P = 0.35)				
2 Children and Adolescents				
Morice 2008	0/415	0/207		0.0 [0.0, 0.0]
Pohunek 2006	0/417	0/213		0.0 [0.0, 0.0]
SD-039-0714	0/136	0/134		0.0 [0.0, 0.0]
SD-039-0718	0/128	0/145		0.0 [0.0, 0.0]
SD-039-0719	0/123	0/63		0.0 [0.0, 0.0]
SD-039-0725	0/352	0/169		0.0 [0.0, 0.0]
Tal 2002	0/148	0/138		0.0 [0.0, 0.0]
Subtotal (95% CI)	**1719**	**1069**		**0.0 [0.0, 0.0]**
Total events: 0 (Formoterol and ICS), 0 (Same Dose ICS)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P<0.00001); I^2 =0.0%				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Total (95% CI)	**6594**	**4222**		**2.15 [0.43, 10.67]**
Total events: 4 (Formoterol and ICS), 0 (Same Dose ICS)				
Heterogeneity: Chi^2 = 0.17, df = 3 (P = 0.98); I^2 =0.0%				
Test for overall effect: Z = 0.94 (P = 0.35)				

Analysis 1.9. Comparison 1 Formoterol and ICS versus same dose ICS, Outcome 9 All-cause non-fatal Serious Adverse Events (Mantel-Haenszel fixed).

Review: Regular treatment with formoterol and inhaled steroids for chronic asthma: serious adverse events

Comparison: 1 Formoterol and ICS versus same dose ICS

Outcome: 9 All-cause non-fatal Serious Adverse Events (Mantel-Haenszel fixed)

Study or subgroup	Formoterol and ICS n/N	Same Dose ICS n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 Adults and Adolescents				
Buhl 2003	2/352	2/171		0.48 [0.07, 3.46]
Chuchalin 2002	0/111	2/114		0.20 [0.01, 4.25]
Corren 2007	2/123	0/121		5.00 [0.24, 105.24]
D5896C00001	3/312	0/153		3.47 [0.18, 67.64]
Jenkins 2006	7/341	3/115		0.78 [0.20, 3.08]
Kuna 2006	3/409	4/207		0.38 [0.08, 1.69]
Morice 2007	2/462	2/217		0.47 [0.07, 3.34]
Noonan 2006	7/239	0/109		7.06 [0.40, 124.81]
O'Byrne 2001	20/554	23/550		0.86 [0.47, 1.58]
O'Byrne 2001a	15/315	19/312		0.77 [0.38, 1.55]
Pauwels 1997	10/210	9/213		1.13 [0.45, 2.85]
Pauwels 1997a	15/215	12/214		1.26 [0.58, 2.76]
Peters 2008	21/443	5/133		1.27 [0.47, 3.45]
Price 2002	2/250	3/255		0.68 [0.11, 4.09]
SD-039-0726	4/301	1/145		1.94 [0.21, 17.51]
Zetterstrom 2001	3/238	1/124		1.57 [0.16, 15.25]
Subtotal (95% CI)	**4875**	**3153**		**0.98 [0.74, 1.31]**
Total events: 116 (Formoterol and ICS), 86 (Same Dose ICS)				
Heterogeneity: Chi^2 = 9.46, df = 15 (P = 0.85); I^2 =0.0%				
Test for overall effect: Z = 0.12 (P = 0.91)				
2 Children and Adolescents				
Morice 2008	2/415	3/207		0.33 [0.05, 1.99]
Pohunek 2006	8/417	3/213		1.37 [0.36, 5.21]
SD-039-0714	1/136	1/134		0.99 [0.06, 15.91]
SD-039-0718	0/128	0/145		0.0 [0.0, 0.0]
SD-039-0719	2/123	1/63		1.02 [0.09, 11.52]

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Study or subgroup	Formoterol and ICS n/N	Same Dose ICS n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
SD-039-0725	5/352	1/169		2.42 [0.28, 20.88]
Tal 2002	7/148	0/138		14.68 [0.83, 259.54]
Subtotal (95% CI)	**1719**	**1069**		**1.62 [0.77, 3.38]**
Total events: 25 (Formoterol and ICS), 9 (Same Dose ICS)				
Heterogeneity: Chi^2 = 5.73, df = 5 (P = 0.33); I^2 =13%				
Test for overall effect: Z = 1.27 (P = 0.20)				
Total (95% CI)	**6594**	**4222**		**1.06 [0.81, 1.38]**
Total events: 141 (Formoterol and ICS), 95 (Same Dose ICS)				
Heterogeneity: Chi^2 = 15.48, df = 21 (P = 0.80); I^2 =0.0%				
Test for overall effect: Z = 0.40 (P = 0.69)				

Analysis 1.10. Comparison 1 Formoterol and ICS versus same dose ICS, Outcome 10 All-cause non-fatal Serious Adverse Events (sensitivity analysis without unblinded study).

Review: Regular treatment with formoterol and inhaled steroids for chronic asthma: serious adverse events

Comparison: 1 Formoterol and ICS versus same dose ICS

Outcome: 10 All-cause non-fatal Serious Adverse Events (sensitivity analysis without unblinded study)

Study or subgroup	Formoterol and ICS n/N	Same Dose ICS n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
1 Adults and Adolescents				
Buhl 2003	2/352	2/171		0.45 [0.06, 3.68]
Chuchalin 2002	0/111	2/114		0.14 [0.01, 2.22]
Corren 2007	2/123	0/121		7.33 [0.46, 117.87]
D5896C00001	3/312	0/153		4.47 [0.40, 49.92]
Jenkins 2006	7/341	3/115		0.77 [0.18, 3.26]
Kuna 2006	3/409	4/207		0.34 [0.07, 1.67]
Morice 2007	2/462	2/217		0.43 [0.05, 3.57]
Noonan 2006	7/239	0/109		4.40 [0.88, 22.04]

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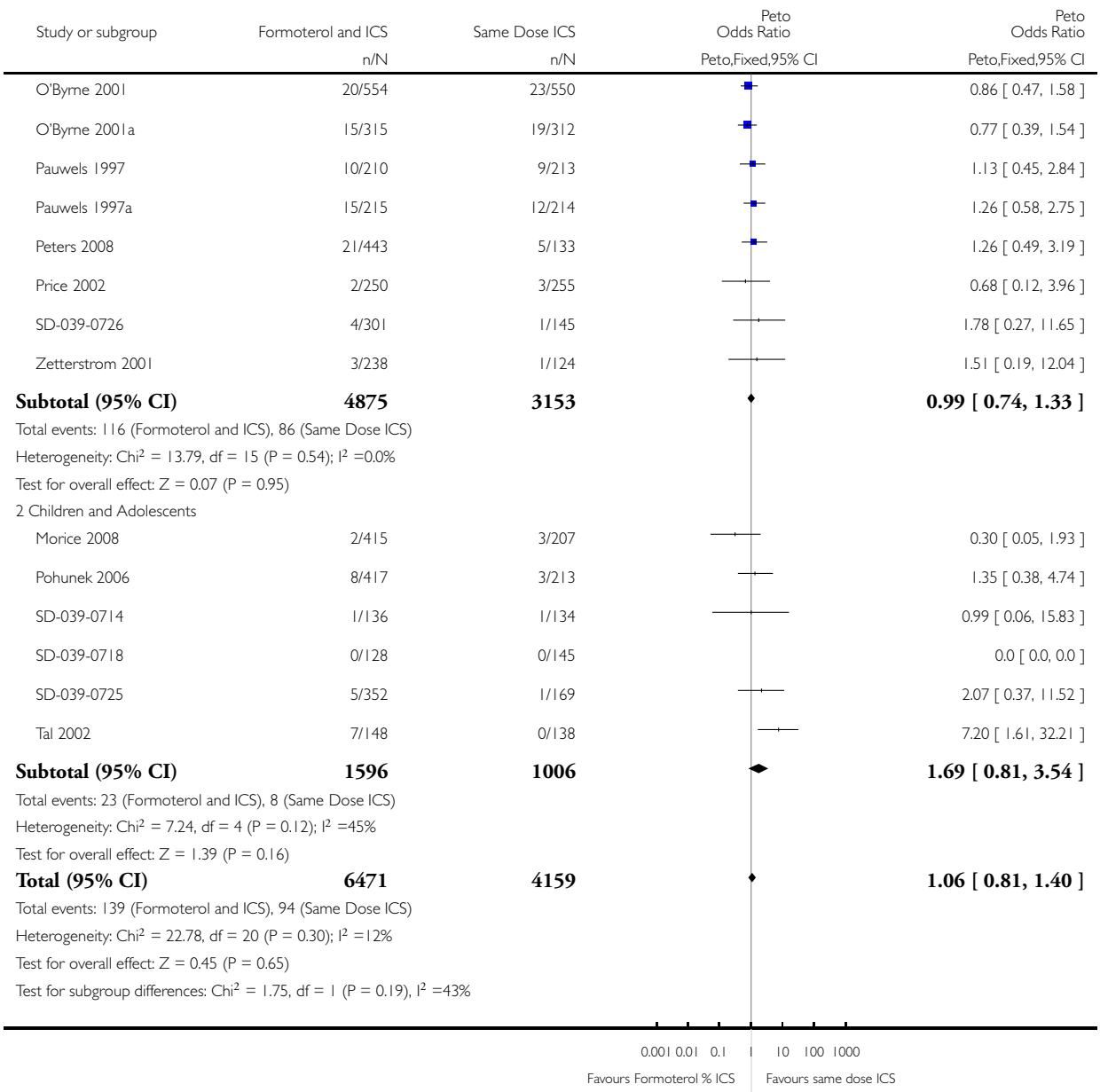

ADDITIONAL TABLES

Table 1. Dose and delivery of budesonide and formoterol

Study ID	Daily Dose of Budesonide (mcg metered dose)	Daily Dose of Formoterol (mcg metered dose)	Once	Twice	Combined	Separate	DPI	PMDI
Buhl 2003	400	12	1	1	1		1	
Chuchalin 2002	400	24		1		1	1	
Corren 2007	400	24		1	1		1	
D5896C0000	400	12/24	1	1	1			1
Jenkins 2006	1600	48		1	1	1	1	
Kuna 2006	200	12	1	1	1		1	
Morice 2007	800	24		1	1		1	1
Morice 2008	200 (children)	24		1	1		1	1
Noonan 2006	400	24		1	1	1	1	1
O'Byrne 2001	400	12		1		1	1	
O'Byrne 2001a	800	12		1		1	1	
Pauwels 1997	200	24		1		1	1	
Pauwels 1997a	800	24		1		1	1	
Peters 2008	1600	48		1	1			1
Pohunek 2006	400 (children)	24		1	1	1	1	
Price 2002	800	24		1		1	1	

Table 1. Dose and delivery of budesonide and formoterol (*Continued*)

SD-039-0714	400 (adolescents)	12		1	1		1	
SD-039-0718	200 (children)	24		1	1			1
SD-039-0719	400 (children)	24		1	1			1
SD-039-0725	200 (children)	12/24	1	1	1			1
SD-039-0726	200	12/24	1	1	1			1
Tal 2002	400 (children)	24		1	1		1	
Zetterstrom 2001	800	24		1	1	1	1	

APPENDICES

Appendix 1. Pharmacology of beta$_2$-agonists

ß-agonists are thought to cause bronchodilation primarily through binding beta$_2$-adrenoceptors on airways smooth muscle (ASM), with subsequent activation of both membrane-bound potassium channels and a signalling cascade involving enzyme activation and changes in intracellular calcium levels following a rise in cyclic adenosine monophosphate (cAMP) (Barnes 1993). However, beta$_2$-adrenoceptors are also expressed on a wide range of cell types where beta$_2$-agonists may have a clinically significant effect including airway epithelium (Morrison 1993), mast cells, post capillary venules, sensory and cholinergic nerves and dendritic cells (Anderson 2006). Beta$_2$-agonists will also cross-react to some extent with other beta-adrenoceptors including beta$_1$-adrenoceptors on the heart. The *in vivo* effect of any beta$_2$-agonist will depend on a number of factors relating to both the drug and the patient. The degree to which a drug binds to one receptor over another is known as *selectivity,* which can be defined as absolute binding ratios to different receptors *in vitro*, whilst *functional selectivity* is measured from downstream effects of drugs in different tissue types *in vitro* or *in vivo.* All of the beta$_2$-agonists described thus far are more beta$_2$ selective than their predecessor isoprenaline *in vitro*. However, because attempts to differentiate selectivity between the newer agents are confounded by so many factors, it is difficult to draw conclusions about *in vitro* selectivity studies and probably best to concentrate on specific adverse side-effects in human subjects at doses which cause the same degree of bronchodilatation. The *potency* of a drug refers to the concentration that achieves half the maximal receptor activation of which that drug is capable but it is not very important clinically as for each drug, manufacturers will alter the dose to try to achieve a therapeutic ratio of desired to undesired effects. In contrast *efficacy* refers to the ability of a drug to activate its receptor independent of drug concentration. Drugs that fully activate a receptor are known as full agonists and those that partially activate a receptor are known as partial agonists. Efficacy also is very much dependent on the system in which it is being tested and is affected by factors including the number of receptors available and the presence of other agonists and antagonists. Thus whilst salmeterol acts as a partial agonist *in vitro* it causes a similar degree of bronchodilation to the strong agonist formoterol in stable asthmatic patients (vanNoord 1996), presumably because there are an abundance of well-coupled beta$_2$-adrenoceptors available with few downstream

antagonising signals. In contrast, with repetitive dosing formoterol is significantly better than salmeterol at preventing methacholine-induced bronchoconstriction (Palmqvist 1999). These differences have led to attempts to define the "intrinsic efficacy" of a drug independent of tissue conditions (Hanania 2002), as shown in Table 1. The clinical significance of intrinsic efficacy remains unclear.

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Appendix 2. Possible mechanisms of increased asthma mortality with beta-agonists

Direct toxicity

This hypothesis states that direct adverse effects of $beta_2$-agonists are responsible for an associated increase in mortality and most research in the area has concentrated on effects detrimental to the heart. Whilst it is often assumed that cardiac side-effects of $beta_2$-agonists are due to cross-reactivity with $beta_1$-adrenoceptors (i.e. poor selectivity), it is worth noting that human myocardium also contains an abundance of $beta_2$-adrenoceptors capable of triggering positive chronotropic and inotropic responses (Lipworth 1992). Indeed, there is good evidence that cardiovascular side-effects of isoprenaline (Arnold 1985) and $beta_2$-agonists including salbutamol (Hall 1989) are mediated predominantly via cardiac $beta_2$-adrenoceptors thus making the concept of *in vitro* selectivity less relevant. Generalised $beta_2$-adrenoceptor activation can also cause hypokalaemia (Brown 1983) and it has been proposed that, through these and other actions, $beta_2$-agonists may predispose to life-threatening dysrhythmias or cause other adverse cardiac effects.

During the 1960s epidemic most deaths occurred in patients with severe asthma and it was originally assumed that asthma and its sequelae, including hypoxia, were the primary cause of death. However, mucus plugging and hypoxia does not preclude a cardiac event as the final cause of death, and one might expect those with severe asthma to take more doses of a prescribed inhaler. As noted by Speizer and Doll most deaths in the 1960s were in the 10-19 age group and "at these ages children have begun to act independently and may be particularly prone to misuse a self-administered form of treatment" (Speizer 1968). If toxicity were related to increasing doses of $beta_2$-agonists one might expect most deaths to occur in hospital where high doses are typically used and this was not the case. One possible explanation for this anomaly was provided by animal experiments in which large doses of isoprenaline caused little ill effect in anaesthetised dogs with normal arterial oxygenation whereas much smaller doses caused fatal cardiac depression and asystole (although no obvious dysrhythmia) when hypoxic (Collins 1969; McDevitt 1974). It has been hypothesised therefore that such events would be less likely in hospital where supplemental oxygen is routinely given. The clinical relevance of these studies remains unclear although there is some evidence of a synergistic effect between hypoxia and salbutamol use in asthmatic patients in reducing total peripheral vascular resistance (Burggraaf 2001) - another $beta_2$ mediated effect which could be detrimental to the heart during an acute asthma attack through a reduction in diastolic blood pressure. Other potential mechanisms of isoprenaline toxicity include a potential increase in mucous plugging and worsening of ventilation perfusion mismatch despite bronchodilation (Pearce 1990).

Further concerns about a possible toxic effect of $beta_2$-agonists were raised during the New Zealand epidemic in the 1970s. In 1981 Wilson et al who first reported the epidemic reviewed 22 fatal cases of asthma and noted "In 16 patients death was seen to be sudden and unexpected. Although all were experiencing respiratory distress, most were not cyanosed and the precipitate nature of their death suggested a cardiac event, such as an arrest, inappropriate to the severity of their respiratory problem" (Wilson 1981). In humans, fenoterol causes significantly greater chronotropic, inotropic and electrocardiographic side-effects than salbutamol in asthmatic patients (Wong 1990). Interestingly, across the same parameters fenoterol also causes more side-effects than isoprenaline (Burgess 1991).

In patients with mild asthma and without a bronchoconstrictor challenge, salmeterol and salbutamol cause a similar degree of near maximal bronchodilation at low doses (Bennett 1994). However, whilst as a one off dose salbutamol is typically used at 2-4 times the concentration of salmeterol, the dose equivalences for salmeterol versus salbutamol in increasing heart rate and decreasing potassium concentration and diastolic blood pressure were 17.7, 7.8 and 7.6 respectively (i.e. salmeterol had a greater effect across all parameters). Given the lower intrinsic efficacy of salmeterol (Table 2), these results highlight the importance of *in vivo* factors; one possible explanation for the difference is the increased lipophilicity of salmeterol compared to salbutamol contributing to higher systemic absorption (Bennett 1994).

When comparing increasing actuations of standard doses of formoterol and salmeterol inhalers in stable asthmatic patients, relatively similar cardiovascular effects are seen at lower doses (Guhan 2000). However, at the highest doses (above those recommended by the manufacturers) there were trends towards an increase in systolic blood pressure with formoterol; in comparison there was a trend towards a decrease in diastolic blood pressure and an increase in QTc interval with salmeterol although no statistical analysis of the difference was performed. In contrast in asthmatic patients with methacholine-induced bronchoconstriction there was no significant

difference between salmeterol and formoterol in causing increased heart rate and QTc interval although formoterol caused significantly greater bronchodilation and hypokalaemia (Palmqvist 1999). Whilst there is good evidence of cardiovascular and metabolic side-effects with increasing doses of beta$_2$-agonists, it is a little difficult to envisage serious adverse effects of this nature when using LABAs at manufacturer-recommended preventative doses. However, it is possible that some patients choose to use repeated doses of LABAs during exacerbations.

Tolerance

In this setting, the term *tolerance* refers to an impaired response to beta$_2$-agonists in patients who have been using regular beta$_2$-agonist treatment previously (Haney 2006). Tolerance is likely to result from a combination of reduced receptor numbers secondary to receptor internalisation and reduced production and also uncoupling of receptors to downstream signalling pathways following repeated activation (Barnes 1995). This phenomenon is likely to explain the beneficial reduction in systemic side effects seen with regular use of beta$_2$-agonists including salbutamol after 1-2 weeks (Lipworth 1989). However, the same effect on beta$_2$-adrenoceptors in the lung might be expected to produce a diminished response to the bronchodilating activity of beta$_2$-agonists following regular use. In patients with stable asthma, whilst there is some evidence of tolerance to both salbutamol (Nelson 1977) and terbutaline (Weber 1982) other studies have been less conclusive (Harvey 1982; Lipworth 1989). However, evidence of tolerance to short and long-acting beta$_2$-agonists in both protecting against and reducing bronchoconstriction is much stronger in the setting of an acute bronchoconstrictor challenge with chemical, allergen and 'natural' stimuli (Haney 2006; Lipworth 1997).

Studies comparing salmeterol and formoterol have shown that both cause tolerance compared to placebo but there was no significant difference between the drugs (van der Woude 2001). There also appears to be little difference in the tolerance induced by regular formoterol and regular salbutamol treatment (Hancox 1999; Jones 2001). To the authors' knowledge no studies have looked specifically at the degree of tolerance caused by isoprenaline and fenoterol in the setting of acute bronchoconstriction. Tolerance to bronchodilation has been shown to clearly occur with addition of inhaled corticosteroids to salmeterol and formoterol (Lee 2003) and terbutaline (Yates 1996). There is conflicting evidence as to whether high dose steroids can reverse tolerance in the acute setting (Lipworth 2000; Jones 2001).

At first glance the toxicity and tolerance hypotheses might appear incompatible as systemic and cardiovascular tolerance ought to protect against toxicity in the acute setting and there is good evidence that such tolerance occurs in stable asthmatic patients (Lipworth 1989). However, whilst this study showed that changes in heart rate and potassium levels were blunted by previous beta$_2$-agonist use, they were not abolished; furthermore, at the doses studied these side-effects appear to follow an exponential pattern (Lipworth 1989). In contrast, in the presence of bronchoconstrictor stimuli the bronchodilator response to beta$_2$-agonists follows a flatter curve (Wong 1990; Hancox 1999) and as previously discussed this curve is shifted downwards by previous beta$_2$-agonist exposure (Hancox 1999). Thus, it is theoretically possible that in the setting of an acute asthmatic attack and strong bronchoconstricting stimuli, bronchodilator tolerance could lead to repetitive beta$_2$-agonist use and ultimately more systemic side-effects than would otherwise have occurred. Of course, other sequelae of inadequate bronchodilation including airway obstruction will be detrimental in this setting.

Whilst the tolerance hypothesis is often cited as contributing towards the asthma mortality epidemics it is difficult to argue that reduced efficacy of a drug can cause increased mortality relative to a time when that drug was not used at all. However, tolerance to the bronchodilating effect of endogenous circulating adrenaline is theoretically possible and there is also evidence of rebound bronchoconstriction when stopping fenoterol (Sears 1990), which may be detrimental. Furthermore, it appears that regular salbutamol treatment can actually increase airway responsiveness to allergen (Cockcroft 1993) a potentially important effect that could form a variant of the toxicity hypothesis. Differences between beta$_2$-agonists in this regard are unclear, but the combination of rebound hyperresponsiveness and tolerance of the bronchodilator effect with regular beta$_2$-agonist exposure has been recently advocated as a possible mechanism to explain the association between beta$_2$-agonists and asthma mortality (Hancox 2006).

Other explanations

Confounding by severity

Historically, this hypothesis has been used extensively to try to explain the association between mortality and the use of fenoterol during the 1970s New Zealand epidemic (see Pearce 2007) and is still quoted today. The hypothesis essentially relies on the supposition that patients with more severe asthma are more likely to take either higher doses of beta$_2$-agonists or a particular beta$_2$-agonist (such as fenoterol) thereby explaining the association. This hypothesis was carefully ruled out in the three case-control studies by comparing the association between fenoterol and mortality in patients with varying severity of disease (Crane 1989; Pearce 1990; Grainger 1991).

Furthermore, the hypothesis cannot explain the overall increase in mortality in the 1960s and 1970s nor can it explain any significant increase in mortality (whether taking inhaled steroids or not) from randomised controlled trial data.

The delay hypothesis

This hypothesis accepts that beta$_2$-agonists or a particular beta$_2$-agonist cause an increased risk of mortality but indirectly by causing patients to delay before getting medical help and further treatments including high dose steroids and oxygen. There is evidence that both salmeterol and formoterol can reduce awareness of worsening underlying inflammation (Bijl-Hofland 2001; McIvor 1998). It is difficult to rule out the delay hypothesis in either explaining or contributing towards both the asthma mortality epidemics and an association with regular use of LABAs. There is evidence that beta$_2$-agonists with higher intrinsic efficacy are more effective at relieving bronchoconstriction in the acute setting (Hanania 2007) and could paradoxically cause patients to delay seeking medical help for longer. For the delay hypothesis to explain the increase in mortality during the 1960s and 1970s one has to imply that hospital treatment of asthma when mortality rates were low during the earlier years of the 20^{th} century was effective. It is difficult to say exactly how effective such treatment is likely to have been.

Reduced corticosteroid treatment

A slight but significant variation of the delay hypothesis suggests that patients who have separate beta$_2$-agonists and corticosteroid inhalers may choose to take less corticosteroid because of better symptom control from the inhaled beta$_2$-agonists and it is reduced corticosteroid treatment that contributes to a rise in mortality. It is rather difficult to see how this hypothesis explains the epidemics of asthma deaths in the 1960s and 1970s relative to the 1920s and 30s (Figure 1), given that corticosteroids were not used for the treatment of asthma in the earlier decades. If this hypothesis were to explain increased mortality from more recent randomised controlled trial data one would not expect to see an increase in mortality in those taking LABAs alone.

Appendix 3. Definition of Serious Adverse Events

The Expert Working Group (Efficacy) of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) define serious adverse events as follows (ICHE2a 1995):
“A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.

NOTE: The term ”life-threatening“ in the definition of ”serious“ refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.”

HISTORY

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CONTRIBUTIONS OF AUTHORS

CJC: Conception of the idea and co-writing of protocol with MJC.

TL: Co-writing of the protocol, trial selection, data extraction and co-writing the review.

RJ: Trial selection, data extraction and co-writing the review.

DECLARATIONS OF INTEREST

None known for CJC, TL. RJ has received on one occasion honorarium and travel support from Glaxo Smtih Kline for lecture related to the topic of this review and is a deputy editor of a medical journal financed partially by drug advertising, including medications for asthma.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Peto OR was used for primary meta-analysis of Odds Ratios, as otherwise the results are largely dependent on the zero correction adopted. Single inhaler therapy and adjustable maintenance dosing were not included in the review, nor was comparison to higher dose ICS. This was because we decided to restrict our attention to the question of regular formoterol used in addition to the same ICS regimen in both active and control arms. Subgroup analysis was not attempted on the basis of asthma severity or dose of ICS.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Inhalation; Adolescent; Adrenal Cortex Hormones [*adverse effects; therapeutic use]; Adrenergic beta-Agonists [administration & dosage; *adverse effects]; Anti-Asthmatic Agents [administration & dosage; *adverse effects]; Asthma [drug therapy; *mortality]; Ethanolamines [administration & dosage; *adverse effects]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Child; Humans