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

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TABLE OF CONTENTS

[Intervention Review]

Regular treatment with formoterol 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.

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 versus placebo or regular short-acting beta$_2$-agonists.

Search methods

We identified trials using the Cochrane Airways Group Specialised Register of trials. We checked websites of clinical trial registers for unpublished trial data and Food and Drug Administration (FDA) submissions in relation to formoterol. The date of the most recent search was January 2012.

Selection criteria

We included controlled, parallel design clinical trials on patients of any age and severity of asthma if they randomised patients to treatment with regular formoterol and were of at least 12 weeks' duration. Concomitant use of inhaled corticosteroids was allowed, as long as this was not part of the randomised treatment regimen.

Data collection and analysis

Two authors independently selected trials for inclusion in the review. One author extracted outcome data and the second author checked them. We sought unpublished data on mortality and serious adverse events.

Main results

The review includes 22 studies (8032 participants) comparing regular formoterol to placebo and salbutamol. Non-fatal serious adverse event data could be obtained for all participants from published studies comparing formoterol and placebo but only 80% of those comparing formoterol with salbutamol or terbutaline.

Three deaths occurred on regular formoterol and none on placebo; this difference was not statistically significant. It was not possible to assess disease-specific mortality in view of the small number of deaths. Non-fatal serious adverse events were significantly increased

when regular formoterol was compared with placebo (Peto odds ratio (OR) 1.57; 95% CI 1.06 to 2.31). One extra serious adverse event occurred over 16 weeks for every 149 people treated with regular formoterol (95% CI 66 to 1407 people). The increase was larger in children than in adults, but the impact of age was not statistically significant. Data submitted to the FDA indicate that the increase in asthma-related serious adverse events remained significant in patients taking regular formoterol who were also on inhaled corticosteroids.

No significant increase in fatal or non-fatal serious adverse events was found when regular formoterol was compared with regular salbutamol or terbutaline.

Authors' conclusions

In comparison with placebo, we have found an increased risk of serious adverse events with regular formoterol, and this does not appear to be abolished in patients taking inhaled corticosteroids. The effect on serious adverse events of regular formoterol in children was greater than the effect in adults, but the difference between age groups was not significant.

Data on all-cause serious adverse events should be more fully reported in journal articles, and not combined with all severities of adverse events or limited to those events that are thought by the investigator to be drug-related.

PLAIN LANGUAGE SUMMARY

Does daily treatment with formoterol result in more serious adverse events compared to placebo or daily salbutamol?

Asthma is a common condition that affects the airways - the small tubes that carry air in and out of the lungs. When a person with asthma comes into contact with an irritant (an asthma trigger), the muscles around the walls of the airways tighten, the airways become narrower, and the lining of the airways becomes inflamed and starts to swell. This leads to the symptoms of asthma - wheezing, coughing and difficulty in breathing. They can lead to an asthma attack or exacerbation. People can have underlying inflammation in their lungs and sticky mucus or phlegm may build up, which can further narrow the airways. There is no cure for asthma; however there are medications that allow most people to control their asthma so they can get on with daily life.

Long-acting beta$_2$-agonists, such as formoterol, work by reversing the narrowing of the airways that occurs during an asthma attack. These drugs - taken by inhaler - are known to improve lung function, symptoms, quality of life and reduce the number of asthma attacks. However, there are concerns about the safety of long-acting beta$_2$-agonists, particularly in people who are not taking inhaled corticosteroids to control the underlying inflammation. We did this review to take a closer look at the safety of people taking formoterol daily compared to people on placebo or the short acting beta$_2$-agonist salbutamol.

There was no statistically significant difference in the number of people who died during treatment with formoterol compared with placebo or salbutamol. Because so few people die of asthma, huge trials or observational studies are normally required to detect a difference in death rates from asthma. There were more non-fatal serious adverse events in people taking formoterol compared to those on placebo; for every 149 people treated with formoterol for 16 weeks, one extra non-fatal event occurred in comparison with placebo. There was no significant difference in serious adverse events in people on formoterol compared to regular salbutamol.

We conclude that regular formoterol should not be taken by people who are not taking regular inhaled steroids due to the increased risk of serious adverse events. Formoterol should not be used as a substitute for inhaled corticosteroids, and adherence with inhaled steroids should be kept under review if separate inhalers are used when formoterol is added to inhaled corticosteroids.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Regular formoterol versus placebo or salbutamol for chronic asthma: SAEs in adults and children

Patient or population: patients with chronic asthma
Settings: community
Intervention: regular formoterol versus placebo or salbutamol

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Regular formoterol versus placebo or salbutamol				
SAEs - formoterol versus placebo (follow-up: mean 16 weeks)	**Medium-risk population**		**OR 1.57** (1.05 to 2.37)	6646 (19)	⊕⊕⊕⊕ **high**	
	10 per 1000	**16 per 1000** (10 to 23)				
SAEs - formoterol versus salbutamol (follow-up: mean 13 weeks)	**Medium-risk population**		**OR 0.72** (0.37 to 1.43)	2119 (9)	⊕⊕⊕◯ **moderate**[1]	
	23 per 1000	**17 per 1000** (9 to 33)				

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

CI: Confidence interval; OR: Odds ratio; SAE: serious adverse event

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

[1] Confidence interval includes the possibility of harm or benefit

BACKGROUND

Description of the condition

There is currently no universally accepted definition of the term 'asthma'. This is in part due to an overlap of asthmatic symptoms with those of other diseases such as chronic obstructive pulmonary disease (COPD), but is also due to the probable existence of more than one underlying pathophysiological process. There are, for example, wide variations in the age of onset, symptoms, triggers, associations with allergic disease and the type of inflammatory cell infiltrate seen in patients diagnosed with severe asthma (Miranda 2004). Patients with all forms and severity of disease will typically have intermittent symptoms of cough, wheeze and/or breathlessness. Underlying these symptoms there is a process of variable, at least partially reversible airway obstruction, airway hyper responsiveness and, in most cases, chronic inflammation.

Airway obstruction

Patients with a history of asthma demonstrate chronic changes within the airways including goblet cell hyperplasia, airway smooth muscle (ASM) hyperplasia and hypertrophy (Ebina 1993; Ordonez 2001; Woodruff 2004) and excess myofibroblasts with increased subepithelial collagen deposition (Brewster 1990). In the acute setting, in patients who have died of status asthmaticus, airway obstruction is evident from air-trapping and lung hyperinflation with mucus plugging of the small and large airways (Dunnill 1960; Kuyper 2003). There is also shedding of ciliated bronchial mucosal cells, inflammatory cell infiltrates and submucosal oedema with transudation of fluid into the bronchial lumen (Carroll 1993). It is more difficult to measure the degree of ASM contraction (bronchoconstriction) in post-mortem studies although evidence for a role of bronchoconstriction in airway narrowing comes from other sources.

Airway hyper responsiveness

Patients with asthma typically display a degree of 'airway hyper responsiveness' to inhaled allergens (Cockcroft 2006), and to a variety of chemical stimuli including histamine, serotonin, bradykinin, prostaglandins, methacholine and acetylcholine as well as other triggers such as exercise, deep inhalation and inhalation of cold air (Boushey 1980). Bronchoconstriction is implicated as the primary effector mechanism of airway narrowing in these responses. This is because of both the short time frame of the response and because many of these stimuli typically either cause bronchoconstriction directly *in vitro* or promote bronchoconstriction through interference with the autonomic control of ASM. Further evidence comes from findings that this response can be abolished or diminished by bronchodilator medications such as atropine and beta$_2$-agonists (Phillips 1990; Simonsson 1967); although beta$_2$-agonists in particular may have additional mechanisms of action. Whether airway hyper responsiveness relates primarily to an abnormality of ASM, to increased ASM bulk (Wiggs 1990), to aberrant autonomic control or reflex pathways, or to physical damage to the airway epithelium remains to be established. Regular use of salbutamol has, however, been shown to increase airway hyper responsiveness to allergen exposure and produce tolerance to the protective effect of salbutamol against bronchoconstriction induced by both methacholine and allergens (Cockcroft 1993).

Inflammation

It has long been thought that the histological changes described above and the phenomenon of airway hyper responsiveness are due to a combined acute and chronic inflammatory response (Bousquet 2000). Patients with status asthmaticus have increased numbers of inflammatory cells including eosinophils and neutrophils, as well as a variety of pro-inflammatory cytokines and chemokines found in bronchial alveolar lavage (Tonnel 2001). In patients with chronic asthma there is also evidence of increased eosinophil numbers (Bousquet 1990), inflammatory cell adhesion molecules (Vignola 1993) and some evidence of an association between the extent of inflammation, disease severity and hyperreactivity. This association has however been questioned on the background of a number of negative results (Brusasco 1998), although it is made difficult to prove by the lack of a consistent marker of a sequential and variable inflammatory response (Haley 1998).

Description of the intervention

Beta$_2$-agonists and mortality: an historical perspective

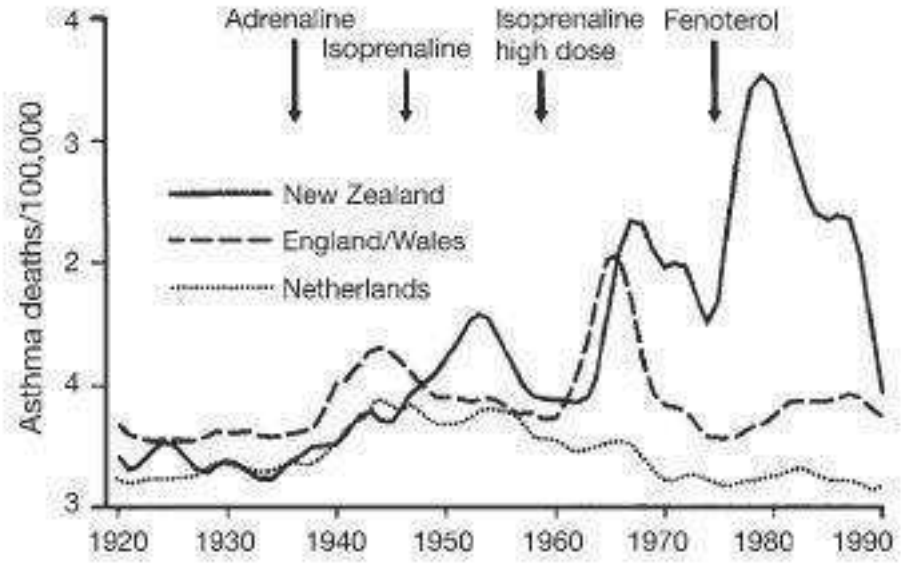
Time trend data and case-control studies

Adrenaline was successfully used in the symptomatic treatment of asthma as far back as 1903 (Tattersfield 2006). Initially given subcutaneously, the inhaled route was tried in 1929 to reduce adverse effects but these remained a problem and in 1940 details of a new agent, isoprenaline (isoproterenol), were published in Germany (Konzett 1940). Although isoprenaline was more selective for beta- as opposed to alpha-adrenoreceptors, adverse effects including palpitations were still a major problem, particularly with oral administration (Gay 1949) and it first became available as atomiser spray for use in the UK in 1948 (Pearce 2001).

Prior to the 1940s, mortality rates from asthma in a number of countries were stable and low at less than 1 asthma death per

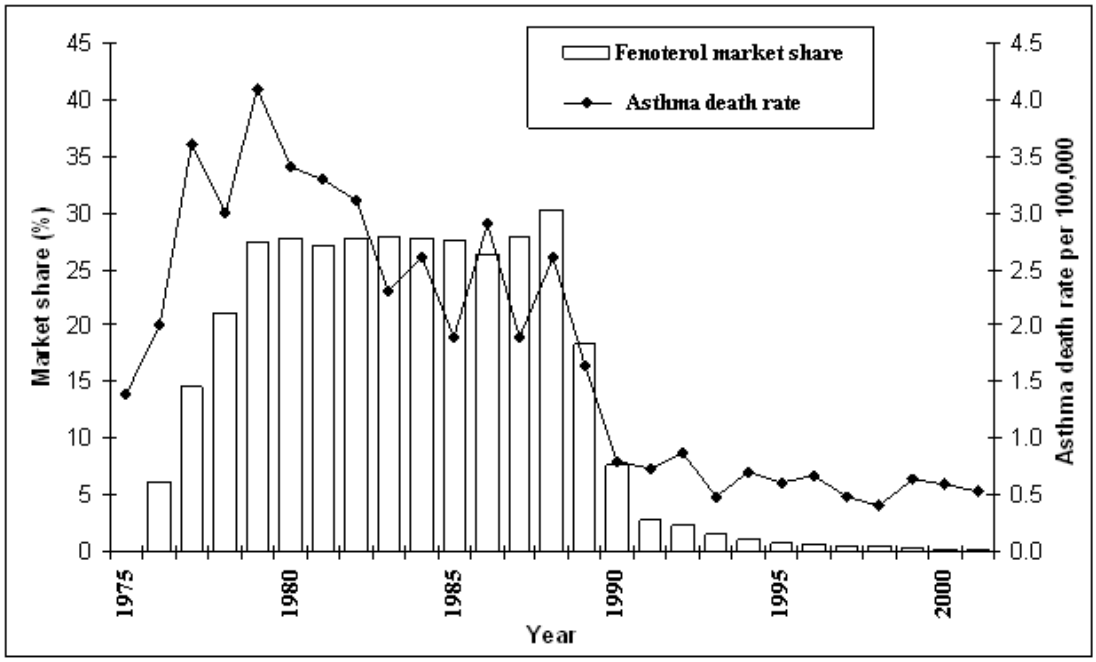
100,000 people per year (Pearce 2001; Figure 1). During the 1940s and 50s there was a slight rise in mortality rates and concerns about a possible link to inhaled adrenaline were raised at an early stage (Benson 1948). However, the rise was small and the cause unclear and sales continued to increase with the introduction of aerosol or metered-dose inhalers in the early 1960s. During this decade there was an epidemic of asthma deaths in at least six countries including England, Wales and New Zealand (Figure 1). In all six countries the epidemics coincided with the licensing of an aerosol called 'Isoprenaline Forte', which contained five times the dose of isoprenaline per administration than the standard preparation (Stolley 1972). In other countries including the Netherlands, where isoprenaline forte was introduced late and sales volumes low, and in the US, where isoprenaline forte was not licensed, no increase in asthma mortality occurred. This was despite an approximate trebling in per capita alternative bronchodilator sales between 1962 and 1968 in the US (Stolley 1972). A detailed review of the epidemic in England and Wales concluded it was not due to changes in death certification, disease classification or an increase in asthma prevalence, but instead was most likely due to new methods of treatment (Speizer 1968). In England and Wales mortality rates fell following health warnings about the overuse of inhalers and banning of over the counter sales in 1968. It was around this time that more selective beta$_2$-agonists such as terbutaline (Bergman 1969) and salbutamol (albuterol) (Cullum 1969) were being developed.

Figure 1. Changes in asthma mortality (5 to 34 age group) in three countries in relation to the introduction of isoprenaline forte in the UK and New Zealand and of fenoterol in New Zealand. (From Blauw 1995. With permission from the Lancet).



In the late 1970s a second epidemic of asthma deaths occurred in New Zealand (Figure 1). It was later shown that this epidemic coincided with the introduction and rising sales of fenoterol, a new short-acting beta$_2$-agonist (Crane 1989; Figure 2). A significant association between mortality and fenoterol use was demonstrated in three consecutive case-control studies, the latter studies addressing criticisms of the first (Crane 1989; Grainger 1991; Pearce 1990). Furthermore the relative risk of asthma death in patients prescribed fenoterol increased markedly when analysis was restricted to subgroups defined by markers of severity, including previous hospital admission and use of oral corticosteroids. Following the publication of the first case-control study, the fenoterol market share in New Zealand fell from 30% in 1988 to 3% in 1991 and by the early 1990s the mortality epidemic appeared to be over (Figure 2). During the gradual decline in mortality in New Zealand from its peak in 1979, total sales of alternative beta$_2$-agonists, including salbutamol, gradually rose and the use of inhaled corticosteroids also increased during the latter half of the 1980s (Pearce 2007).

Figure 2. Inhaled fenoterol market share and annual asthma mortality in New Zealand in persons aged 5 to 34



The introduction of long-acting beta$_2$-agonists

Given the relatively short action of beta$_2$-agonists such as salbutamol, in the late 1980s efforts were made to develop longer-acting compounds. Subsequently the long-acting beta$_2$-agonists (LABAs), salmeterol and formoterol were released by GlaxoSmithKline (GSK) and Novartis, respectively. Both drugs cause bronchodilation that lasts for more than 12 hours although formoterol has a faster onset of action (Kemp 1993; Ringdal 1998). Given previous concerns about the safety profile of some of the short acting beta$_2$-agonists, salmeterol and formoterol were subject to randomised controlled trials on larger numbers of patients. Using these trials several Cochrane reviews have addressed the efficacy of LABAs in addition to inhaled corticosteroids (Ni Chroinin 2004; Ni Chroinin 2005), in comparison with placebo (Walters 2007), short-acting beta2-agonists (Walters 2002), leukotriene-receptor antagonists (Ducharme 2006), and increased doses of inhaled corticosteroids (Greenstone 2005). The beneficial effects of LABAs on lung function, symptoms, quality of life and exacerbations requiring oral steroids have been demonstrated. However, with some studies demonstrating an associated increase in mortality concerns about the safety profile of LABAs have heightened and there has been much debate about the potential protective role of inhaled corticosteroids.

How the intervention might work

We have outlined the pharmacology of beta$_2$-agonists in detail in Appendix 1. Since the early epidemics in asthma mortality, a number of potential mechanisms have been proposed to explain a relationship to the use of beta$_2$-agonists. We discuss these mechanisms in detail in Appendix 2; they include direct toxicity, tolerance, delay in seeking help and reduction in use of inhaled corticosteroids.

Why it is important to do this review

We have taken a different approach from Salpeter 2006, in that we have not assumed a class effect of long-acting beta$_2$-agonists, but we have considered trials comparing regular formoterol to placebo or regular salbutamol/terbutaline. We have chosen not to include results from trials on salmeterol in this review, as there are known differences in the pharmacological properties of salmeterol and formoterol (Ringdal 1998; Van Noord 1996). This review forms part of a set of reviews on the safety of regular salmeterol and formoterol that has now been published (Cates 2008; Cates 2009;

Cates 2009a; Cates 2011). We have also excluded studies which randomised participants to formoterol and inhaled corticosteroids for this review, as these are considered in another review (Cates 2009a).

In view of the difficulty in ascertaining the causation of deaths and serious adverse events (SAEs), we have considered all-cause fatal and non-fatal SAEs as the main outcomes of this review, with asthma-related and cardiovascular events as secondary outcomes.

OBJECTIVES

To assess the risk of mortality and non-fatal serious adverse events in trials which randomise patients with chronic asthma to formoterol alone

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised trials (RCTs) of parallel design, with or without blinding, in which formoterol alone was randomly assigned to patients with chronic asthma. We excluded studies on acute asthma and exercise-induced bronchospasm.

Types of participants

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

Types of interventions

We included trials that randomised patients to receive inhaled formoterol twice daily for a period of at least 12 weeks, at any dose and delivered by any device (metered-dose inhalers (MDIs) with chlorofluorocarbons (CFCs) or hydrofluoroalkane (HFAs), or dry powder inhalers (DPIs)). We included studies that used comparison groups with placebo or short-acting beta$_2$-agonists, and co-intervention with leukotriene receptor antagonists, inhaled or oral corticosteroids or theophylline was allowed as long as they are not part of the randomised intervention. We excluded studies that randomised patients to formoterol for intermittent use as a reliever, and studies that compared different doses of formoterol, or different delivery devices or propellants (with no placebo arm). We also excluded studies in which formoterol was randomised together with an inhaled steroid (in separate inhalers or a combined inhaler) from this review; however these are considered in a separate review (Cates 2009a).

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)

We did not restrict outcomes to those that the trial investigators considered to be related to trial medication.

Search methods for identification of studies

Electronic searches

We identified trials using the Cochrane Airways Group Specialised Register of trials, which is derived from systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED and PsycINFO, and handsearching of respiratory journals and meeting abstracts (see Appendix 3 for details). All records in the Specialised Register coded as 'asthma' were last searched in January 2012 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

We checked reference lists of all primary studies and review articles for additional references. We also checked websites of clinical trial registers for unpublished trial data and FDA submissions in relation to formoterol.

Data collection and analysis

Selection of studies

Both authors (CJC, MJC) independently assessed studies identified in the literature searches by examining titles, abstract and keywords fields. We obtained studies that potentially fulfilled the inclusion criteria in full text. We independently assessed these full-text trial reports for inclusion. We resolved disagreements by consensus. We kept a record of decisions.

Data extraction and management

We extracted data using a prepared checklist before entering into Rev Man 5.0. We entered data on characteristics of included studies (methods, participants, interventions, outcomes) and results of the included studies. We contacted authors or manufacturers if serious adverse event data were not included in the trial report, and searched manufacturers' and FDA websites for further details of adverse events.

Assessment of risk of bias in included studies

Both authors 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). We resolved disagreements by consensus.

Measures of treatment effect

We recorded the number of participants with a serious adverse event of any cause (fatal and non-fatal), and in view of the difficulty in deciding whether events are asthma-related, we noted details of the cause of death and serious adverse events where they were available. We noted the definition of serious adverse events, and sought further information if this was not clear (particularly in relation to hospital admissions and serious adverse events).

Unit of analysis issues

We extracted data using the number of participants who suffered one or more serious adverse events, in order to avoid double-counting events from the same participant.

Assessment of heterogeneity

We assessed heterogeneity in the pooled odds ratio using the I^2 statistic in RevMan 5.0.

Assessment of reporting biases

We assessed reporting bias by comparing the published and unpublished serious adverse events, and by comparing all serious adverse events with those that were thought to be drug-related. We also compared serious events with all adverse events (whether serious or not).

Data synthesis

The outcomes of this review were dichotomous and we recorded the number of participants with each outcome event, by allocated treated group. We planned to analyse mortality using risk difference, as many studies did not have any deaths in either arm. However, the recently revised *Cochrane Handbook for Systematic Reviews of Interventions* advises against this approach, so we only used the risk differences to estimate the absolute impact of treatment (Higgins 2008). Although meta-analysis with Peto odds ratio has advantages when events are rare (Bradburn 2007), it performs less well with unbalanced treatment arms and large effect sizes, and therefore we calculated the results for serious adverse events and mortality in RevMan 5.0 as pooled odds ratios using the Mantel-Haenszel (MH) fixed-effect model. We compared the results of this model to the Peto method and MH random-effects models (as sensitivity analysis), although Bradburn 2007 cautions against the random-effects model as the variance calculations are based on large sample assumptions. We explored heterogeneity on the basis of the subgroup and sensitivity analyses outlined below. We inspected funnel plots to assess publication bias.

Subgroup analysis and investigation of heterogeneity

We conducted subgroup analyses on the primary outcomes on the basis of dose of formoterol (usual dose versus high dose), age (adults versus children) and comparator used. We planned to carry out subgroup analysis based on reported corticosteroid use, but none of the studies reported whether the patients who actually suffered serious adverse events were taking inhaled corticosteroids or not. We compared subgroups using tests for interaction (Altman 2003).

The definition of serious adverse events was rarely reported in the trials, but there is a standard definition used by industry in clinical study reports (ICHE2a 1995) and this is listed in Appendix 4.

Sensitivity analysis

We checked the overall results for the primary outcomes to assess the impact of removing the results from unblinded studies, and also those participants that were randomised to high-dose formoterol (24 µg twice daily). We also checked the impact of using fixed or random-effects models for meta-analysis.

RESULTS

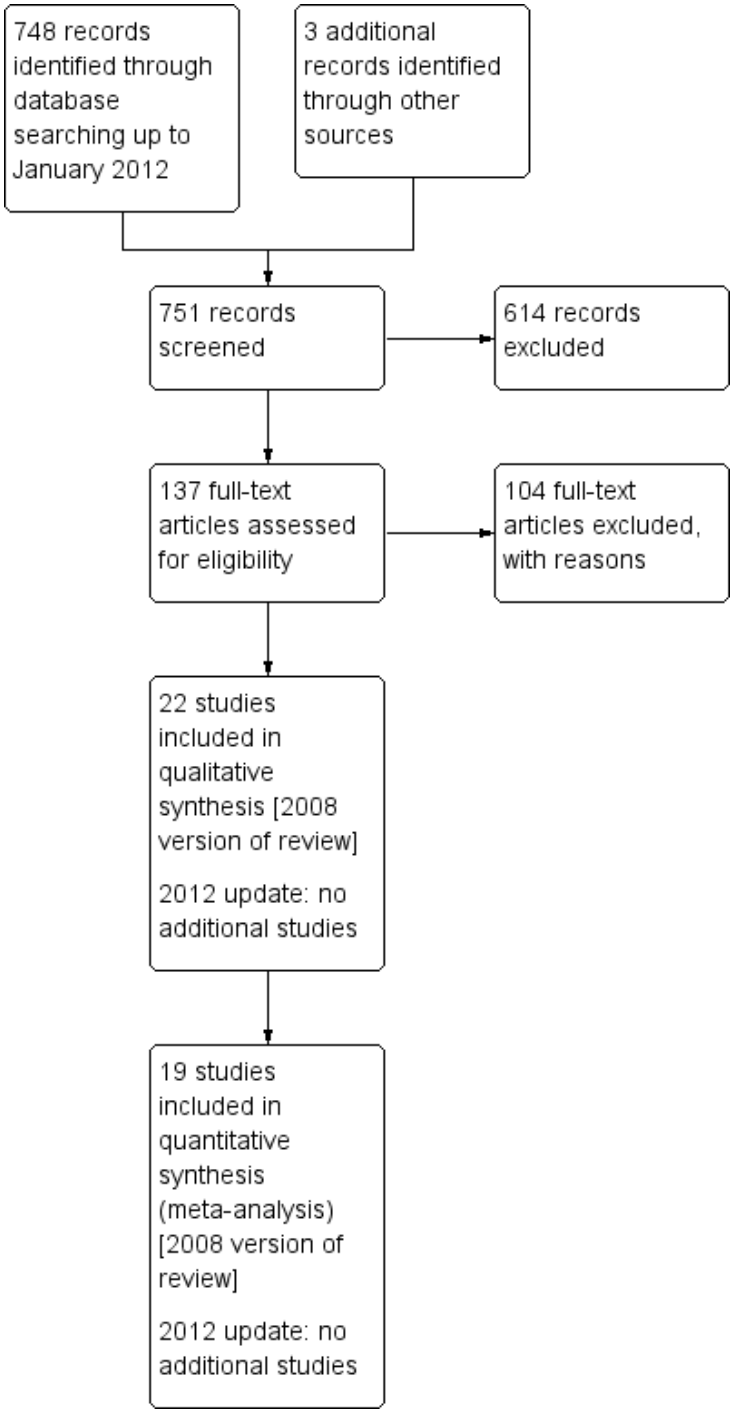
Description of studies

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

Results of the search

See Figure 3 for the study flow diagram. We found 512 abstracts from the initial search in October 2007 (reduced to 504 after removing duplicates). We identified 128 relevant abstracts that related to formoterol alone. We included 22 studies (32 references) in the review and excluded 95 others (see Excluded studies). Of those excluded 53 were less than 12 weeks in duration, (including 29 single-dose studies), three were not RCTs, eight were dose or device comparison studies, nine were on exercise-induced bronchospasm or acute asthma, nine used formoterol as reliever medication, eight were cross-over in design, three randomised to formoterol and budesonide and five were excluded for other reasons. One study that was included in Salpeter 2006 was excluded from this review because formoterol was randomised with budesonide (Price 2002) and therefore did not fit the inclusion criteria for this review. Both authors reached consensus on all the included studies after inspection of the full text from papers and websites.

Figure 3. Study flow diagram.



We repeated the search in July 2008, when we found 48 further abstracts. Six were relevant to this review but we excluded five as they were short-term studies, and one was on exercise-induced bronchospasm; we found no new studies meeting the inclusion criteria. Similarly a further search in January 2012 (cumulative total of 748 citations) identified three potentially relevant studies (Happonen 2009; Kamenov 2007; Price 2008). On checking the full text, none of these yielded new trials that were suitable for inclusion (see Excluded studies).

We identified one additional included study from other reviews; this was a trial on the AstraZeneca controlled trials register (SD-037-0344) which is otherwise unpublished. Additionally two documents on the FDA website provided additional serious adverse event information for four of the included studies (Bensch 2001; Bensch 2002; Pleskow 2003; Wolfe 2006). Additionally 22 studies of at least four weeks duration are listed in the appendix to a Novartis FDA submission (NovartisNDA20-831 2005), but it is not clear how these relate to the 10 included studies that we found which were supported by Novartis.

Included studies

We included 22 studies on 8032 participants (6693 adults and 1339 children); the characteristics of these studies are fully described in Characteristics of included studies. Sponsorship of the studies is also listed in Table 1.

Eight studies enrolled adults over 18 years of age (Ekstrom 1998; Ekstrom 1998a; FitzGerald 1999; Hekking 1990; Kesten 1991; Molimard 2001; Steffensen 1995; van der Molen 1997), one study adults over 16 years of age (van Schayck 2002), eight studies adults and adolescents over 12 years of age (Bensch 2001; Busse 2004; Corren 2007; LaForce 2005; Noonan 2006; Pleskow 2003; SD-037-0344; Wolfe 2006) and five enrolled children from five up to 12 or 16 years of age (Bensch 2002; Kozlik-Feldmann 1996; Levy 2005; Von Berg 2003; Zimmerman 2004).

All of the studies were of 12 weeks duration with the exception of Bensch 2002 (52 weeks), FitzGerald 1999 (24 weeks), van der Molen 1997 (24 weeks) and Wolfe 2006 (16 weeks). This gives a weighted mean duration of 16 weeks for the 19 studies with a placebo arm.

Since many of the studies randomised patients to more than two treatment arms, we have reported the overall number of patients randomised to treatment categories under investigation. Adults and adolescents are combined, as separate data for adolescents were not provided in any of the studies. In total 8032 participants were randomised (6693 adults and 1339 children); of these 2146 adults and 483 children received placebo, 2483 adults and 568 children received formoterol up to 12 µg twice daily, 921 adults and 277 children received formoterol 24 µg twice daily, and 1143 adults and 11 children received regular salbutamol or terbutaline. Although Molimard 2001 was an open study that did not use a placebo group, we included it in the placebo comparisons as on-demand salbutamol was used by patients in both the formoterol and the comparison arm.

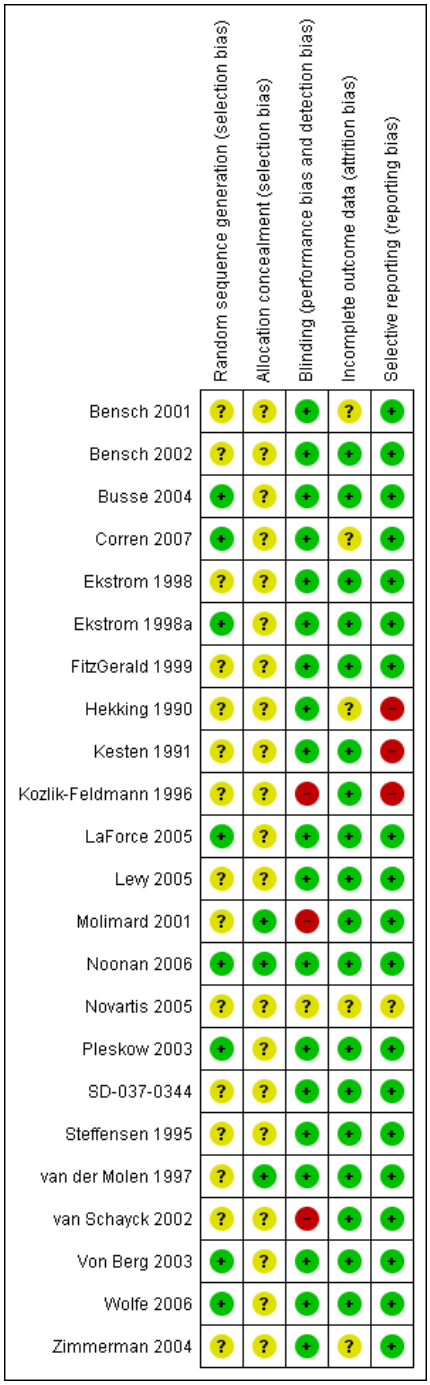
Doses of formoterol ranged from 4.5 µg to 24 µg twice daily in children and 6 µg to 24 µg twice daily in adults (but different delivery devices mean that the delivered dose may not be identical between studies, even if the nominal dose is the same). We have considered high-dose formoterol to be 24 µg twice daily.

Concurrent use of inhaled corticosteroids varied in the included studies from zero to 100%; Table 2 lists the inhaled steroid use by study. In almost all the studies at least half of the patients were taking inhaled corticosteroids at baseline.

Risk of bias in included studies

Figure 4 show a graphical representation of the domains of risk of bias across each study.

Figure 4. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Allocation

Allocation concealment and sequence generation were often poorly reported in the included studies. However, the majority of the studies are supported by manufacturers of formoterol (see Table 1) and are therefore likely to have had appropriate protection against selection bias.

Blinding

All studies were double-blind except for Kozlik-Feldmann 1996, Molimard 2001 and van Schayck 2002, and of these only Molimard 2001 has contributed data to the primary outcomes.

Incomplete outcome data

The included studies generally had withdrawal rates of less than 20% with the exception of Corren 2007 (51% dropout in the placebo group), and Noonan 2006 (60% withdrawals in placebo arm and 51.2% in formoterol arm).

Selective reporting

Although paper reports of studies often did not include usable information on all-cause serious adverse events, it has proved possible to obtain serious adverse events information from 19 of the 22 included studies. This represents 100% of participants randomised to formoterol or placebo, but only 80% of participants compared to regular salbutamol or terbutaline. There are clear guidelines for the reporting of serious adverse events for industry (ICHE3 2007). These all have to be listed in detail for the regulatory authorities, but there is clearly no similar expectation from medical journals. Twenty-two studies of at least four weeks duration are listed in the appendix to a Novartis FDA submission (NovartisNDA20-831 2005), but it is not clear how many of these would fulfil the criteria for inclusion in this review, or how they related to the 10 Novartis studies included in this review (Table 1). It has not been possible to obtain further information from the sponsors.

Effects of interventions

See: **Summary of findings for the main comparison** Summary of findings - SAE all ages; **Summary of findings 2** Summary of findings - mortality (all-cause); **Summary of findings 3** Summary of findings - SAE children

Primary outcomes

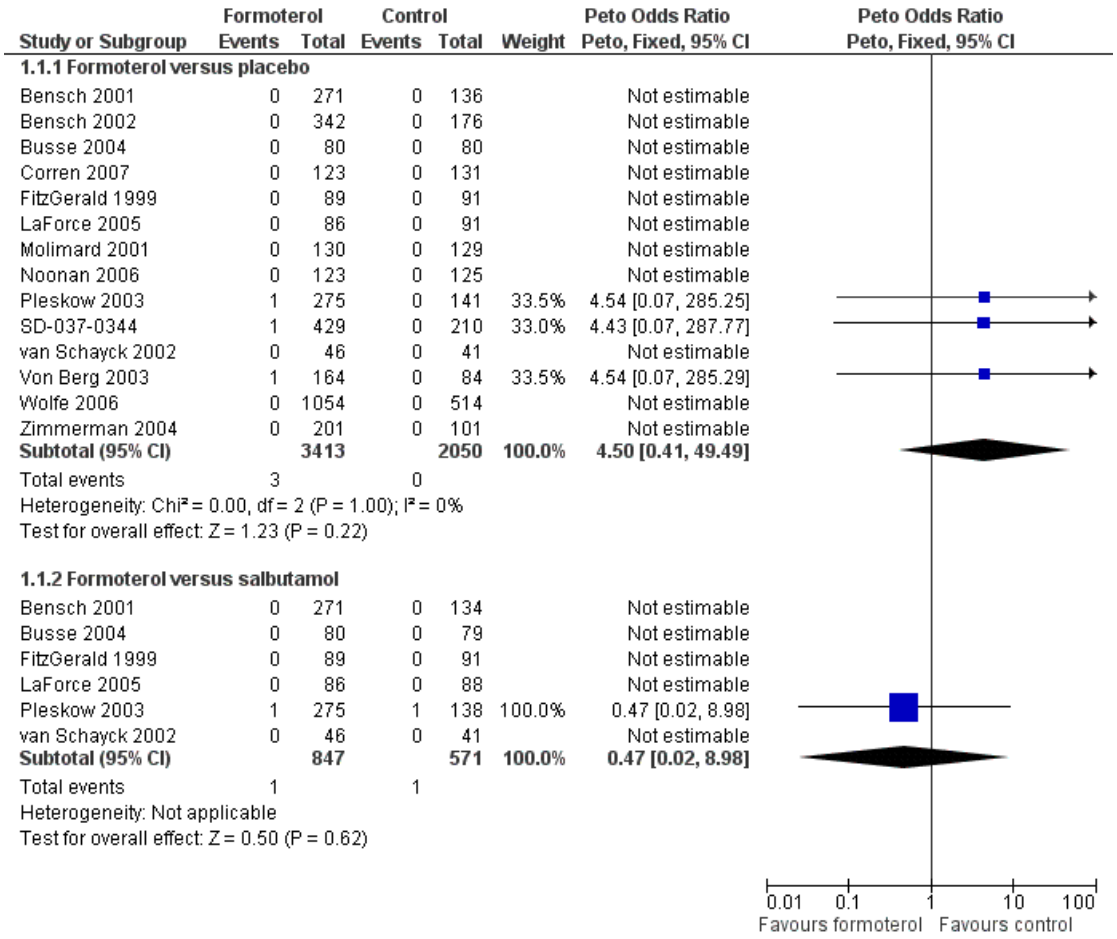
All-cause mortality

Events were sparse in the trials and the presence or absence of mortality was not always reported in the paper publications.

Formoterol versus placebo

Data were available from 14 studies comparing formoterol (N = 3413) with placebo (N = 2050); this represents 80% of the randomised patients for this comparison. Three deaths occurred in these trials (two adults and one child), and overall there were three deaths on formoterol and none on placebo. The cause of death for one adult was not reported in SD-037-0344, there was one adult death from asthma in Pleskow 2003, and one child died of a subarachnoid haemorrhage in Von Berg 2003. The pooled odds ratio (OR) was not statistically significant (Peto OR 4.50; 95% confidence interval (CI) 0.41 to 49.49), see Figure 5. The confidence interval and point estimate are somewhat different for a Mantel-Haenszel OR 1.52 (95% CI 0.24 to 9.71) using fixed or random-effects models. This discrepancy is due to the continuity correction required for zero cells in the Mantel-Haenszel method. The point estimate of the pooled risk difference (RD) was an increase of 4 deaths per 10,000 treated with regular formoterol over 16 weeks, with a confidence interval from 20 fewer deaths to 28 more deaths per 10,000. There was no statistical heterogeneity in this outcome.

Figure 5. Forest plot of comparison: 1 All-cause mortality, outcome: 1.1 Overall results.



Formoterol versus salbutamol

Data were available from six studies comparing formoterol (N = 847) to salbutamol/albuterol (N = 571), representing 49% of the randomised patients for this comparison. Only two deaths occurred, both in Pleskow 2003; one in the formoterol arm (from asthma as reported above) and one in the salbutamol arm (from pancreatitis), and again the difference was not statistically significant. As only one study contributed to this outcome, we calculated no pooled OR.

Subgroup analyses

No subgroup analyses were possible for all-cause mortality as the data were too sparse.

Serious adverse events (SAEs) (non-fatal all-cause)

An example of the definition of a serious adverse event (SAE) is given in Pleskow 2003: "A serious adverse event was defined as any experience that was fatal or life-threatening, permanently disabling, requiring in-patient or prolonged hospitalisation, or was a congenital abnormality, cancer or drug overdose." This is in line with the definition in Appendix 4, and we have assumed that this definition was used in the other trials (even though this was often not made explicit). In most cases the events were defined as serious because they were associated with hospital admission.

Formoterol versus placebo

Combined data from adults and children

Data were available on non-fatal SAEs for 19 studies comparing regular formoterol (N = 4017) to placebo (N = 2629); this represents all of the randomised patients from published studies for this comparison. The studies were largely on adults (N = 5311), but five trials were in children (N = 1335).

The overall result indicated an increased risk of SAEs with formoterol (Peto OR 1.57; 95% CI 1.06 to 2.31) with low heterogeneity (I^2 = 0%), Figure 6. SAEs were rare in the studies (occurring in 1.2% of patients on placebo over a weighted mean of 16 weeks), so the pooled risk difference is small at 0.007 (95% CI 0.0012 to 0.013) and using a weighted mean of the placebo arms, over a 16-week period there would need to be 149 patients treated (95% CI 66 to 1407) for one extra serious adverse event to occur; this number needed to treat was calculated by Visual Rx using the pooled odds ratio and baseline risk of 1%. This is illustrated in Figure 7 which shows that for every thousand patients treated over 16 weeks with formoterol there are an extra six patients who will suffer a serious adverse event, so that in comparison to 10 per thousand in the placebo group this rises to 16 per thousand on regular formoterol.

Figure 6. Forest plot of comparison: 2 Adults and children non-fatal serious adverse events, outcome: 2.1 Formoterol versus placebo or salbutamol.

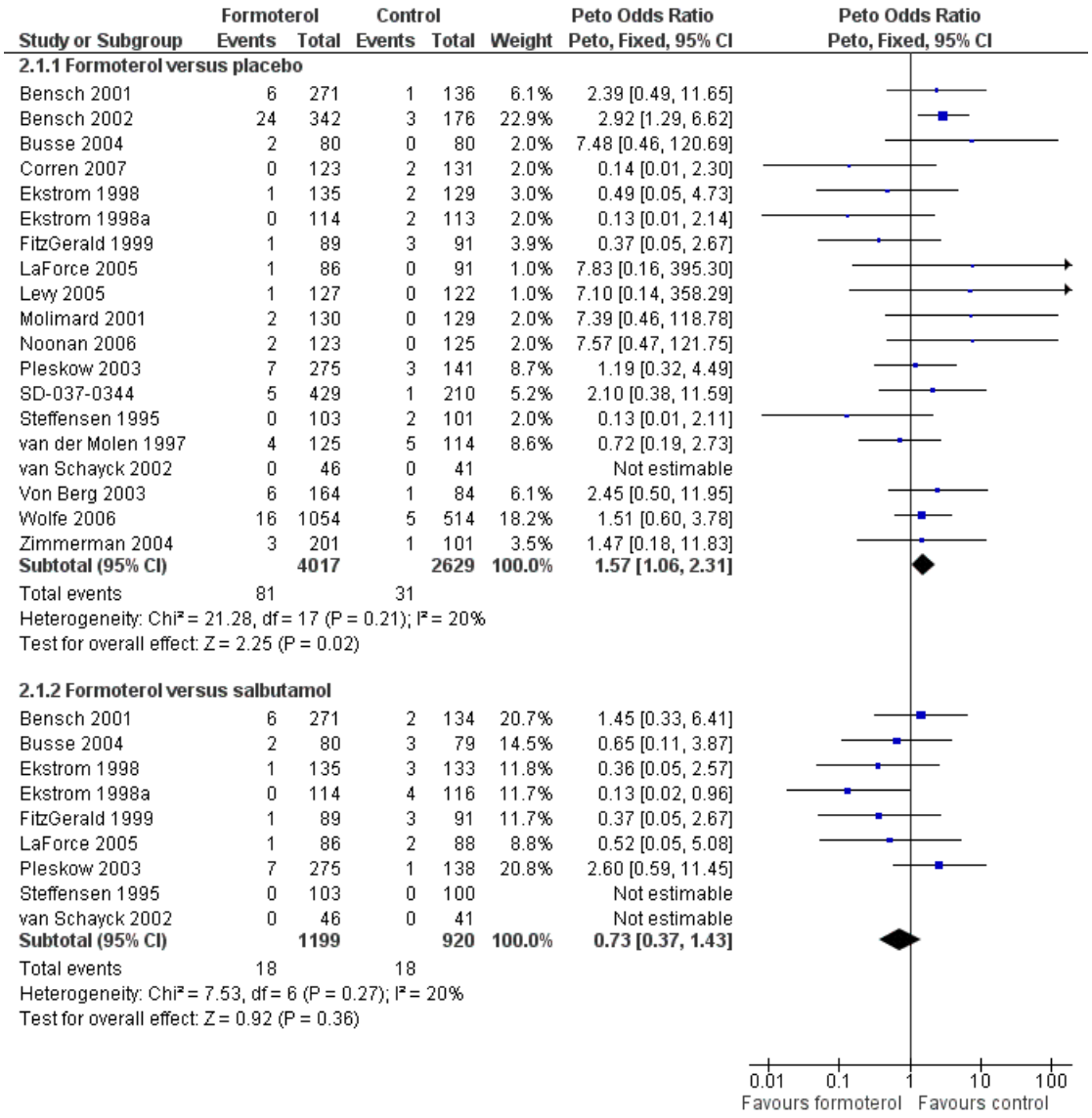
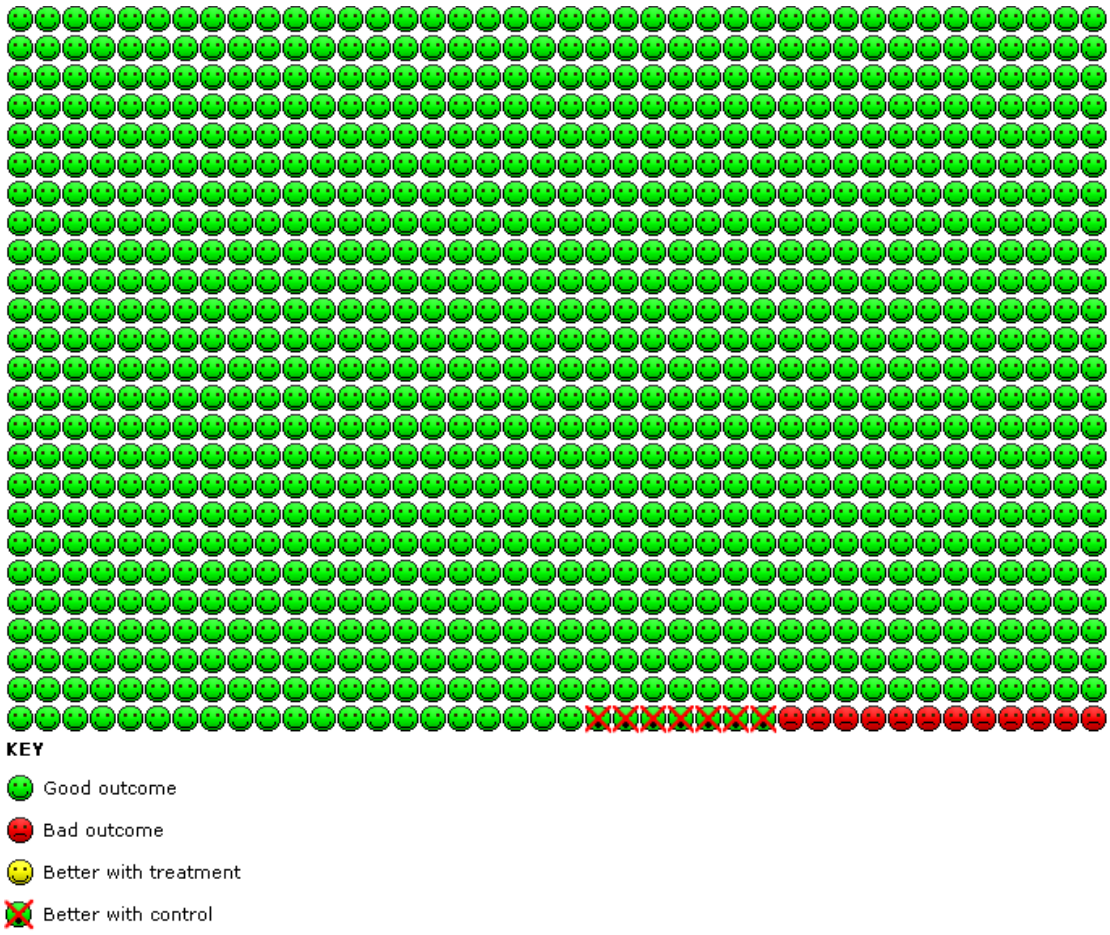


Figure 7. Serious adverse events with regular formoterol compared to placebo. In the control group 12 people out of 1000 had serious adverse events over 16 weeks, compared to 19 (95% CI 13 to 27) out of 1000 for the active treatment group.



Sensitivity analysis by applying the Mantel-Haenszel method gave a very similar result, OR 1.57 (95% CI 1.05 to 2.37). Using a random-effects model (which is not recommended for rare events due to an increased risk of bias (Bradburn 2007)), the point estimate was similar but the confidence interval widened: OR 1.52 (95% CI 0.96 to 2.40). When we excluded the participants receiving high-dose formoterol (24 µg) arms from the analysis the confidence interval again widened (Peto OR 1.55; 95% CI 0.97 to 2.48)(Analysis 3.1).

Adults with non-fatal serious adverse events

When the adult data comparing regular formoterol (N = 3170) with placebo (N = 2137) were considered on their own, the results showed a smaller increase in risk which did not reach statistical significance (Peto OR 1.23; 95% CI 0.76 to 1.99)(Analysis 4.1). The Mantel-Haenszel method gave very similar results, OR 1.22 (95% CI 0.76 to 1.96).

Children with non-fatal serious adverse events

Although fewer children were studied, regular formoterol (N = 843) compared with placebo (N = 492), the separate results for children showed a larger increase in serious adverse events with regular formoterol (Peto OR 2.48; 95% CI 1.27 to 4.83)(Analysis 5.1). Again the Mantel-Haenszel method gave a very similar result, OR 2.92 (95% CI 1.26 to 6.74). There was low heterogeneity in this outcome (I^2 = 0%), and the result in children remained significant when the data on high-dose formoterol were excluded (Peto OR 2.52; 95% CI 1.15 to 5.51) and Mantel-Haenszel OR 2.59 (95% CI 1.08 to 6.19)(Analysis 6.1).

When the results in children are compared with adults using a test for interaction (Altman 2003), the increased risk in children relative to adults is a relative OR of 2.39 (95% CI 0.91 to 6.27) using the Mantel-Haenszel odds ratio, which is not statistically significant. The results are very similar when the Peto OR is compared between adults and children (relative OR 2.02; 95% CI 0.89 to 4.59).

High-dose formoterol versus lower doses

When the study arms using formoterol 24 µg twice daily were compared to those using lower doses (formoterol 12 µg twice daily), no significant difference was found in adults (Peto OR 1.35; 95% CI 0.64 to 2.85)(Analysis 7.1). The confidence interval for this result is too wide to rule out a difference in relation to dose, and although the three adult studies all used the same dry powder delivery device (Aerolizer), there is a high level of heterogeneity between studies (I^2 = 74%), which is unexplained.

Moreover the data from the Novartis database of published and unpublished placebo-controlled studies of at least four weeks duration has been included for comparison (Novartis 2005); the Novartis data show a significantly higher risk of asthma-related serious adverse events with formoterol 24 µg twice daily in comparison to 12 µg twice daily (Peto OR 2.16; 95% CI 1.13 to 4.11) and Mantel-Haenszel OR 2.08 (95% CI 1.11 to 3.89).

Formoterol versus salbutamol

Adults with non-fatal serious adverse events

In contrast, the results from nine studies in adults comparing regular formoterol (N = 1119) to salbutamol (N = 920), representing 80% of the randomised patients for this comparison, showed a non-significant reduction in the risk of SAEs (Peto OR 0.73; 95% CI 0.37 to 1.43)(Analysis 4.1). However, when the results from patients using high-dose formoterol were excluded, there was a significant reduction in risk for formoterol in comparison with salbutamol or terbutaline (Peto OR 0.41; 95% CI 0.19 to 0.90) and Mantel-Haenszel OR 0.40 (95% CI 0.17 to 0.94) (Analysis 3.1).

A test for interaction between the results comparing formoterol with placebo and salbutamol was not significant; the risk in trials against regular salbutamol compared to those against placebo using Mantel-Haenszel OR gives a relative OR of 0.46 (95% CI 0.21 to 1.01), whilst for the Peto method the relative OR is 0.59 (95% CI 0.26 to 1.36).

No studies were found comparing regular formoterol to regular salbutamol or terbutaline in children.

SAEs all-cause (fatal and non-fatal combined)

When fatal and non-fatal SAEs are considered together the findings are very similar to those for the non-fatal events, with a significant increase in risk with regular formoterol in comparison with placebo (Peto OR 1.61; 95% CI 1.09 to 2.37) and Mantel-Haenszel OR 1.63 (95% CI 1.08 to 2.44), but not in comparison with regular salbutamol (see Analysis 8.1).

Secondary outcomes

Mortality by cause of death

Asthma mortality and cardiovascular mortality

Only one death related to asthma was reported using formoterol 24 µg in Pleskow 2003, and one death in Von Berg 2003 from sub-arachnoid haemorrhage on formoterol 9 µg, so there are insufficient data to assess the impact of formoterol on disease-specific mortality. The third death in SD-037-0344 has no reported cause.

SAEs related to asthma and the cardiovascular system

When formoterol is compared to placebo, there is a significant increase in asthma-related serious adverse events on regular formoterol (Peto OR 1.99; 95% CI 1.12 to 3.53) and Mantel-Haenszel OR 1.90 (95% CI 1.03 to 3.48)(Analysis 11.1). This finding is also apparent from the Novartis integrated database (Novartis 2005), which is concordant with the results of the 10 Novartis studies included in the review as shown in Analysis 12.1.

In comparison with regular salbutamol there is a decrease in asthma-related serious adverse events on regular formoterol but this is not significant (Peto OR 0.74; 95% CI 0.29 to 1.88) and Mantel-Haenszel OR 0.72 (95% CI 0.32 to 1.76)(Analysis 11.1). There is a significant increase in hospital admissions for asthma when regular formoterol is compared to placebo: Peto OR 3.28; 95% CI 1.65 to 6.52 and Mantel-Haenszel OR 4.28; 95% CI 1.60 to 11.46 (Analysis 13.1). For this outcome we assumed that all the patients with asthma-related SAE documented in the FDA submission were admitted to hospital; in Pleskow 2003 this is clearly stated to be the case for two patients on placebo and five on

formoterol 24 µg, but is not clearly reported for the single patient on formoterol 12 µg (Mann 2003). No significant difference was seen when regular formoterol is compared to regular salbutamol. Very few events relating to the cardiovascular system were reported, so although the direction of effect is in favour of formoterol the confidence intervals in comparison to placebo and salbutamol are very wide (Analysis 14.1).

Impact of inhaled corticosteroids

It has not been possible to assess whether inhaled corticosteroids have an impact on SAEs with regular formoterol from the included studies, as this would require individual patient data relating inhaled corticosteroid usage to those patients who suffered the events, and these data are not available. However, data are presented in Novartis 2005 in which patients on inhaled corticosteroids are compared with those who are not, for asthma-related serious adverse events. Although the increased risk is larger without inhaled corticosteroids (Peto OR 3.22; 95% CI 1.17 to 8.89) and Mantel Haenszel OR 7.31 (95% CI 0.97 to 55.06), than with inhaled corticosteroids (Peto OR 2.58; 95% CI 1.21 to 5.49) and Mantel-Haenszel OR 3.47 (95% CI 1.21 to 9.97), the confidence intervals are wide and there is no statistically significant interaction between the increased risk and use of inhaled corticosteroids. Moreover there remains a significant three-fold increase in odds for patients who were taking inhaled corticosteroids, and this is maintained when the data on formoterol 24 µg twice daily are excluded (Peto OR 2.76; 95% CI 1.06 to 7.15) and Mantel-Haenszel OR 3.11 (95% CI 1.01 to 9.55)(Analysis 15.1).

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Regular formoterol versus placebo or salbutamol for chronic asthma

Patient or population: patients with chronic asthma
Settings: community
Intervention: regular formoterol
Comparison: placebo or salbutamol

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo or salbutamol	Regular formoterol				
Mortality (all-cause) - formoterol versus placebo (follow-up: mean 16 weeks)	**Medium-risk population**		**OR 1.52** (0.24 to 9.71)	5463 (14)	⊕⊕⊕◯ **moderate**[1]	
	0 per 1000	**0 per 1000** (0 to 0)				
Mortality (all-cause) - formoterol versus salbutamol (follow-up: mean 13 weeks)	**Medium-risk population**		**OR 0.5** (0.03 to 8.05)	1418 (6)	⊕⊕⊕◯ **moderate**[1]	
	0 per 1000	**0 per 1000** (0 to 0)				

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

CI: Confidence interval; OR: Odds ratio;

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

[1] Not enough data to assess this outcome

Regular formoterol versus placebo or salbutamol for children with chronic asthma: serious adverse events

Patient or population: patients with chronic asthma (children)
Settings: community
Intervention: regular formoterol versus placebo or salbutamol

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Regular formoterol versus placebo or salbutamol				
SAEs - formoterol versus placebo (follow-up: mean 23 weeks)	**Medium-risk population**		**OR 2.82** (1.16 to 6.83)	1335 (5)	⊕⊕⊕⊕ **high**	
	12 per 1000	**33 per 1000** (14 to 77)				
SAEs - formoterol versus salbutamol	See comment	See comment	Not estimable	-	See comment	

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

CI: Confidence interval; OR: Odds ratio; SAE: serious adverse event

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

DISCUSSION

Summary of main results

Three deaths occurred on regular formoterol and none on placebo; this difference was not statistically significant. It was not possible to assess disease-specific mortality in view of the small number of deaths.

Non-fatal serious adverse events (SAEs) were significantly increased in comparison with placebo. These events were rare, occurring in 1.0% of patients in the placebo arms over an average of 16 weeks; in comparison 1.6% of those given regular formoterol suffered a SAE (Figure 7). One additional participant with a SAE was found to occur for every 149 people treated with regular formoterol over 16 weeks, and the play of chance is compatible with one extra event for every 66 to 1407 given regular formoterol. The majority of these extra events appear to be asthma-related, and data from unpublished studies on the Novartis integrated database of placebo-controlled trials suggest that there may be a significant increase in the risk of asthma-related SAEs with regular formoterol even in those patients who were taking inhaled corticosteroids (Analysis 15.1).

The increased risk is larger in children than in adults, but the difference between the results in children and adults is not statistically significant. No significant overall differences were found for all-cause mortality or non-fatal SAEs in trials comparing regular formoterol with salbutamol or terbutaline.

Overall completeness and applicability of evidence

Although large numbers of participants have been treated with regular formoterol, the rarity of mortality and SAEs means that there is still considerable uncertainty in relation to the size of the effects being investigated. There is insufficient evidence to be sure whether the larger increase in SAEs found in children is significantly different from the smaller increase in adults. We have received additional information relating to eight studies from authors and manufacturers, but data have not been forthcoming for three of the included studies. The missing data represent a moderate proportion of the participants who are in trials comparing formoterol with salbutamol, but they could alter the point estimates and confidence intervals for this comparison. Whilst it has not been possible to obtain details of unpublished Novartis studies submitted to the FDA, the pooled data from the Novartis trials has been used in this review (but not combined with the included studies as there is an unknown degree of overlap).

Information from papers published in medical journals

All-cause non-fatal SAEs were published in the paper reports of studies for 31 patients on formoterol and seven patients on placebo; this less than half of the total number of events found from all sources. Considering only the data from paper reports there is still a significant increase with regular formoterol (Peto odds ratio (OR) 2.31; 95% confidence interval (CI) 1.17 to 4.53), see Analysis 16.1.

Serious and non-serious adverse events

All adverse events are shown in Analysis 17.1, and published adverse events in Analysis 18.1. Both show small increases with regular formoterol that do not reach statistical significance, which may be because the larger number of minor adverse events are not altered by formoterol. Published drug-related adverse events showed a significant increase as shown in Analysis 19.1.

Drug-related serious adverse events

If the analysis had been confined to SAEs that were thought to be drug-related, only five of the 136 SAEs would have been included, and because there is a wide confidence interval around this small number of events, no significant increase in drug-related SAEs was found (Peto OR 1.45; 95% CI 0.18 to 11.61) and Mantel-Haenszel OR 0.90 (95% CI 0.19 to 4.24) (Analysis 20.1).

Quality of the evidence

All the studies were double-blind with the exception of LaForce 2005, Molimard 2001 and van Schayck 2002. Of these, only Molimard 2001 contributed data to SAEs with regular formoterol in comparison with placebo, and if the meta-analysis is confined to the double-blind trials the increase remains significant (Peto OR 1.52; 95% CI 1.02 to 2.25). There are methodological concerns in relation to data from the Novartis integrated database, as these are not presented for the individual studies, but where it has been possible to compare results from the database with the Novartis studies included in the review the results are very similar (Analysis 12.1).

Agreements and disagreements with other studies or reviews

The findings of this review are similar to those of our review comparing regular salmeterol to placebo and regular salbutamol (Cates 2008). Both reviews show that, in comparison with placebo, there are significant increases in all-cause SAEs with the use of regular long-acting beta$_2$-agonists. The size of this increase is comparable for regular salmeterol (Peto OR 1.15; 95% CI 1.02 to 1.29) and regular formoterol (Peto OR 1.57; 95% CI 1.06 to 2.31). The placebo group event rates were different in the two reviews, so it would be misleading to try to compare the absolute increases in

risk between salmeterol and formoterol. Similarly, although the increase in events reached statistical significance in adults (but not children) for salmeterol, and in children (but not adults) for formoterol, these age group differences may be due to the play of chance, as the test for interaction between age group and treatment effect was not significant in either case (Altman 2003).

The number of participants is too small to assess the impact of regular formoterol on all-cause or asthma-related mortality, so it is not possible to compare these results with the increased asthma mortality found in SMART 2006. However, data submitted by Novartis to the FDA (Novartis 2005) do indicate a significant increase in asthma-related serious adverse events, even in patients taking regular inhaled corticosteroids (Analysis 15.1).

A recent meta-analysis of individual patient data from trials of all FDA-approved LABAs found a higher risk of serious asthma-related events in children as compared to adults (McMahon 2011), which is in keeping with the results of this review. This increased risk in children persisted in those who were given concomitant ICS, but not in the trials in which participants were assigned to ICS as part of their randomised treatment.

AUTHORS' CONCLUSIONS

Implications for practice

In comparison with placebo, we have found an increased risk of serious adverse events with regular formoterol, and this does not appear to be abolished in patients taking inhaled corticosteroids. The effect on serious adverse events of regular formoterol in children was greater than the effect in adults, but the difference between age groups was not significant.

Implications for research

Data on all-cause serious adverse events should be more fully reported in medical journals, and not combined with all adverse events or limited to those events that are thought by the investigator to be drug-related.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Bensch 2001

Methods	A randomised, double-blind, double-dummy, placebo-controlled, multicentre parallel-group study over 12 weeks at 26 trial sites in the USA. 2-week, single-blind, placebo lead-in period
Participants	**Population**: 541 adolescents and adults (12 to 75) years with mild to moderate persistent asthma **Baseline characteristics**: mean age 35.5 years. FEV_1 66% predicted. Concomitant inhaled corticosteroids used by 51% of participants. **Inclusion criteria**: mild to moderate persistent asthma requiring daily use of an inhaled B_2-selective adrenergic agent (short- or long-acting). FEV_1 between 40% and 80% predicted after an 8-hour period of abstinence from short-acting B_2- adrenergic agonist use. Bronchodilator reversibility at least a 15% increase in FEV_1 within 30 minutes after inhalation of 180 µg of albuterol delivered via MDI. Co-interventions permitted: ICS 51%, slow release theophylline 17% **Exclusion criteria**: URTI, hospitalisation/asthma exacerbation < 4 weeks, serious illness
Interventions	1. Formoterol 12/24 µg BD 2. Albuterol 180 µg QDS 3. Placebo QDS Formoterol delivered by Aerolizer (dry powder) and albuterol by MDI
Outcomes	Primary outcome: FEV_1 . Safety was evaluated by adverse event reports. Paper report: "Adverse events, whether or not trial drug related, were reported by 68% of patients on formoterol 12 mcg, 76% on formoterol 24 mcg, 70% on albuterol and 71% on placebo. No deaths occurred during the study." No SAE data reported but the numbers match FDA submission for study 040 (http://www.fda.gov/cder/foi/nda/2001/20831_Foradil_medr_P1.pdf). This lists all (asthma-related in brackets) SAEs as: 1 (0) on formoterol 12 µg, 5 (4) on formoterol 24 µg, 2 (2) on albuterol and 1 (0) on placebo
Notes	Supported by Novartis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) Adverse Events	Low risk	Double-blind, double-dummy. Matching capsules and devices

Bensch 2001 (*Continued*)

Incomplete outcome data (attrition bias) Adverse Events	Unclear risk	All patients included in the safety analysis
Selective reporting (reporting bias)	Low risk	No SAE data in paper publication, but FDA submission provided SAE information

Bensch 2002

Methods	A randomised, double-blind, placebo-controlled, multinational, multicentre, paediatric study over 52 weeks at 42 centres. Initial run-in period of 2 weeks
Participants	**Population**: 518 children (5 to 12) years with persistent asthma on preventer therapy **Baseline characteristics**: mean age 9 years. FEV_1 71% predicted. At least 69% were taking ICS, with 26% on sodium cromoglycate and 5% nedocromil sodium. **Inclusion criteria**: persistent asthma diagnosed by ATS criteria. Sodium cromoglycate, nedocromil sodium and/or ICS for at least 4 weeks before entry in the study, but still required daily use of inhaled salbutamol (albutamol) to control symptoms. Baseline FEV_1 ranged from 50% to 85% of predicted and increased by 15% or more within 30 minutes after inhaling 200 µg salbutamol (180 µg albuterol in the United States) delivered by a metered-dose inhaler. Co-interventions: 70% on ICS, 30% on cromones (all stable dosage) **Exclusion criteria**: unstable asthma, URTI, OS course or exacerbation asthma within 4 weeks, QT interval on ECG > 0.46 sec
Interventions	1. Formoterol 12 µg or 24 µg BD 2. Placebo BD delivery was Aerolizer
Outcomes	Primary outcome: FEV_1 (area under curve) Paper reports: "There were no deaths in this study." Table 4 in the paper reports SAE data but not in a way that allows all-cause SAE data to be extracted. Full SAE data found on FDA website
Notes	Supported by Novartis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) Adverse Events	Low risk	Double-blind

Bensch 2002 (*Continued*)

Incomplete outcome data (attrition bias) Adverse Events	Low risk	407/518 (78%) completed the study
Selective reporting (reporting bias)	Low risk	All-cause SAE data not extractable from published paper, but present in FDA web report

Busse 2004

Methods	Randomised, double-blind, double-dummy, placebo-controlled, parallel-group study over 12 weeks in outpatient clinics at 18 US centres. Run-in 2 weeks single-blind placebo
Participants	239 adolescents and adults (13 to 85) years with persistent asthma. (9 patients were aged less than 18 years old) **Baseline characteristics**: mean age 38 years. FEV_1 65% predicted. Concomitant inhaled corticosteroids used by 64% of participants. **Inclusion criteria**: persistent asthma, requiring regular or on-demand bronchodilators, FEV_1 % predicted at least 40%, bronchodilator reversibility by either an increase of at least 15% in FEV_1 over baseline or increases of at least 12% and 200 mL in FEV_1 over baseline within 30 minutes of inhaling albuterol 180 to 360 µg (2 to 4 puffs) via pMDI. Co-interventions permitted: ICS, cromolyn, montelukast, theophyllines, intra nasal ICS **Exclusion criteria**: RT infection, use of OCS, parenteral CS or hospitalisation for asthma due to exacerbation < 1 month, use of unstable anti-inflammatory regime, corrected QT interval > 460 ms, current smoker, ex smoker > 10 Pack years, serious medical condition, pregnancy, lactation, use of oral beta blocker, non-potassium sparing diuretic, anti-arrhythmic, tricyclic antidepressant, MAOI, NSAIDS
Interventions	1. Formoterol 10µg BD 2. Placebo BD 3. Albuterol 180 µg QDS Delivery was DPI for formoterol and MDI for albuterol (salbutamol)
Outcomes	The primary efficacy variable was the 12-hour AUC of FEV_1 after 12 weeks' treatment No deaths in the study. Non-fatal SAEs: formoterol 2 (1 asthma exacerbation and 1 basal cell carcinoma). Albuterol 3 (1 eating disorder, 1 renal calculi and 1 pneumonia). Placebo 0. No events were considered to be related to study medication Any AE: formoterol 43, albuterol 47 and placebo 48
Notes	Funding Novartis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	1:1:1 ratio using computer-generated list of random numbers

Busse 2004 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) Adverse Events	Low risk	Double-dummy matched devices
Incomplete outcome data (attrition bias) Adverse Events	Low risk	209/239 (87%) completed the study; SAE reported for both those who withdrew and those who continued in the study
Selective reporting (reporting bias)	Low risk	Serious adverse events (fatal and non-fatal) documented in the paper publication

Corren 2007

Methods	Randomised, double-blind, double-dummy, multicentre, placebo-controlled study over 12 weeks at 56 US centres from July 2002 to September 2003. Run-in 7 to 21 days in which usual asthma therapy was withdrawn
Participants	**Population**: 480 adolescents and adults (12 to 78) years with mild to moderate persistent asthma. The web report also includes results from a further 31 children aged 6 to 11 years **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 to 4 inhalations (90 µg per inhalation)) **Exclusion criteria**: reasons for exclusion from the study included severe asthma (as judged by the investigator), asthma requiring hospitalisation 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. Formoterol 9 µg (DPI) 2. Placebo BID (pMDI) The Symbicort and budesonide arms of this study are not 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 2 serious adverse events in the placebo group (intestinal obstruction, abdominal pain) reported on the website. One of these presumably occurred in a child under 12 years, as the paper reports 1 serious adverse event in those aged over 12 years. No cardiac-related serious adverse events were reported in any group. No deaths occurred in any group

Corren 2007 (*Continued*)

	(website data)
Notes	Study sponsored by AstraZeneca http://www.astrazenecaclinicaltrials.com/Article/525476.aspx accessed 16 June 2008 for web data

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	By study site, computer-generated allocation schedule using balanced blocks of 4
Allocation concealment (selection bias)	Unclear risk	No information
Blinding (performance bias and detection bias) Adverse Events	Low risk	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 (attrition bias) Adverse Events	Unclear risk	ITT analysis used for adverse events. High dropout rate in placebo group (51%)
Selective reporting (reporting bias)	Low risk	Serious adverse events reported in paper publication

Ekstrom 1998

Methods	A randomised, double-blind, double-dummy, placebo-controlled, parallel-group, multicentre, multinational study (Sweden, Norway, Spain, Italy) over 12 weeks at 25 centres. Run-in: 2 weeks single-blind placebo
Participants	**Population**: 397 adults (18 to 79) with mild to moderate asthma **Baseline characteristics**: mean age 47 years. FEV_1 62% predicted. Concomitant inhaled corticosteroids used by 86% of participants **Inclusion criteria**: diagnosis asthma by ATS criteria. FEV_1 of 40% to 80% predicted, bronchodilator reversibility by an increase of at least 15% in FEV_1 over baseline and at least 200 ml, measured after inhalation of 0.5 mg terbutaline via Turbuhaler **Exclusion criteria**: not reported
Interventions	1. Formoterol 6 µg BD 2. Terbutaline 500 µg QDS 3. Placebo: placebo QDS Delivery was dry powder device
Outcomes	Primary outcome PEF. Adverse events were assessed by asking patients if they had experienced any health problems or symptoms not usually associated with their asthma "Asthma aggravation accounted for two serious adverse events in the terbutaline group

Ekstrom 1998 (*Continued*)

	and one serious adverse event in the placebo group." Manufacturers asked for all-cause serious adverse event data, and these have been provided as 1 patient on formoterol, 3 patients on terbutaline and 2 patients on placebo
Notes	Author affiliation includes Astra Draco

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) Adverse Events	Low risk	Double-blind, double-dummy, matching devices
Incomplete outcome data (attrition bias) Adverse Events	Low risk	359/397 (90%) completed the study
Selective reporting (reporting bias)	Low risk	All-cause SAE data have been provided by sponsors

Ekstrom 1998a

Methods	A randomised, double-blind, double-dummy, placebo-controlled, parallel-group, multicentre study over 12 weeks at 28 centres in Scandinavia. Run-in 1 week single blind
Participants	**Population**: 343 adults (18 to 82) with moderate stable asthma **Baseline characteristics**: mean age 48 years. FEV_1 61% predicted. Concomitant inhaled corticosteroids used by 89% of participants **Inclusion criteria**: diagnosis asthma by ATS criteria. FEV_1 of 40% to 80% predicted, bronchodilator reversibility by an increase of at least 15% in FEV_1 over baseline 15 minutes after inhalation of 0.5 mg terbutaline sulphate via Turbuhaler Co-interventions: ICS 89%, cromones 2% - stable doses OS 2 participants **Exclusion criteria**: not reported
Interventions	1. Formoterol 12 µg BD 2. Terbutaline 500 µg QDS 3. Placebo QDS Delivery was dry powder device - Turbuhaler
Outcomes	FEV1, PEF, rescue use, asthma symptom score, adverse events, asthma deterioration Primary outcome PEF. Adverse events were assessed by asking patients if they had experienced any health problems or symptoms not usually associated with their asthma No SAE reporting at all in the paper. Manufacturers asked for all-cause serious adverse

Ekstrom 1998a (*Continued*)

	event data: 4 patients with SAE in terbutaline group and 2 on placebo. Of these 3 and 2 were asthma-related
Notes	Author affiliation includes Astra Draco

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random order, balanced blocks
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) Adverse Events	Low risk	Double-blind, double-dummy, matching devices
Incomplete outcome data (attrition bias) Adverse Events	Low risk	311/343 (90%) completed the study
Selective reporting (reporting bias)	Low risk	SAE results provided by sponsors

FitzGerald 1999

Methods	A randomised, double-blind, double-dummy, placebo-controlled, parallel-group, multicentre study over 24 weeks at 15 centres in Canada. Run-in 2 weeks single-blind
Participants	**Population**: 271 adults with moderate to severe asthma **Baseline characteristics**: mean age 36 years. FEV_1 79% predicted. Concomitant inhaled corticosteroids used by all the participants **Inclusion criteria**: diagnosis asthma by ATS criteria. Using ICS at a constant dose of 400 to 1200 mg/day and inhaled SABA for at least 1 month Bronchodilator reversibility as a 15% or greater increase in FEV_1 15 to 30 minutes after inhalation of a B_2-agonist, and increased sensitivity to inhaled methacholine, defined as a PC_{20} less than or equal to 8 mg/mL. Rescue albuterol required on 5 out of 7 days of run-in period **Exclusion criteria**: URTI/change in asthma medication/exacerbation of asthma within 2 months. Smoking
Interventions	1. Formoterol 12 µg BD 2. Placebo QDS 3. Albuterol 200 µg QDS Delivery was dry powder device
Outcomes	The primary end point of this trial was the methacholine PC_{20} at the end of the double-blind phase (visit 6) No SAE data published for this study, but unpublished serious adverse event data pro-

FitzGerald 1999 (*Continued*)

	vided by the authors "Drug-related adverse events were reported by 15%, 12% and 10% of the formoterol, regular albuterol and on-demand albuterol patients, respectively."
Notes	Supported by a grant from Novartis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) Adverse Events	Low risk	Double-blind, double-dummy, matching devices
Incomplete outcome data (attrition bias) Adverse Events	Low risk	
Selective reporting (reporting bias)	Low risk	No SAE reporting in paper and no web data found, but data provided by the authors

Hekking 1990

Methods	Randomised, double-blind, double-dummy, multicentre, parallel-group study of outpatients over 12 weeks in The Netherlands. Washout period of 12 hours for inhaled and 24 hours for oral medication
Participants	**Population**: 301 adults (18 to 70) years with stable-phase asthma **Baseline characteristics**: mean age 40 years. FEV_1 not reported. Concomitant inhaled corticosteroids use not reported (but allowed in protocol). **Inclusion criteria**: stable-phase asthma, FEV_1 % predicted less than 80%, bronchodilator reversibility greater than 15% in FEV_1 over baseline **Exclusion criteria**: use of theophyllines, oral $beta_2$ agonists or anticholinergics
Interventions	1. Formoterol 12 µg BD 2. Salbutamol 200 µg QDS Delivery was MDI
Outcomes	PEF, rescue use, asthma attacks, efficacy rating No report in paper in relation to serious adverse events
Notes	

Risk of bias

Hekking 1990 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) Adverse Events	Low risk	Double-blind, double-dummy
Incomplete outcome data (attrition bias) Adverse Events	Unclear risk	15 of 150 formoterol patients and 30 of 151 salbutamol patients were withdrawn
Selective reporting (reporting bias)	High risk	No SAE reporting in the paper

Kesten 1991

Methods	A randomised, double-blind, double-dummy, parallel-group, multicentre, multinational study (Canada, UK), over 12 weeks at 7 centres. Run-in 4 weeks double-blind cross-over
Participants	**Population**: 145 adults (18 to 65) years with stable, symptomatic asthma **Baseline characteristics**: mean age not reported. Mean baseline FEV_1 for the formoterol group was 2.14 L and 1.98 L for the albuterol group. Concomitant inhaled corticosteroids used by 62% of participants **Inclusion criteria**: diagnosis of asthma requiring daily treatment with an inhaled B_2-agonist. FEV_1 % predicted at least 40%, bronchodilator reversibility by an increase of at least 15% in FEV_1 30 minutes after inhalation of 200 µg of albuterol by metered-dose inhaler. Use of rescue albuterol greater during the placebo treatment period than during the albuterol treatment period by an average of 2 puffs per day or more. Co-interventions: none 32%, ICS 62 %, cromones 7%, theophylline 32% **Exclusion criteria**: use of OS, exacerbation asthma within 1 month, significant non-respiratory illnesses and women of childbearing potential
Interventions	1. Formoterol 10 µg BD 2. Albuterol 180 µg QDS Delivery was MDI
Outcomes	FEV_1, FVC, FEV 25% to 75%, PEF, rescue use, rate asthma attacks day and night, adverse events, exacerbations, efficacy rating No serious adverse event data reported in the paper. No web data found
Notes	Supported by Ciba-Geigy (now Novartis)

Risk of bias

Bias	Authors' judgement	Support for judgement

Kesten 1991 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Unclear risk	No information
Blinding (performance bias and detection bias) Adverse Events	Low risk	Double-blind, double-dummy, matching inhalers
Incomplete outcome data (attrition bias) Adverse Events	Low risk	133/145 (91%) completed the study
Selective reporting (reporting bias)	High risk	No published SAE data

Kozlik-Feldmann 1996

Methods	A randomised, parallel-group, single-centre study over 12 weeks in Germany
Participants	**Population**: 22 children with clinically stable asthma **Baseline characteristics**: mean age 10 years. Before treatment, all values for FEV_1 were found beyond 100% of that predicted. **Inclusion criteria**: mild asthma, requiring no preventive therapy. The patients needed no further therapy, i.e. with corticosteroids or theophyllines **Exclusion criteria**: requiring additional therapy for asthma
Interventions	1. Formoterol 24 µg BD 2. Salbutamol 200 µg QDS Delivery was not reported
Outcomes	FEV_1, FVC, histamine provocation, beta-receptor binding sites on mononuclear leucocytes, adverse events "No side effects due to $beta_2$-agonist therapy were seen".
Notes	No indication of sponsorship for this study

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Unclear risk	No information
Blinding (performance bias and detection bias) Adverse Events	High risk	Open

Kozlik-Feldmann 1996 (*Continued*)

Incomplete outcome data (attrition bias) Adverse Events	Low risk	All patients completed the study
Selective reporting (reporting bias)	High risk	No serious adverse event data documented

LaForce 2005

Methods	Randomised, double-blind, multicentre, parallel-group study over 12 weeks at 22 sites in the US. Run-in 2 weeks
Participants	**Population**: 265 adolescents and adults (13 to 81) years with persistent asthma **Baseline characteristics**: mean age 37 years. FEV_1 68% predicted. Concomitant inhaled corticosteroids used by 67% of participants. **Inclusion criteria**: persistent asthma. FEV_1 % predicted at least 40%, bronchodilator reversibility by an increase of at least 15% in FEV_1 over baseline within 30 minutes of inhaling albuterol (180 to 320 µg) (still eligible if the increase in FEV_1 was 12% or greater and at least 0.2 L over baseline) **Exclusion criteria**: pregnant/lactating women; smoking history > 10 pack-years; history of malignancy; RTI or hospitalisation with exacerbation in previous month; treatment with systemic steroids
Interventions	1. Formoterol 10 µg BID 2. Placebo 3. Salbutamol 180 µg QID Delivery was DPI (pMDI for salbutamol)
Outcomes	The primary efficacy variable was 12-hour AUC of FEV_1 after 12 weeks' treatment. "There were no deaths in the study. A total of three patients experienced serious adverse events and were withdrawn from the study." Formoterol 1 small cell lung cancer, albuterol 1 increase in heart rate and 1 coronary artery stenosis
Notes	Sponsored by Novartis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	1:1:1 using a computer-generated sequence
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) Adverse Events	Low risk	Double-blind, double-dummy
Incomplete outcome data (attrition bias) Adverse Events	Low risk	235/265 (89%) completed the study

Selective reporting (reporting bias)	Low risk	Deaths and serious adverse events reported in the paper

Levy 2005

Methods	Randomised, double-blind, placebo-controlled, multicentre, parallel-group study over 12 weeks in 22 US centres. Run-in 2 weeks single-blind placebo
Participants	**Population**: 249 children (5 to 13) years with mild to moderate persistent asthma **Baseline characteristics**: mean age 9 years. FEV_1 75% predicted. Concomitant inhaled corticosteroids used by 72% of participants. **Inclusion criteria**: mild to moderate persistent asthma. FEV_1 % predicted at least 50%, bronchodilator reversibility by an increase of at least 15% in FEV_1 over baseline within 30 min of inhaling albuterol 180 µg via MDI, regular use of an on-demand bronchodilator **Exclusion criteria**: history of respiratory tract infection, hospitalisation due to an asthma exacerbation in the month prior to visit 1, clinically significant medical condition, history of allergy to any inhaled medications, QTc interval > 0.46 seconds, or used parenteral or oral corticosteroids in the month prior to visit 1
Interventions	1. Formoterol 10 µg BD 2. Placebo BD Delivery was DPI
Outcomes	The primary efficacy variable was the 12-hour AUC of FEV_1 at 12 weeks "One formoterol-treated patient experienced a serious adverse event (asthma exacerbation), which led to hospitalisation and discontinuation from the study. The event was not suspected as study-drug related by the investigator." No web report found
Notes	Sponsored by Novartis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Unclear risk	No information
Blinding (performance bias and detection bias) Adverse Events	Low risk	Double-blind, matched placebo
Incomplete outcome data (attrition bias) Adverse Events	Low risk	227/249 (91%) completed the study

Levy 2005 (*Continued*)

Selective reporting (reporting bias)	Low risk	Serious adverse events reported in the paper

Molimard 2001

Methods	Randomised, outpatients, open, parallel-group study over 3 months from February 1998 to March 1999 in France. Run-in 2 to 3 weeks
Participants	**Population**: 259 adults (18+) years with moderate persistent asthma **Baseline characteristics**: mean age 39 years. FEV_1 73% predicted. Concomitant inhaled corticosteroids used by 100% of participants. **Inclusion criteria**: moderate persistent asthma, daily treatment with an inhaled corticosteroid (the same product at a stable dose for at least 1 month prior to the first visit) and daily treatment with inhaled bronchodilators (taken regularly or on demand). FEV_1 % predicted at least 60%, bronchodilator reversibility by an increase of at least 10% in FEV_1 over baseline to be documented at the first visit or 3 months prior. **Exclusion criteria**: known hypersensitivity to sympathic amines or to lactose, pregnancy or breast-feeding, women of childbearing potential who did not use a reliable contraceptive method, significant change in the regular asthma medication, asthma exacerbation or respiratory tract infection in the month prior to the first visit, incapacity to use a metered-dose inhaler correctly or to complete the patient diary
Interventions	1. Formoterol dry-powder capsule 12 µg BD 2. Salbutamol on-demand via MDI
Outcomes	The primary efficacy variable was the mean change in morning predose PEF for the entire treatment period "No drug-related serious AE was reported". No report in paper of mortality or all-cause SAE, but authors have provided additional information: "If we consider all-cause SAE, no SAE was reported in the on-demand salbutamol group and two SAEs were reported in the formoterol group (not suspected to be drug-related) : one case of hospitalisation due to a malignant tumour of breast and one case of hospitalisation due to an uterine haemorrhage. No death was reported in this study."
Notes	Supported by Novartis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Low risk	Centralised phone randomisation was used to avoid inclusion bias
Blinding (performance bias and detection bias) Adverse Events	High risk	Open

Molimard 2001 (*Continued*)

Incomplete outcome data (attrition bias) Adverse Events	Low risk	229/259 (88%) completed the study
Selective reporting (reporting bias)	Low risk	All-cause SAE information provided by authors

Noonan 2006

Methods	Randomised, double-blind, double-dummy, multicentre, 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 to 87) years with moderate to severe persistent asthma **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. Symbicort 320 µg/9 µg BD pMDI 2. Budesonide 320 µg BD pMDI 3. Formoterol 9 µg BD DPI 4. Placebo DPI and pMDI Only the formoterol and placebo arms are included in this review
Outcomes	The co-primary efficacy variables were baseline adjusted average 12-hour FEV_1 and predose FEV_1. No all-cause SAE data reported in the paper but website indicates 2 SAEs on formoterol and none on placebo. There were no deaths Web data found on AstraZeneca clinical trials website SD-039-0717
Notes	Sponsored by AstraZeneca

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated allocation schedule
Allocation concealment (selection bias)	Low risk	Identical packages shipped to centres

Noonan 2006 (*Continued*)

Blinding (performance bias and detection bias) Adverse Events	Low risk	Double-blind
Incomplete outcome data (attrition bias) Adverse Events	Low risk	60% withdrawals in placebo arm and 51.2% in formoterol arm
Selective reporting (reporting bias)	Low risk	Full SAE data on website

Novartis 2005

Methods	This represents results from placebo-controlled trials of at least 4 weeks duration from the Integrated Database of Novartis Clinical Trials
Participants	
Interventions	1. Formoterol 24 µg bd via Aerolizer or Certihaler 2. Formoterol 12 µg bd via Aerolizer or Certihaler 3. Placebo 4. Albuterol
Outcomes	Asthma-related SAE data
Notes	These data have been entered as a separate subgroup and not combined with other studies as 5 of the 22 studies are already included in this review, but no separate information has yet been received in relation to the other 17 studies

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No individual study data available
Allocation concealment (selection bias)	Unclear risk	No individual study data available
Blinding (performance bias and detection bias) Adverse Events	Unclear risk	No individual study data available
Incomplete outcome data (attrition bias) Adverse Events	Unclear risk	No individual study data available
Selective reporting (reporting bias)	Unclear risk	No individual study data available

Pleskow 2003

Methods	A randomised, double-blind, double-dummy, placebo-controlled, multicentre, parallel-group study over 12 weeks
Participants	**Population**: 554 adults and adolescents (12 to 75) years with mild to moderate persistent asthma **Baseline characteristics**: mean age 33 years. FEV_1 66% predicted. Concomitant inhaled corticosteroids used by 44% of participants **Inclusion criteria**: mild-to-moderate asthma, inhaled B_2-selective adrenoreceptor agonist on a daily basis for 2 or more months, FEV_1 % predicted between 40% to 80%, bronchodilator reversibility by an increase of at least 15% in FEV_1 within 30 min after inhalation of albuterol 180 µg, chest x-ray with normal findings or findings consistent with asthma **Exclusion criteria**: pregnant women/women child-bearing potential who did not have reliable form of contraception; significant coronary heart disease; prior MI; uncontrolled hypertension; diabetes; convulsive disorder; intolerance of beta-agonists; URTI within 1 month of study entry; hospitalisation for acute asthma within 1 month of study entry or during run-in; non-compliance to medical regimes; parenteral/oral steroids in month prior to visit 1; newly instituted/modified ICS therapy (including discontinuation); disodium cromoglycate; oral/inhaled anticholinergics; desensitisation therapy; recent use of astemizole; use of theophylline in month prior to visit 1; use of antiarrhythmics; use of Prozac; vaccination with live virus in month prior to visit 1; weight 35% above or 25% predicted; significant smoking history; malignancy
Interventions	1. Formoterol 12/24 µg BD 2. Albuterol 180 µg QDS 3. Placebo QDS Formoterol delivered by Aerolizer (dry powder) and albuterol by MDI
Outcomes	Primary outcome: FEV_1. Safety was evaluated by adverse event reports. 13 serious adverse events are reported in the paper but not attributed to treatment groups. 2 deaths are fully described as below No Novartis web report found for this study. FDA submission for study 041 (http://www.fda.gov/cder/foi/nda/2001/20831_Foradil_medr_P1.pdf). This lists all (asthma-related in brackets) SAE as: 1 (1) on formoterol 12 µg, 7 (5) on formoterol 24 µg, 2 (0) on albuterol and 3 (2) on placebo FDA documents also show 1 death from asthma with formoterol 24 µg and 1 death from pancreatitis with albuterol (which are included in the above SAE totals)
Notes	Sponsored by Novartis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated sequence
Allocation concealment (selection bias)	Unclear risk	No information available

Pleskow 2003 (*Continued*)

Blinding (performance bias and detection bias) Adverse Events	Low risk	Double-blind, double-dummy
Incomplete outcome data (attrition bias) Adverse Events	Low risk	484/554 (87%) completed the study
Selective reporting (reporting bias)	Low risk	Full SAE data from FDA submission

SD-037-0344

Methods	Randomised, double-blind, double-dummy, parallel-group, placebo-controlled, multi-centre, 12-week study with a 2-week run-in period. This study was performed in 48 centres across 7 countries (Argentina, Brazil, Greece, Mexico, Philippines, Poland, South Africa)
Participants	**Population**: 639 adolescents and adults (12 to 80) years with asthma **Baseline characteristics**: mean age 35 years. FEV_1 not reported. Concomitant inhaled corticosteroids used by 100% of participants. **Inclusion criteria**: treated with 200 to 1000 µg/day of inhaled steroids for the previous 3 months and on a stable dose for 30 days prior to the start of the run-in period. For inclusion to the treatment period, total asthma symptom score (night-time plus day-time) of greater than 1 on at least 4 of the last 7 days of the run-in period
Interventions	1. Formoterol (HFA) 9 µg BD (pMDI) 2. Formoterol 9 µg BD (Turbuhaler) 2. Placebo BD
Outcomes	Primary variable was the change from baseline (mean over last 10 days of run-in period) to treatment (mean for the 12-week treatment period) in morning PEF before inhalation of study treatment "One subject, a 66-year-old male, died during this study, after 55 days of treatment with formoterol HFA pMDI 9 mg; the investigator considered that there was no relationship between study medication and death. Six subjects experienced a serious adverse event (SAE) during treatment." No paper publication. "The HFA product will not be available on the market."
Notes	Sponsored by AstraZeneca

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Unclear risk	No information

SD-037-0344 (*Continued*)

Blinding (performance bias and detection bias) Adverse Events	Low risk	Double-blind, double-dummy
Incomplete outcome data (attrition bias) Adverse Events	Low risk	630/639 (97%) completed the study
Selective reporting (reporting bias)	Low risk	Full SAE data reported

Steffensen 1995

Methods	A randomised, double-blind, double-dummy, placebo-controlled, multicentre, parallel-group study over 12 weeks at 20 centres in Scandinavia. Run-in 2 weeks
Participants	**Population**: 304 adolescents and adults (18 to 79) years with clinically stable asthma **Baseline characteristics**: mean age 48 years. Concomitant inhaled corticosteroids used by 87% of participants. FEV_1 66% predicted. **Inclusion criteria**: clinically stable and use of inhaled, short-acting B_2-agonist at least 1 month before the start of the trial, clinical history of reversible obstructive airway disease, FEV_1 % predicted at least 40%, bronchodilator reversibility of 15% in FEV_1 over baseline 15 to 30 min after inhalation of salbutamol 400 µg **Exclusion criteria**: unstable asthma, altered dose medication
Interventions	1. Formoterol 12 µg BD 2. Salbutamol 400 µg QDS 3. Placebo QDS Delivery was dry powder device
Outcomes	FEV_1, FVC, PEF, rescue use, asthma symptom score. Adverse events, including asthma exacerbations, efficacy rating
Notes	Funding from Ciba Geigy (later Novartis)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Unclear risk	No information
Blinding (performance bias and detection bias) Adverse Events	Low risk	Double-blind, double-dummy, matching devices
Incomplete outcome data (attrition bias) Adverse Events	Low risk	260/304 (85%) completed the study

Steffensen 1995 (*Continued*)

Selective reporting (reporting bias)	Low risk	All-cause SAE described in paper by treatment group

van der Molen 1997

Methods	Randomised, double-blind, multicentre, placebo-controlled, parallel-group study over 24 weeks in 16 centres in Canada and The Netherlands. Patients were recruited from 10 outpatient hospital clinics in Canada and 5 out-patient clinics and 1 co-ordinating centre for 44 Dutch general practitioners in The Netherlands. Run-in 4 weeks
Participants	**Population**: 239 adults with mild to moderate asthma **Baseline characteristics**: mean age 43 years. FEV_1 67% predicted. Concomitant inhaled corticosteroids used by 100% of participants. **Inclusion criteria**: mild to moderate asthma, regular use of any dose of inhaled corticosteroids, at least 5 inhalations of a short acting B_2-agonist per week before the entry visit, bronchodilator reversibility by an increase of at least 15% in FEV_1 over baseline after 2 inhalations of 250 µg terbutaline or the equivalent dose of salbutamol **Exclusion criteria**: oral corticosteroids at any time in the last month, smoking history of greater than 20 pack-years, FEV_1 less than 40% predicted, or an exacerbation of asthma symptoms during the previous month
Interventions	1. Formoterol 24 µg BD 2. Placebo BD Delivery was DPI
Outcomes	The primary variable in the study was the total daily score of asthma symptoms. No reporting in the paper of serious adverse events No website found. Manufacturers asked for all-cause serious adverse event data. These data gave no indication of any deaths. 4 patients with SAE on formoterol and 5 on placebo. 1 and 3 had asthma-related SAE
Notes	Supported by Astra Draco SD-037-3008

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Low risk	Blocks of 4 to 1 of the 2 treatment groups of equal size
Blinding (performance bias and detection bias) Adverse Events	Low risk	Double-blind

van der Molen 1997 (*Continued*)

Incomplete outcome data (attrition bias) Adverse Events	Low risk	208/239 (87%) completed the study
Selective reporting (reporting bias)	Low risk	SAE data provided by sponsors

van Schayck 2002

Methods	Randomised study over 12 weeks at a lung function laboratory in The Netherlands. Run-in 8 weeks
Participants	**Population**: 162 adolescents and adults (16 to 60) years **Baseline characteristics**: mean age 35 years, FEV_1 86% predicted. Concomitant inhaled corticosteroids used by 95% of participants **Inclusion criteria**: history of bronchial symptoms or a clinical diagnosis of asthma, FEV_1 % predicted at least 50%, and either PC_{20} on histamine < 8 mg/mL^{-1} or bronchodilator reversibility by an increase of at least 15% in FEV_1 over baseline after inhalation of 800 µg salbutamol **Exclusion criteria**: not reported At the start of the 8-week washout period, patients to cease all their pulmonary medication (inhaled corticosteroids, cromoglycates, bronchodilators) and to use only rescue medication on demand
Interventions	1. Salbutamol 100 µg BD 2. Formoterol 12 µg BD 3. Placebo Delivery was MDI
Outcomes	The effects of bronchodilator use on the perception of airway obstruction There is no indication that data on adverse events were collected. Author has confirmed that no serious adverse events were reported in this study
Notes	No support declared

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Unclear risk	No information
Blinding (performance bias and detection bias) Adverse Events	High risk	Open?
Incomplete outcome data (attrition bias) Adverse Events	Low risk	128/162 (79%) completed the study

Selective reporting (reporting bias)	Low risk	No information on SAEs in paper but data provided by author

Von Berg 2003

Methods	A randomised, double-blind, placebo-controlled study over 12 weeks at 32 centres in 5 countries in Europe. Run-in 2 weeks
Participants	**Population**: 248 children (6 to 17) years with mild to moderate asthma **Baseline characteristics**: mean age 11 years. FEV_1 81% predicted. Concomitant inhaled corticosteroids used by 82% of participants. **Inclusion criteria**: 6 to 17 years, diagnosis of asthma, ATS guidelines, at least 6 months previously, FEV_1 % predicted at least 40%, receiving anti-inflammatory agents (ICS, OCS, nedocromil, cromones) at stable dose for 30 days, able to use Turbuhaler, and peak flow meter, bronchodilator reversibility by either an increase of at least 15% in FEV_1 over baseline or an increase of at least 9% in FEV_1 predicted or an increase of at least 15% am PEF 4/8 days run-in **Exclusion criteria**: use of astemizole within 60 days before inclusion, regular nasal corticosteroids or antihistamines within 30 days, immunotherapy less than 90 days, significant seasonal asthma or allergy, significant medical condition
Interventions	1. Formoterol 9 µg BD 2. Formoterol 4.5 µg BD 3. Placebo Delivery was Turbuhaler
Outcomes	The primary efficacy variable was morning PEF, recorded in patients' diaries "Nine serious AEs (SAEs) were reported in eight patients in the formoterol groups (n=3 formoterol 4.5 mcg and n=5 in formoterol 9 mcg) and one SAE in the placebo group; none of the SAEs was considered causally related to the study drug. One death was reported in the formoterol 9 mcg group, from a subarachnoid haemorrhage, which was judged unlikely to be due to the study drug." Further information has been provided by the author to clarify that 2 patients in the formoterol 9 µg arm suffered 2 serious adverse events (asthma and haematuria in 1 patient, and abdominal pain and appendicitis in 1 patient), so 3 patients in each formoterol arm and 1 in the placebo arm had any SAE. The author also confirmed that the participant who died was not included in the 9 SAE events, but was one of the 8 patients who suffered a SAE
Notes	No sponsorship reported in the paper but the author confirms that the study was sponsored by Astra

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Consecutive patient number, 1:1:1 ratio using computer-generated schedule

Von Berg 2003 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	No information
Blinding (performance bias and detection bias) Adverse Events	Low risk	Double-blind, identical devices
Incomplete outcome data (attrition bias) Adverse Events	Low risk	225/248 (91%) completed the study
Selective reporting (reporting bias)	Low risk	SAE report in the paper

Wolfe 2006

Methods	Randomised, double-blind, multicentre, placebo-controlled, parallel-group study over 16 weeks in 194 outpatient clinics in the US. Run-in 2 weeks single-blind placebo
Participants	**Population**: 2085 adolescents and adults (12 to 82) years with stable, persistent asthma **Baseline characteristics**: mean age 38 years. FEV_1 69% predicted. Concomitant inhaled corticosteroids used by 62% of participants. **Inclusion criteria**: persistent asthma, use of inhaled beta-agonist for 2 months prior to study entry, FEV_1 at least 40% of predicted normal following washout from inhaled bronchodilator treatment, FEV_1 reversibility at least 12% after inhalation of up to 4 puffs of albuterol (360 µg) at screening or documented within the past year **Exclusion criteria**: hospitalisation within 1 month/treatment of exacerbation of asthma in month prior to study entry; evidence/array of other systemic diseases; pregnancy/ failure to use reliable contraception; change to ongoing medication used to treat chronic asthma
Interventions	1. Formoterol 12 µg BID 2. Placebo 3. Formoterol 24 µg BID 4. Open-label formoterol 12 µg BID (with up to 2 uses prn per day). This arm was not included in the review Delivery was DPI (Aerolizer)
Outcomes	Serious asthma exacerbations (life-threatening or requiring hospitalisation) were the primary end point "There were no deaths in the study." SAE data not reported for all causes in the paper but available from FDA documentation Web data available from documents on FDA website but not yet on Novartis Clinical Trials (16 June 2008)
Notes	Sponsored by Novartis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Wolfe 2006 (*Continued*)

Random sequence generation (selection bias)	Low risk	1:1:1 ratio using computer-generated list of random numbers
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) Adverse Events	Low risk	Double-blind
Incomplete outcome data (attrition bias) Adverse Events	Low risk	1791/2085 (86%) completed the study
Selective reporting (reporting bias)	Low risk	Paper report is not transparent on serious adverse events from any cause in each arm of the trial, but these data are available from FDA documentation

Zimmerman 2004

Methods	Randomised, double-blind, placebo-controlled, multicentre, parallel-group study over 12 weeks at 27 centres in Canada. Run-in 2 weeks
Participants	**Population**: 302 children (6 to 11) years with asthma not optimally treated with inhaled corticosteroids alone **Baseline characteristics**: mean age 9 years. FEV_1 78% predicted. Concomitant inhaled corticosteroids used by 100% of participants. **Inclusion criteria**: aged 6 to 11 years with a clinical diagnosis of asthma according to American Thoracic Society criteria for at least 6 months, FEV_1 % predicted of 50% to 90%, bronchodilator reversibility of at least 15%, or at least 9% of predicted normal, treatment with regular inhaled corticosteroids for at least 3 months before trial entry, asthma symptoms sufficient to suggest that additional therapy might be needed **Exclusion criteria**: known or suspected hypersensitivity to formoterol or inhaled lactose, deteriorating asthma or a respiratory infection, clinically significant concurrent disease, significant seasonal allergy, or if smokers, taken disallowed asthma medications before trial entry, oral corticosteroids or antileukotrienes within 30 days, astemizole within 60 days, sodium cromoglycate or ketotifen within 7 days, salmeterol or formoterol within 72 hours, xanthines or antihistamines within 48 hours
Interventions	1. Formoterol 4.5 µg or 9 µg BD 2. Placebo BD Delivery was DPI
Outcomes	The primary efficacy variable was change from baseline in morning peak expiratory flow (PEF) No information in the paper on SAEs. Manufacturers asked for all-cause serious adverse event data: no deaths were reported. Placebo - 1 patient with SAE due to asthma. Formoterol 4.5 - 1 patient with SAE due to dog bite. Formoterol 9 - 2 patients with SAE due to URTI and asthma

Zimmerman 2004 (*Continued*)

	AZ study code DC-037-0002	
Notes	No support declared in the paper, but data on file with AstraZeneca	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Unclear risk	No information
Blinding (performance bias and detection bias) Adverse Events	Low risk	Double-blind
Incomplete outcome data (attrition bias) Adverse Events	Unclear risk	267/302 (88%) completed the study
Selective reporting (reporting bias)	Low risk	SAE data provided by sponsors

AE: adverse event; ATS: American Thoracic Society; AUC: area under curve; BD: twice a day; BDP: budesonide dipropionate; CS: corticosteroids; DPI: dry powder inhaler; ECG: electrocardiogram; FDA: Food and Drug Administration (USA); FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; ICS: inhaled corticosteroids; ITT: intention-to-treat; MAOI: monoamine oxidase inhibitors; MDI: metered-dose inhaler; MI: myocardial infarction; NSAIDs: nonsteroidal anti-inflammatory drugs; OS: oral steroids; PEF: peak expiratory flow; pMDI: pressurised metered-dose inhaler; QDS: four times a day; RT: respiratory tract; SABA: short-acting $beta_2$-agonist; SAE: serious adverse event; URTI: upper respiratory tract infection

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

Study	Reason for exclusion
Adler 2006	2-week study
Akpinarli 1999	6-week treatment periods
Ankerst 2003	Short-term high-dose tolerance study
Arvidsson 1989	2-week study
Aziz 1998	Volunteers (not asthmatics)
Bauer 1995	Single dose

(*Continued*)

Behling 1999	3-week study
Boner 1994	Single dose
Bousquet 2005	Single dose
Bousquet 2005a	Single dose
Brambilla 2003	4-week study
Bronsky 2002	Single dose
Bronsky 2004	Single dose
Brusasco 2002	Single dose
Burgess 1998	Single dose
Cazzola 2002	Single dose
Ceylan 2004	Formoterol versus montelukast
Chetta 1993	Single dose
Cheung 2006	3-week study
Chuchalin 2002	Formoterol randomised with budesonide
Chuchalin 2005	1-week study
Chuchalin 2005a	Formoterol randomised with budesonide
Chung 1995	Cross-over design
Dahl 2004	Device comparison
Daugbjerg 1996	Single dose
Dey 2005	Cross-over design
Dietrich 2006	Device comparison
Dubakiene 2006	Device comparison
Dusser 2005	HFA versus DPI delivery comparison
Ericsson 2006	Randomised with budesonide

(*Continued*)

Eryonucu 2005	Single dose
Ferrari 2000	Single dose
Fitoussi 2002	3-day study
Gessner 2003	8-week study
Graff-Lonnevig 1990	Cross-over design
Green 2006	Cross-over design
Happonen 2009	Cross-over study comparing formoterol Easyhaler with Foradil Aerolizer
Hedenstrom 1992	Cross-over design
Hermansen 2006	EIB single doses
Houghton 2004	Single dose
Ind 2002	Formoterol used as reliever
Jain 2004	Formoterol used as reliever
Jenkins 2005	6-week treatment periods
Kamenov 2007	Formoterol - HFA metered-dose inhaler compared to formoterol dry powder inhaler
Kesten 1992	Not RCT
Kohler 2003	Acute asthma
Kruse 2005	Cross-over design
Lebecque 1994	Single dose
Lebecque 1994a	Single dose
Lee-Wong 2008	Acute asthma
Lemaigre 2006	Single dose
Lotvall 1997	Single dose
Lotvall 2005	Formoterol as reliever
Lotvall 2008	Single dose

(*Continued*)

Lyseng-Williamson 2003	Not RCT
Maesen 1992	Short-term study over 3 days
Maesen 1992a	Delivery device and dose
Malo 1990	Single dose
Malolepszy 2001	Formoterol versus theophylline
Malolepszy 2002	Acute asthma
Mann 2003	Overview of 3 included studies: Bensch 2001; Bensch 2002; Pleskow 2003
Marzo 2000	Healthy volunteers
Matthys 2004	3-week study
Midgren 1992	4-week study
Molimard 2005	Cumulative dose study
Najafizadeh 2007	Acute asthma
Nandeuil 2006	8-day study
Newnham 1994	4-week study
Newnham 1995	4-week study
Novartis 2005b	Both arms received formoterol maintenance
Otto-Knapp 2008	4-week study
Patessio 1991	EIB
Pauwels 2003	Formoterol as reliever
Pearlman 2002	Overview of other studies
Pohunek 2004	Single dose
Price 2002	Randomised together with budesonide
Price 2008	Overview of safety data from AstraZeneca-sponsored trials of duration of at least 4 weeks
Randell 2005	Device comparison

(*Continued*)

Richter 2007	Dosage comparison
Rico-Mendez 1999	Study included patients with chronic bronchitis
Ringdal 1998	Single dose
Rosenborg 2000	Single dose
Rosenborg 2002	Short-term dose-response study
Rosenborg 2002a	Short-term dose-response study
Rubinfeld 2006	Acute asthma
Schlimmer 2002	Acute asthma
Sprogoe 1992	6-week study
Stahl 2003	Formoterol as reliever
Stelmach 2008	Study on exercise-induced bronchospasm
Tattersfield 1999	Description of exacerbations in FACET study
Tattersfield 2001	As-needed formoterol
Totterman 1998	3-day study
van den Berg 1995	8-day study
van der Woude 2004	Single dose
van Veen 2003	2-week cross-over
Verini 1998	5-day study
Villa 2002	As-needed formoterol
Villa 2002a	As-needed formoterol
Vilsvik 2001	EIB
Wallin 1999	8-week study
Wegener 1992	Single dose
Wong 1992	Single dose

(*Continued*)

Yasuo 1984	4-week study
Yasuo 1984a	Single dose
Yasuo 1984b	Single dose
Yates 1995	2-week cross-over
Yurdakul 2002	No placebo or SABA control

DPI: dry powder inhaler; EIB: exercise induced bronchoconstriction; HFA: hydrofluoroalkane; RCT: randomised controlled trial; SABA: short-acting beta$_2$-agonist

DATA AND ANALYSES

Comparison 1. All-cause mortality

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall results	14		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 Formoterol versus placebo	14	5463	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.50 [0.41, 49.49]
1.2 Formoterol versus salbutamol	6	1418	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.47 [0.02, 8.98]

Comparison 2. Adults and children non-fatal serious adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Formoterol versus placebo or salbutamol	19		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 Formoterol versus placebo	19	6646	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.57 [1.06, 2.31]
1.2 Formoterol versus salbutamol	9	2119	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.73 [0.37, 1.43]

Comparison 3. Adults and children non-fatal serious adverse events (without formoterol 24 µg arms)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Formoterol versus placebo or salbutamol	18		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 Formoterol versus placebo	18	5438	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.55 [0.97, 2.48]
1.2 Formoterol versus salbutamol	9	1848	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.41 [0.19, 0.90]

Comparison 4. Adults with non-fatal serious adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Formoterol versus placebo or salbutamol	15		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 Formoterol versus placebo	15	5311	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.23 [0.76, 1.99]
1.2 Formoterol versus salbutamol	9	2119	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.73 [0.37, 1.43]

Comparison 5. Children with non-fatal serious adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Formoterol versus placebo or salbutamol	5		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 Formoterol versus placebo	5	1335	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.48 [1.27, 4.83]
1.2 Formoterol versus salbutamol	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 6. Children with non-fatal serious adverse events (without formoterol 24 µg arms)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Formoterol versus placebo or salbutamol	5		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 Formoterol versus placebo	5	1164	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.52 [1.15, 5.51]
1.2 Formoterol versus salbutamol	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 7. Dose comparison: formoterol 24 µg versus 12 µg twice daily

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Serious adverse events	5		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 Adults (all-cause)	3	1598	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.35 [0.64, 2.85]
1.2 Children (all-cause)	1	342	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.20 [0.52, 2.74]
1.3 Asthma SAE	1	3104	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.16 [1.13, 4.11]

Comparison 8. Adults and children fatal and non-fatal serious adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Formoterol versus placebo or salbutamol	19		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 Formoterol versus placebo	19	6646	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.61 [1.09, 2.37]
1.2 Formoterol versus salbutamol	9	2119	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.71 [0.37, 1.38]

Comparison 9. Asthma mortality

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Formoterol versus placebo or salbutamol	12		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 Formoterol versus placebo	12	4522	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.54 [0.07, 285.25]
1.2 Formoterol versus salbutamol	6	1418	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.49 [0.07, 286.29]

Comparison 10. Cardiovascular mortality

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Formoterol versus placebo or salbutamol	12		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 Formoterol versus placebo	12	4522	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.54 [0.07, 285.29]
1.2 Formoterol versus salbutamol	6	1418	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 11. Adults and children non-fatal asthma-related serious adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Formoterol versus placebo or salbutamol	17		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 Formoterol versus placebo	17	5759	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.99 [1.12, 3.53]
1.2 Formoterol versus salbutamol	9	2119	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.74 [0.29, 1.88]

Comparison 12. Adults and children non-fatal asthma-related serious adverse events (Novartis data)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Formoterol versus placebo or salbutamol	11		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 Formoterol versus placebo (Novartis published data)	10	4138	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.06 [1.57, 5.96]
1.2 Formoterol versus placebo (Novartis integrated database)	1	5631	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.81 [1.54, 5.14]

Comparison 13. Hospitalisations for asthma

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Formoterol versus placebo or salbutamol	7		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 Formoterol versus placebo	7	3433	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.28 [1.65, 6.52]
1.2 Formoterol versus salbutamol	2	593	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.75 [0.41, 7.49]

Comparison 14. Adults and children non-fatal cardiovascular serious adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Formoterol versus placebo or salbutamol	8		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 Formoterol versus placebo	8	3049	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.69 [0.09, 5.21]
1.2 Formoterol versus salbutamol	5	803	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.14 [0.01, 1.33]

Comparison 15. Impact of inhaled corticosteroids on asthma-related SAEs

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Patients with at least one asthma-related SAE	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 Patients taking inhaled corticosteroids (all doses of formoterol))	1	3807	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.58 [1.21, 5.49]
1.2 Patients not taking inhaled corticosteroids (all doses of formoterol)	1	1824	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.22 [1.17, 8.89]
1.3 Patients taking inhaled corticosteroids (formoterol 12 mcg twice daily)	1	2708	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.76 [1.06, 7.15]
1.4 Patients not taking inhaled corticosteroids (formoterol 12 mcg twice daily)	1	1103	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.71 [0.75, 18.48]

Comparison 16. Adults and children published non-fatal serious adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Formoterol versus placebo or salbutamol	7		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 Formoterol versus placebo	7	1792	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.31 [1.17, 4.53]
1.2 Formoterol versus salbutamol	3	536	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.60 [0.15, 2.44]

Comparison 17. Adults and children all adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Formoterol versus placebo or salbutamol	11		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 Formoterol versus placebo	11	4884	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.11 [0.98, 1.25]
1.2 Formoterol versus salbutamol	4	1151	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.98 [0.76, 1.26]

Comparison 18. Adults and children published adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Formoterol versus placebo or salbutamol	8		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Formoterol versus placebo	8	3743	Odds Ratio (M-H, Fixed, 95% CI)	1.09 [0.94, 1.26]
1.2 Formoterol versus salbutamol	4	1151	Odds Ratio (M-H, Fixed, 95% CI)	0.98 [0.76, 1.26]

Comparison 19. Adults and children all published drug-related adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Formoterol versus placebo or salbutamol	4		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 Formoterol versus placebo	4	2112	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.42 [1.07, 1.88]
1.2 Formoterol versus salbutamol	3	542	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.75 [0.48, 1.18]

Comparison 20. Adults and children serious drug-related adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Formoterol versus placebo or salbutamol	9		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 Formoterol versus placebo	9	3618	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.45 [0.18, 11.61]
1.2 Formoterol versus salbutamol	3	746	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.71 [0.04, 12.34]

Analysis 1.1. Comparison 1 All-cause mortality, Outcome 1 Overall results.

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

Comparison: 1 All-cause mortality

Outcome: 1 Overall results

Study or subgroup	Formoterol n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
1 Formoterol versus placebo				
Bensch 2001	0/271	0/136		0.0 [0.0, 0.0]
Bensch 2002	0/342	0/176		0.0 [0.0, 0.0]
Busse 2004	0/80	0/80		0.0 [0.0, 0.0]
Corren 2007	0/123	0/131		0.0 [0.0, 0.0]
FitzGerald 1999	0/89	0/91		0.0 [0.0, 0.0]
LaForce 2005	0/86	0/91		0.0 [0.0, 0.0]
Molimard 2001	0/130	0/129		0.0 [0.0, 0.0]
Noonan 2006	0/123	0/125		0.0 [0.0, 0.0]
Pleskow 2003	1/275	0/141		4.54 [0.07, 285.25]
SD-037-0344	1/429	0/210		4.43 [0.07, 287.77]
van Schayck 2002	0/46	0/41		0.0 [0.0, 0.0]
Von Berg 2003	1/164	0/84		4.54 [0.07, 285.29]
Wolfe 2006	0/1054	0/514		0.0 [0.0, 0.0]
Zimmerman 2004	0/201	0/101		0.0 [0.0, 0.0]
Subtotal (95% CI)	**3413**	**2050**		**4.50 [0.41, 49.49]**
Total events: 3 (Formoterol), 0 (Control)				
Heterogeneity: Chi^2 = 0.00, df = 2 (P = 1.00); I^2 =0.0%				
Test for overall effect: Z = 1.23 (P = 0.22)				
2 Formoterol versus salbutamol				
Bensch 2001	0/271	0/134		0.0 [0.0, 0.0]
Busse 2004	0/80	0/79		0.0 [0.0, 0.0]
FitzGerald 1999	0/89	0/91		0.0 [0.0, 0.0]
LaForce 2005	0/86	0/88		0.0 [0.0, 0.0]
Pleskow 2003	1/275	1/138		0.47 [0.02, 8.98]
van Schayck 2002	0/46	0/41		0.0 [0.0, 0.0]
Subtotal (95% CI)	**847**	**571**		**0.47 [0.02, 8.98]**

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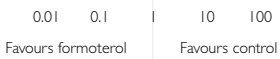
Study or subgroup	Formoterol n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Total events: 1 (Formoterol), 1 (Control)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%				
Test for overall effect: Z = 0.50 (P = 0.62)				



Analysis 2.1. Comparison 2 Adults and children non-fatal serious adverse events, Outcome 1 Formoterol versus placebo or salbutamol.

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

Comparison: 2 Adults and children non-fatal serious adverse events

Outcome: 1 Formoterol versus placebo or salbutamol

Study or subgroup	Formoterol n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
1 Formoterol versus placebo				
Bensch 2001	6/271	1/136		2.39 [0.49, 11.65]
Bensch 2002	24/342	3/176		2.92 [1.29, 6.62]
Busse 2004	2/80	0/80		7.48 [0.46, 120.69]
Corren 2007	0/123	2/131		0.14 [0.01, 2.30]
Ekstrom 1998	1/135	2/129		0.49 [0.05, 4.73]
Ekstrom 1998a	0/114	2/113		0.13 [0.01, 2.14]
FitzGerald 1999	1/89	3/91		0.37 [0.05, 2.67]
LaForce 2005	1/86	0/91		7.83 [0.16, 395.30]
Levy 2005	1/127	0/122		7.10 [0.14, 358.29]
Molimard 2001	2/130	0/129		7.39 [0.46, 118.78]
Noonan 2006	2/123	0/125		7.57 [0.47, 121.75]
Pleskow 2003	7/275	3/141		1.19 [0.32, 4.49]
SD-037-0344	5/429	1/210		2.10 [0.38, 11.59]

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Study or subgroup	Formoterol n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Steffensen 1995	0/103	2/101		0.13 [0.01, 2.11]
van der Molen 1997	4/125	5/114		0.72 [0.19, 2.73]
van Schayck 2002	0/46	0/41		0.0 [0.0, 0.0]
Von Berg 2003	6/164	1/84		2.45 [0.50, 11.95]
Wolfe 2006	16/1054	5/514		1.51 [0.60, 3.78]
Zimmerman 2004	3/201	1/101		1.47 [0.18, 11.83]
Subtotal (95% CI)	**4017**	**2629**		**1.57 [1.06, 2.31]**
Total events: 81 (Formoterol), 31 (Control)				
Heterogeneity: Chi² = 21.28, df = 17 (P = 0.21); I² =20%				
Test for overall effect: Z = 2.25 (P = 0.025)				
2 Formoterol versus salbutamol				
Bensch 2001	6/271	2/134		1.45 [0.33, 6.41]
Busse 2004	2/80	3/79		0.65 [0.11, 3.87]
Ekstrom 1998	1/135	3/133		0.36 [0.05, 2.57]
Ekstrom 1998a	0/114	4/116		0.13 [0.02, 0.96]
FitzGerald 1999	1/89	3/91		0.37 [0.05, 2.67]
LaForce 2005	1/86	2/88		0.52 [0.05, 5.08]
Pleskow 2003	7/275	1/138		2.60 [0.59, 11.45]
Steffensen 1995	0/103	0/100		0.0 [0.0, 0.0]
van Schayck 2002	0/46	0/41		0.0 [0.0, 0.0]
Subtotal (95% CI)	**1199**	**920**		**0.73 [0.37, 1.43]**
Total events: 18 (Formoterol), 18 (Control)				
Heterogeneity: Chi² = 7.53, df = 6 (P = 0.27); I² =20%				
Test for overall effect: Z = 0.92 (P = 0.36)				

Analysis 3.1. Comparison 3 Adults and children non-fatal serious adverse events (without formoterol 24 µg arms), Outcome 1 Formoterol versus placebo or salbutamol.

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

Comparison: 3 Adults and children non-fatal serious adverse events (without formoterol 24 g arms)

Outcome: 1 Formoterol versus placebo or salbutamol

Study or subgroup	Formoterol n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
1 Formoterol versus placebo				
Bensch 2001	1/136	1/136		1.00 [0.06, 16.07]
Bensch 2002	11/171	3/176		3.38 [1.16, 9.83]
Busse 2004	2/80	0/80		7.48 [0.46, 120.69]
Corren 2007	0/123	2/131		0.14 [0.01, 2.30]
Ekstrom 1998	1/135	2/129		0.49 [0.05, 4.73]
Ekstrom 1998a	0/114	2/113		0.13 [0.01, 2.14]
FitzGerald 1999	1/89	3/91		0.37 [0.05, 2.67]
LaForce 2005	1/86	0/91		7.83 [0.16, 395.30]
Levy 2005	1/127	0/122		7.10 [0.14, 358.29]
Molimard 2001	2/130	0/129		7.39 [0.46, 118.78]
Noonan 2006	2/123	0/125		7.57 [0.47, 121.75]
Pleskow 2003	1/139	3/141		0.37 [0.05, 2.65]
SD-037-0344	5/429	1/210		2.10 [0.38, 11.59]
Steffensen 1995	0/103	2/101		0.13 [0.01, 2.11]
van Schayck 2002	0/46	0/41		0.0 [0.0, 0.0]
Von Berg 2003	6/164	1/84		2.45 [0.50, 11.95]
Wolfe 2006	10/527	5/514		1.92 [0.69, 5.31]
Zimmerman 2004	3/201	1/101		1.47 [0.18, 11.83]
Subtotal (95% CI)	**2923**	**2515**		**1.55 [0.97, 2.48]**
Total events: 47 (Formoterol), 26 (Control)				
Heterogeneity: Chi² = 21.60, df = 16 (P = 0.16); I² =26%				
Test for overall effect: Z = 1.84 (P = 0.065)				
2 Formoterol versus salbutamol				
Bensch 2001	1/136	2/134		0.50 [0.05, 4.88]
Busse 2004	2/80	3/79		0.65 [0.11, 3.87]

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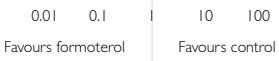
Study or subgroup	Formoterol n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Ekstrom 1998	1/135	3/133		0.36 [0.05, 2.57]
Ekstrom 1998a	0/114	4/116		0.13 [0.02, 0.96]
FitzGerald 1999	1/89	3/91		0.37 [0.05, 2.67]
LaForce 2005	1/86	2/88		0.52 [0.05, 5.08]
Pleskow 2003	1/139	1/138		0.99 [0.06, 15.95]
Steffensen 1995	0/103	0/100		0.0 [0.0, 0.0]
van Schayck 2002	0/46	0/41		0.0 [0.0, 0.0]
Subtotal (95% CI)	**928**	**920**		**0.41 [0.19, 0.90]**
Total events: 7 (Formoterol), 18 (Control)				
Heterogeneity: Chi^2 = 1.99, df = 6 (P = 0.92); I^2 =0.0%				
Test for overall effect: Z = 2.21 (P = 0.027)				

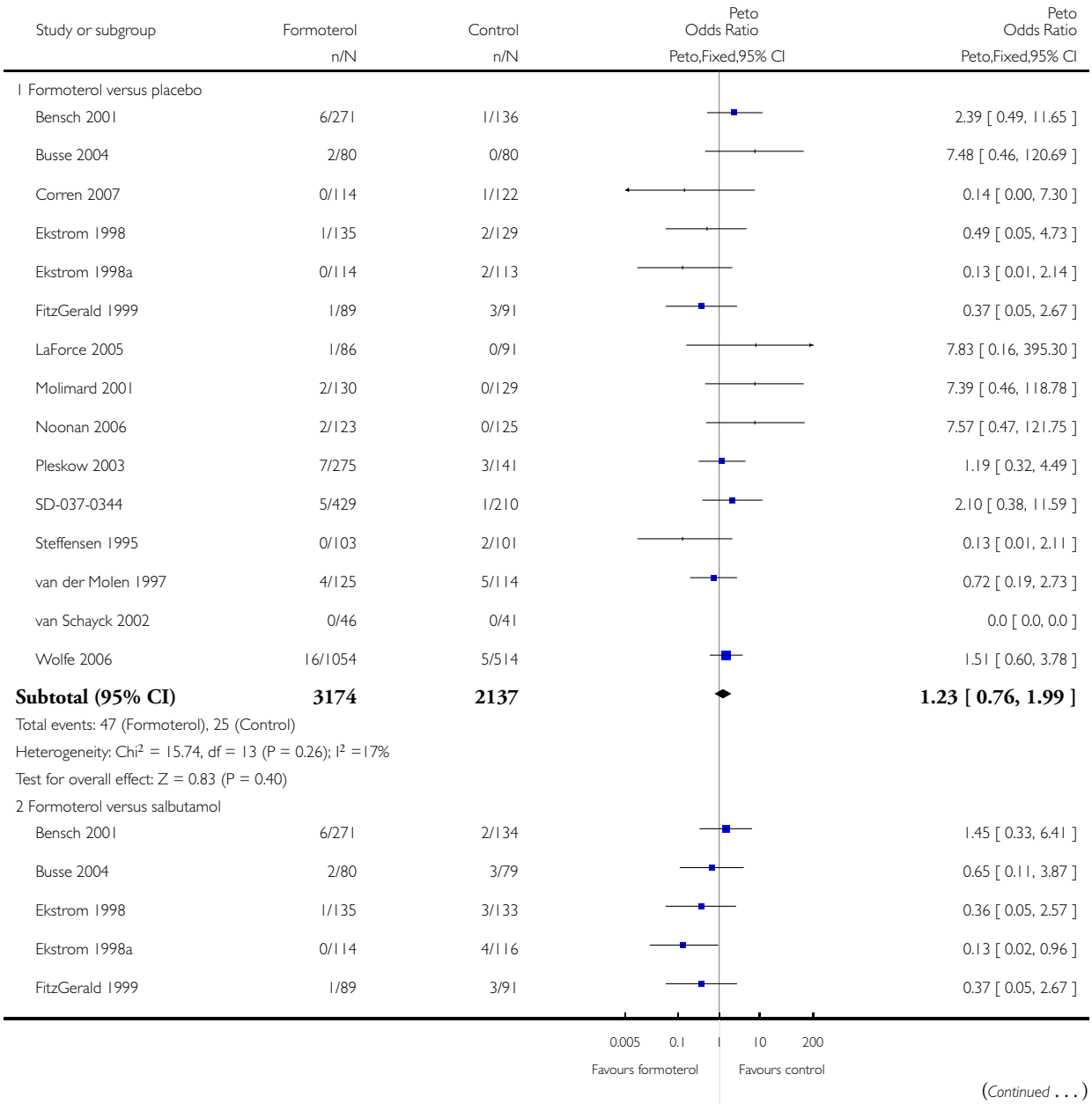


Analysis 4.1. Comparison 4 Adults with non-fatal serious adverse events, Outcome 1 Formoterol versus placebo or salbutamol.

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

Comparison: 4 Adults with non-fatal serious adverse events

Outcome: 1 Formoterol versus placebo or salbutamol



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Study or subgroup	Formoterol n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
LaForce 2005	1/86	2/88		0.52 [0.05, 5.08]
Pleskow 2003	7/275	1/138		2.60 [0.59, 11.45]
Steffensen 1995	0/103	0/100		0.0 [0.0, 0.0]
van Schayck 2002	0/46	0/41		0.0 [0.0, 0.0]
Subtotal (95% CI)	**1199**	**920**		**0.73 [0.37, 1.43]**
Total events: 18 (Formoterol), 18 (Control)				
Heterogeneity: Chi^2 = 7.53, df = 6 (P = 0.27); I^2 =20%				
Test for overall effect: Z = 0.92 (P = 0.36)				

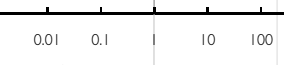
Analysis 5.1. Comparison 5 Children with non-fatal serious adverse events, Outcome 1 Formoterol versus placebo or salbutamol.

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

Comparison: 5 Children with non-fatal serious adverse events

Outcome: 1 Formoterol versus placebo or salbutamol

Study or subgroup	Formoterol n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Formoterol versus placebo					
Bensch 2002	24/342	3/176		66.4 %	2.92 [1.29, 6.62]
Corren 2007	0/9	1/9		2.9 %	0.14 [0.00, 6.82]
Levy 2005	1/127	0/122		2.9 %	7.10 [0.14, 358.29]
Von Berg 2003	6/164	1/84		17.7 %	2.45 [0.50, 11.95]
Zimmerman 2004	3/201	1/101		10.2 %	1.47 [0.18, 11.83]
Subtotal (95% CI)	**843**	**492**		**100.0 %**	**2.48 [1.27, 4.83]**
Total events: 34 (Formoterol), 6 (Control)					
Heterogeneity: Chi^2 = 2.79, df = 4 (P = 0.59); I^2 =0.0%					
Test for overall effect: Z = 2.67 (P = 0.0075)					
2 Formoterol versus salbutamol					



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Study or subgroup	Formoterol n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Formoterol), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 6.1. Comparison 6 Children with non-fatal serious adverse events (without formoterol 24 µg arms), Outcome 1 Formoterol versus placebo or salbutamol.

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

Comparison: 6 Children with non-fatal serious adverse events (without formoterol 24 g arms)

Outcome: 1 Formoterol versus placebo or salbutamol

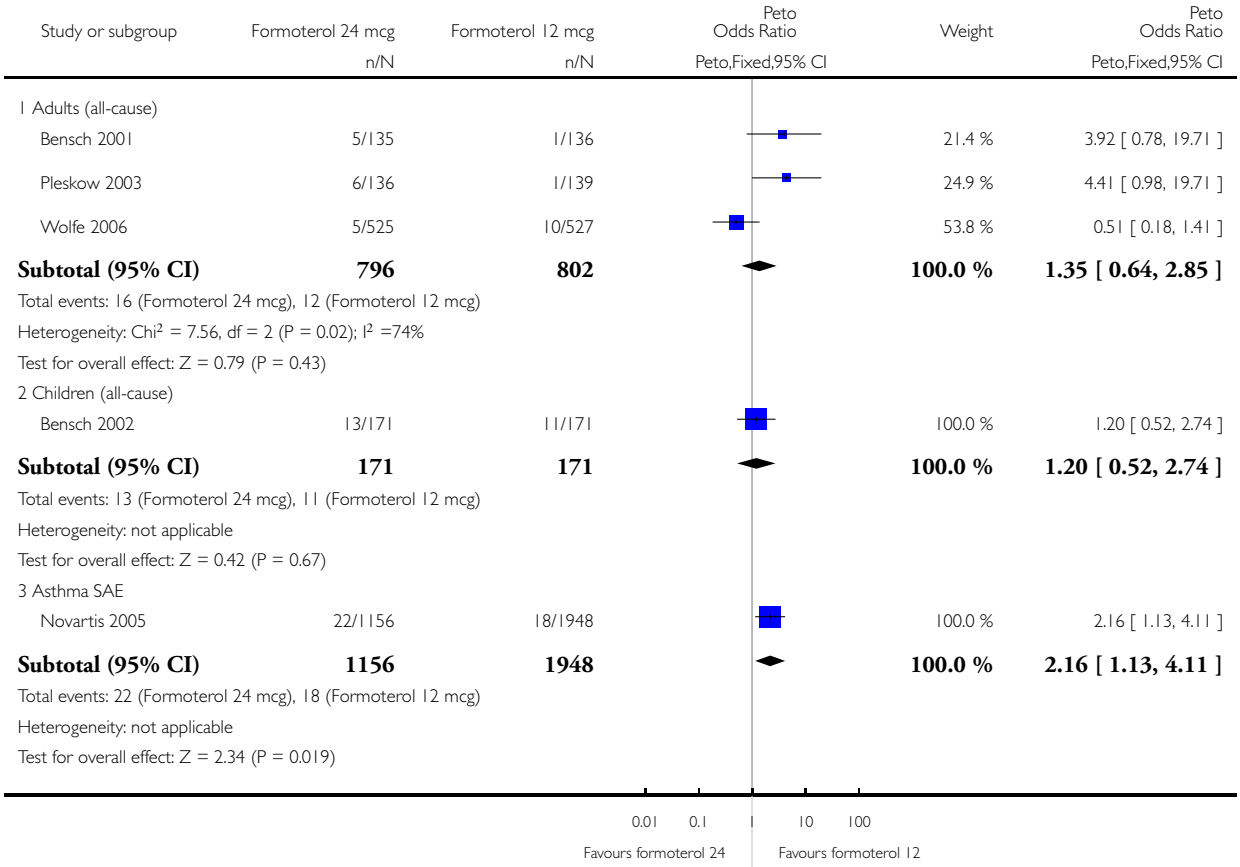
Study or subgroup	Formoterol n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Formoterol versus placebo					
Bensch 2002	11/171	3/176		53.6 %	3.38 [1.16, 9.83]
Corren 2007	0/9	1/9		4.0 %	0.14 [0.00, 6.82]
Levy 2005	1/127	0/122		4.0 %	7.10 [0.14, 358.29]
Von Berg 2003	6/164	1/84		24.4 %	2.45 [0.50, 11.95]
Zimmerman 2004	3/201	1/101		14.0 %	1.47 [0.18, 11.83]
Subtotal (95% CI)	**672**	**492**		**100.0 %**	**2.52 [1.15, 5.51]**
Total events: 21 (Formoterol), 6 (Control)					
Heterogeneity: Chi^2 = 2.96, df = 4 (P = 0.57); I^2 =0.0%					
Test for overall effect: Z = 2.31 (P = 0.021)					
2 Formoterol versus salbutamol					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Formoterol), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 7.1. Comparison 7 Dose comparison: formoterol 24 µg versus 12 µg twice daily, Outcome 1 Serious adverse events.

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

Comparison: 7 Dose comparison: formoterol 24 g versus 12 g twice daily

Outcome: 1 Serious adverse events

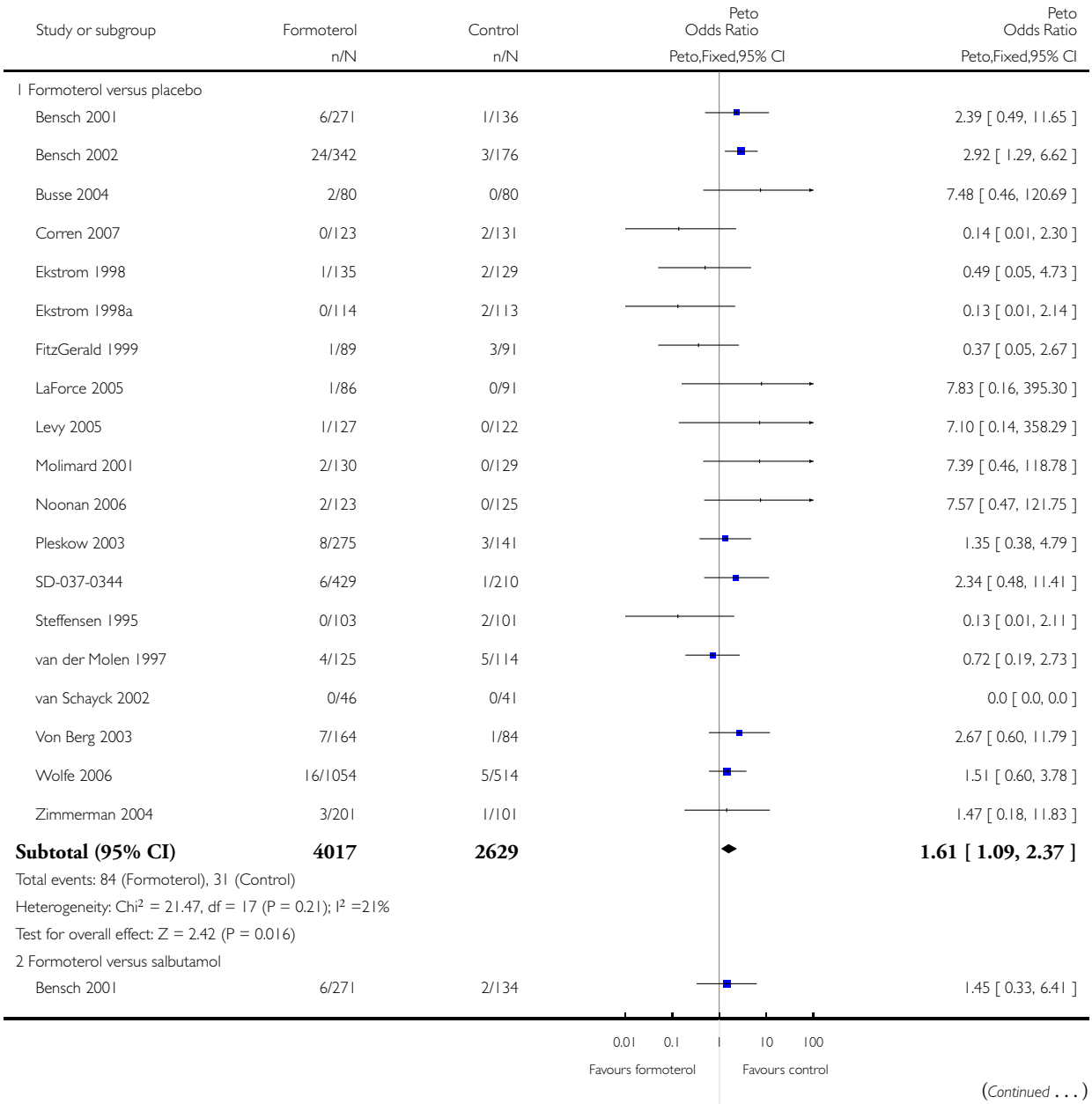


Analysis 8.1. Comparison 8 Adults and children fatal and non-fatal serious adverse events, Outcome 1 Formoterol versus placebo or salbutamol.

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

Comparison: 8 Adults and children fatal and non-fatal serious adverse events

Outcome: 1 Formoterol versus placebo or salbutamol



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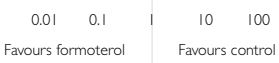
Study or subgroup	Formoterol n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Busse 2004	2/80	3/79		0.65 [0.11, 3.87]
Ekstrom 1998	1/135	3/133		0.36 [0.05, 2.57]
Ekstrom 1998a	0/114	4/116		0.13 [0.02, 0.96]
FitzGerald 1999	1/89	3/91		0.37 [0.05, 2.67]
LaForce 2005	1/86	2/88		0.52 [0.05, 5.08]
Pleskow 2003	8/275	2/138		1.85 [0.49, 6.99]
Steffensen 1995	0/103	0/100		0.0 [0.0, 0.0]
van Schayck 2002	0/46	0/41		0.0 [0.0, 0.0]
Subtotal (95% CI)	**1199**	**920**		**0.71 [0.37, 1.38]**
Total events: 19 (Formoterol), 19 (Control)				
Heterogeneity: Chi^2 = 6.59, df = 6 (P = 0.36); I^2 =9%				
Test for overall effect: Z = 1.00 (P = 0.32)				



Analysis 9.1. Comparison 9 Asthma mortality, Outcome 1 Formoterol versus placebo or salbutamol.

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

Comparison: 9 Asthma mortality

Outcome: 1 Formoterol versus placebo or salbutamol

Study or subgroup	Formoterol n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
1 Formoterol versus placebo				
Bensch 2001	0/271	0/136		0.0 [0.0, 0.0]
Bensch 2002	0/342	0/176		0.0 [0.0, 0.0]
Busse 2004	0/80	0/80		0.0 [0.0, 0.0]
Corren 2007	0/123	0/131		0.0 [0.0, 0.0]
FitzGerald 1999	0/89	0/91		0.0 [0.0, 0.0]
LaForce 2005	0/86	0/91		0.0 [0.0, 0.0]
Molimard 2001	0/130	0/129		0.0 [0.0, 0.0]
Noonan 2006	0/123	0/125		0.0 [0.0, 0.0]
Pleskow 2003	1/275	0/141		4.54 [0.07, 285.25]
van Schayck 2002	0/46	0/41		0.0 [0.0, 0.0]
Von Berg 2003	0/164	0/84		0.0 [0.0, 0.0]
Wolfe 2006	0/1054	0/514		0.0 [0.0, 0.0]
Subtotal (95% CI)	**2783**	**1739**		**4.54 [0.07, 285.25]**
Total events: 1 (Formoterol), 0 (Control)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%				
Test for overall effect: Z = 0.72 (P = 0.47)				
2 Formoterol versus salbutamol				
Bensch 2001	0/271	0/134		0.0 [0.0, 0.0]
Busse 2004	0/80	0/79		0.0 [0.0, 0.0]
FitzGerald 1999	0/89	0/91		0.0 [0.0, 0.0]
LaForce 2005	0/86	0/88		0.0 [0.0, 0.0]
Pleskow 2003	1/275	0/138		4.49 [0.07, 286.29]
van Schayck 2002	0/46	0/41		0.0 [0.0, 0.0]
Subtotal (95% CI)	**847**	**571**		**4.49 [0.07, 286.29]**
Total events: 1 (Formoterol), 0 (Control)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%				
Test for overall effect: Z = 0.71 (P = 0.48)				

Analysis 10.1. Comparison 10 Cardiovascular mortality, Outcome 1 Formoterol versus placebo or salbutamol.

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

Comparison: 10 Cardiovascular mortality

Outcome: 1 Formoterol versus placebo or salbutamol

Study or subgroup	Formoterol n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
1 Formoterol versus placebo				
Bensch 2001	0/271	0/136		0.0 [0.0, 0.0]
Bensch 2002	0/342	0/176		0.0 [0.0, 0.0]
Busse 2004	0/80	0/80		0.0 [0.0, 0.0]
Corren 2007	0/123	0/131		0.0 [0.0, 0.0]
FitzGerald 1999	0/89	0/91		0.0 [0.0, 0.0]
LaForce 2005	0/86	0/91		0.0 [0.0, 0.0]
Molimard 2001	0/130	0/129		0.0 [0.0, 0.0]
Noonan 2006	0/123	0/125		0.0 [0.0, 0.0]
Pleskow 2003	0/275	0/141		0.0 [0.0, 0.0]
van Schayck 2002	0/46	0/41		0.0 [0.0, 0.0]
Von Berg 2003	1/164	0/84		4.54 [0.07, 285.29]
Wolfe 2006	0/1054	0/514		0.0 [0.0, 0.0]
Subtotal (95% CI)	**2783**	**1739**		**4.54 [0.07, 285.29]**
Total events: 1 (Formoterol), 0 (Control)				
Heterogeneity: Chi² = 0.0, df = 0 (P = 1.00); I² =0.0%				
Test for overall effect: Z = 0.72 (P = 0.47)				
2 Formoterol versus salbutamol				
Bensch 2001	0/271	0/134		0.0 [0.0, 0.0]
Busse 2004	0/80	0/79		0.0 [0.0, 0.0]
FitzGerald 1999	0/89	0/91		0.0 [0.0, 0.0]
LaForce 2005	0/86	0/88		0.0 [0.0, 0.0]
Pleskow 2003	0/275	0/138		0.0 [0.0, 0.0]
van Schayck 2002	0/46	0/41		0.0 [0.0, 0.0]
Subtotal (95% CI)	**847**	**571**		**0.0 [0.0, 0.0]**
Total events: 0 (Formoterol), 0 (Control)				
Heterogeneity: Chi² = 0.0, df = 0 (P<0.00001); I² =0.0%				
Test for overall effect: Z = 0.0 (P < 0.00001)				

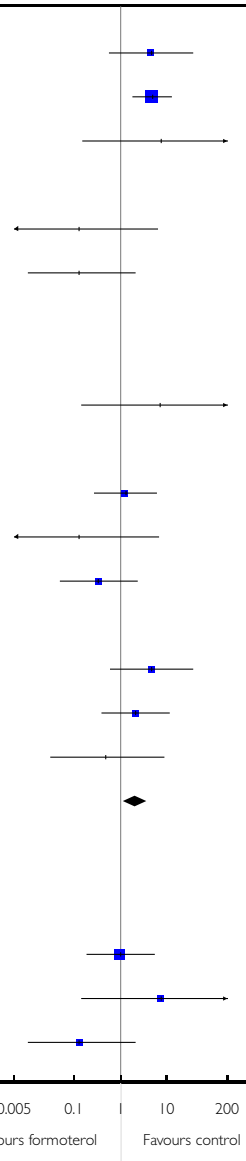
Analysis 11.1. Comparison 11 Adults and children non-fatal asthma-related serious adverse events, Outcome 1 Formoterol versus placebo or salbutamol.

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

Comparison: 11 Adults and children non-fatal asthma-related serious adverse events

Outcome: 1 Formoterol versus placebo or salbutamol

Study or subgroup	Formoterol n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
1 Formoterol versus placebo				
Bensch 2001	4/271	0/136		4.54 [0.56, 36.54]
Bensch 2002	19/342	0/176		4.80 [1.83, 12.62]
Busse 2004	1/80	0/80		7.39 [0.15, 372.38]
Corren 2007	0/123	0/131		0.0 [0.0, 0.0]
Ekstrom 1998	0/135	1/129		0.13 [0.00, 6.52]
Ekstrom 1998a	0/114	2/113		0.13 [0.01, 2.14]
FitzGerald 1999	0/89	0/91		0.0 [0.0, 0.0]
LaForce 2005	0/86	0/91		0.0 [0.0, 0.0]
Levy 2005	1/127	0/122		7.10 [0.14, 358.29]
Molimard 2001	0/130	0/129		0.0 [0.0, 0.0]
Pleskow 2003	5/275	2/141		1.27 [0.26, 6.16]
Steffensen 1995	0/103	1/101		0.13 [0.00, 6.69]
van der Molen 1997	1/125	3/114		0.33 [0.05, 2.38]
van Schayck 2002	0/46	0/41		0.0 [0.0, 0.0]
Von Berg 2003	4/164	0/84		4.62 [0.58, 37.12]
Wolfe 2006	5/1054	1/514		2.08 [0.38, 11.48]
Zimmerman 2004	1/201	1/101		0.47 [0.03, 8.99]
Subtotal (95% CI)	**3465**	**2294**		**1.99 [1.12, 3.53]**
Total events: 41 (Formoterol), 11 (Control)				
Heterogeneity: Chi² = 17.01, df = 11 (P = 0.11); I² =35%				
Test for overall effect: Z = 2.35 (P = 0.019)				
2 Formoterol versus salbutamol				
Bensch 2001	4/271	2/134		0.99 [0.18, 5.47]
Busse 2004	1/80	0/79		7.30 [0.14, 367.79]
Ekstrom 1998	0/135	2/133		0.13 [0.01, 2.13]



(*Continued* . . .)

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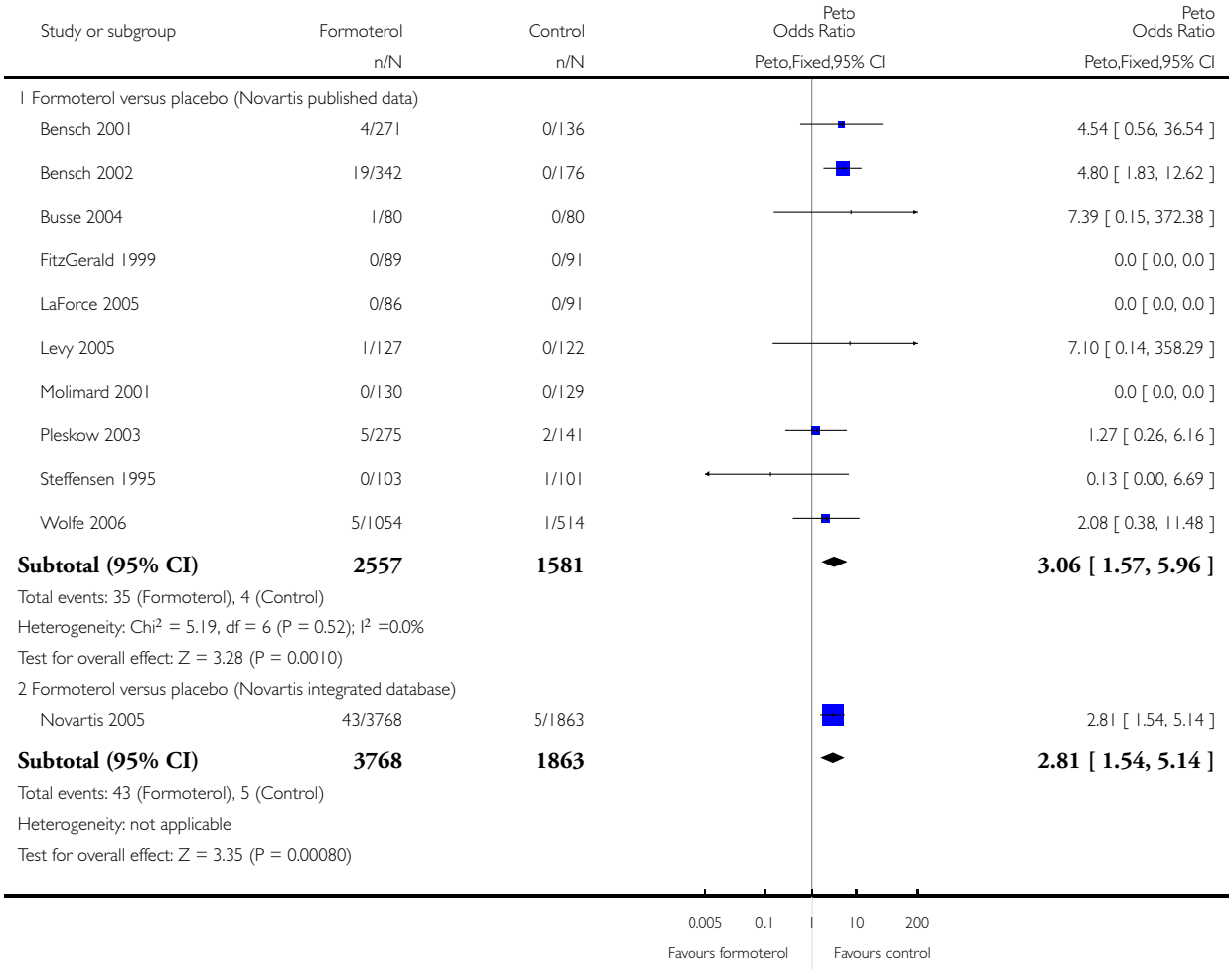
Study or subgroup	Formoterol n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Ekstrom 1998a	0/114	3/116		0.14 [0.01, 1.31]
FitzGerald 1999	0/89	2/91		0.14 [0.01, 2.20]
LaForce 2005	0/86	0/88		0.0 [0.0, 0.0]
Pleskow 2003	5/275	0/138		4.56 [0.70, 29.49]
Steffensen 1995	0/103	0/100		0.0 [0.0, 0.0]
van Schayck 2002	0/46	0/41		0.0 [0.0, 0.0]
Subtotal (95% CI)	**1199**	**920**		**0.74 [0.29, 1.88]**
Total events: 10 (Formoterol), 9 (Control)				
Heterogeneity: Chi^2 = 10.10, df = 5 (P = 0.07); I^2 =50%				
Test for overall effect: Z = 0.63 (P = 0.53)				

Analysis 12.1. Comparison 12 Adults and children non-fatal asthma-related serious adverse events (Novartis data), Outcome 1 Formoterol versus placebo or salbutamol.

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

Comparison: 12 Adults and children non-fatal asthma-related serious adverse events (Novartis data)

Outcome: 1 Formoterol versus placebo or salbutamol



Analysis 13.1. Comparison 13 Hospitalisations for asthma, Outcome 1 Formoterol versus placebo or salbutamol.

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

Comparison: 13 Hospitalisations for asthma

Outcome: 1 Formoterol versus placebo or salbutamol

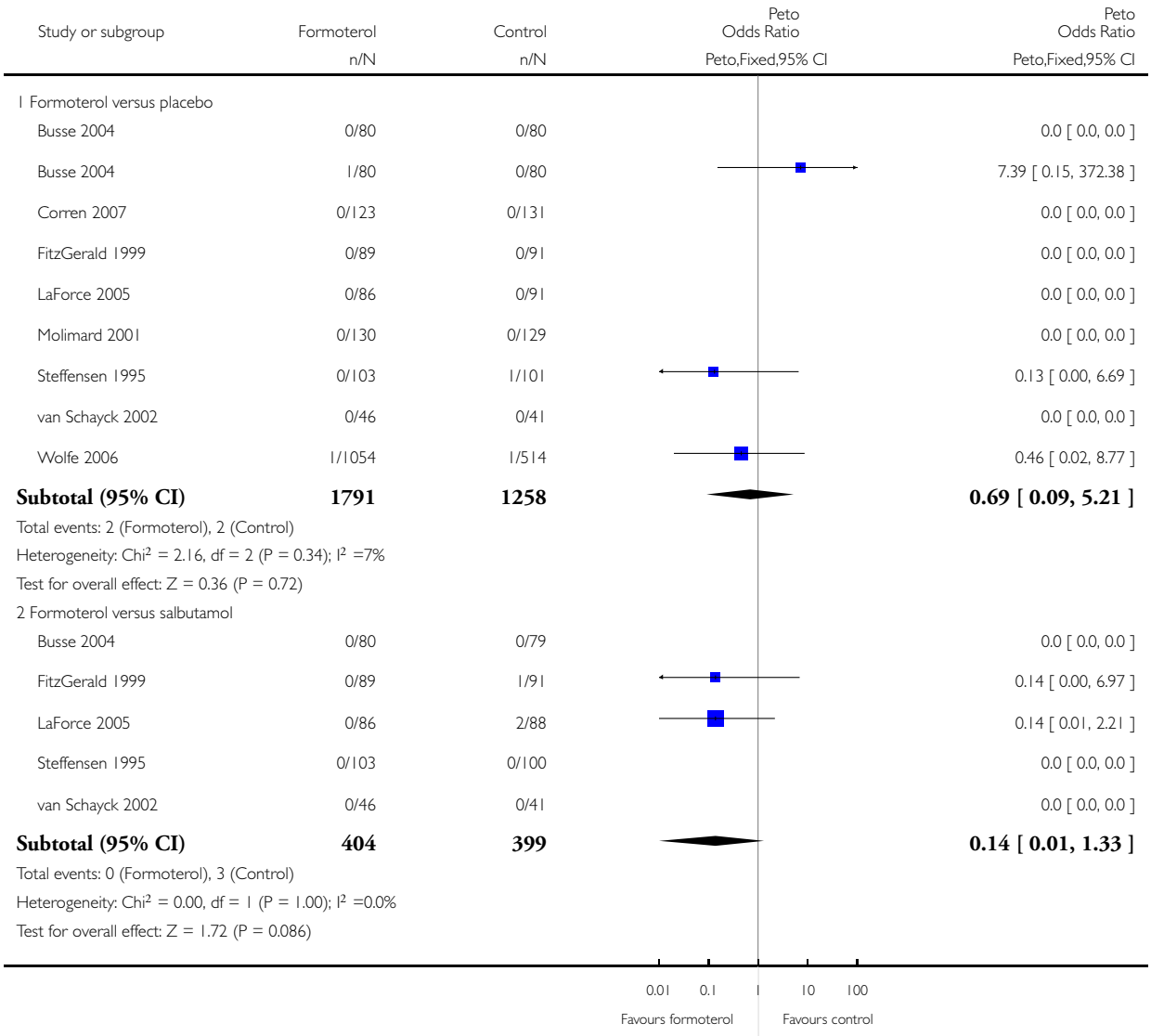
Study or subgroup	Formoterol n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
1 Formoterol versus placebo				
Bensch 2002	18/342	0/176		4.79 [1.78, 12.91]
Corren 2007	0/123	0/131		0.0 [0.0, 0.0]
FitzGerald 1999	0/89	0/91		0.0 [0.0, 0.0]
Levy 2005	1/127	0/122		7.10 [0.14, 358.29]
Pleskow 2003	6/275	2/141		1.50 [0.34, 6.55]
Von Berg 2003	4/164	0/84		4.62 [0.58, 37.12]
Wolfe 2006	5/1054	1/514		2.08 [0.38, 11.48]
Subtotal (95% CI)	**2174**	**1259**		**3.28 [1.65, 6.52]**
Total events: 34 (Formoterol), 3 (Control)				
Heterogeneity: Chi^2 = 2.17, df = 4 (P = 0.71); I^2 =0.0%				
Test for overall effect: Z = 3.38 (P = 0.00072)				
2 Formoterol versus salbutamol				
FitzGerald 1999	0/89	2/91		0.14 [0.01, 2.20]
Pleskow 2003	6/275	0/138		4.57 [0.83, 25.20]
Subtotal (95% CI)	**364**	**229**		**1.75 [0.41, 7.49]**
Total events: 6 (Formoterol), 2 (Control)				
Heterogeneity: Chi^2 = 4.45, df = 1 (P = 0.03); I^2 =78%				
Test for overall effect: Z = 0.75 (P = 0.45)				

Analysis 14.1. Comparison 14 Adults and children non-fatal cardiovascular serious adverse events, Outcome 1 Formoterol versus placebo or salbutamol.

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

Comparison: 14 Adults and children non-fatal cardiovascular serious adverse events

Outcome: 1 Formoterol versus placebo or salbutamol

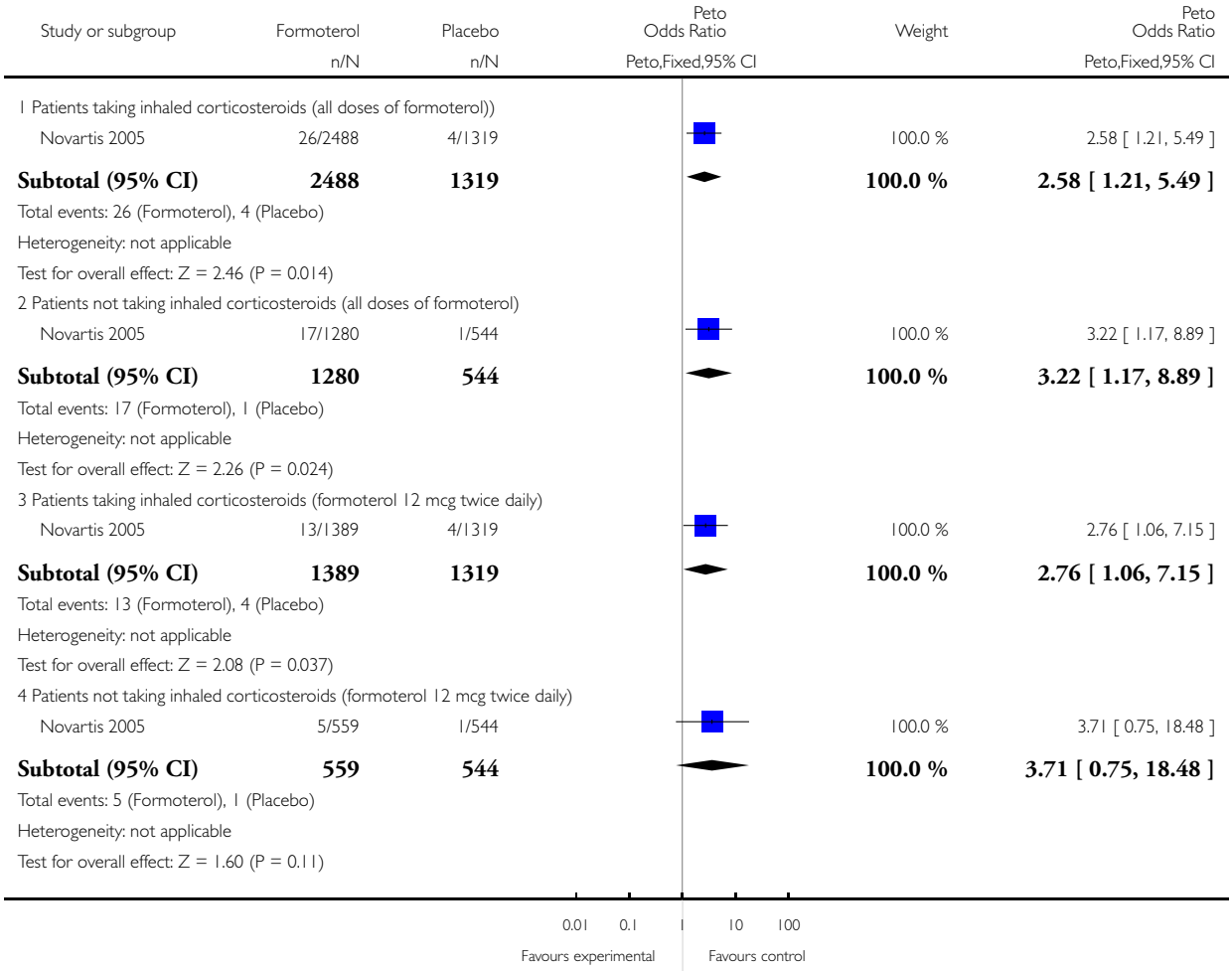


Analysis 15.1. Comparison 15 Impact of inhaled corticosteroids on asthma-related SAEs, Outcome 1 Patients with at least one asthma-related SAE.

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

Comparison: 15 Impact of inhaled corticosteroids on asthma-related SAEs

Outcome: 1 Patients with at least one asthma-related SAE



Analysis 16.1. Comparison 16 Adults and children published non-fatal serious adverse events, Outcome 1 Formoterol versus placebo or salbutamol.

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

Comparison: 16 Adults and children published non-fatal serious adverse events

Outcome: 1 Formoterol versus placebo or salbutamol

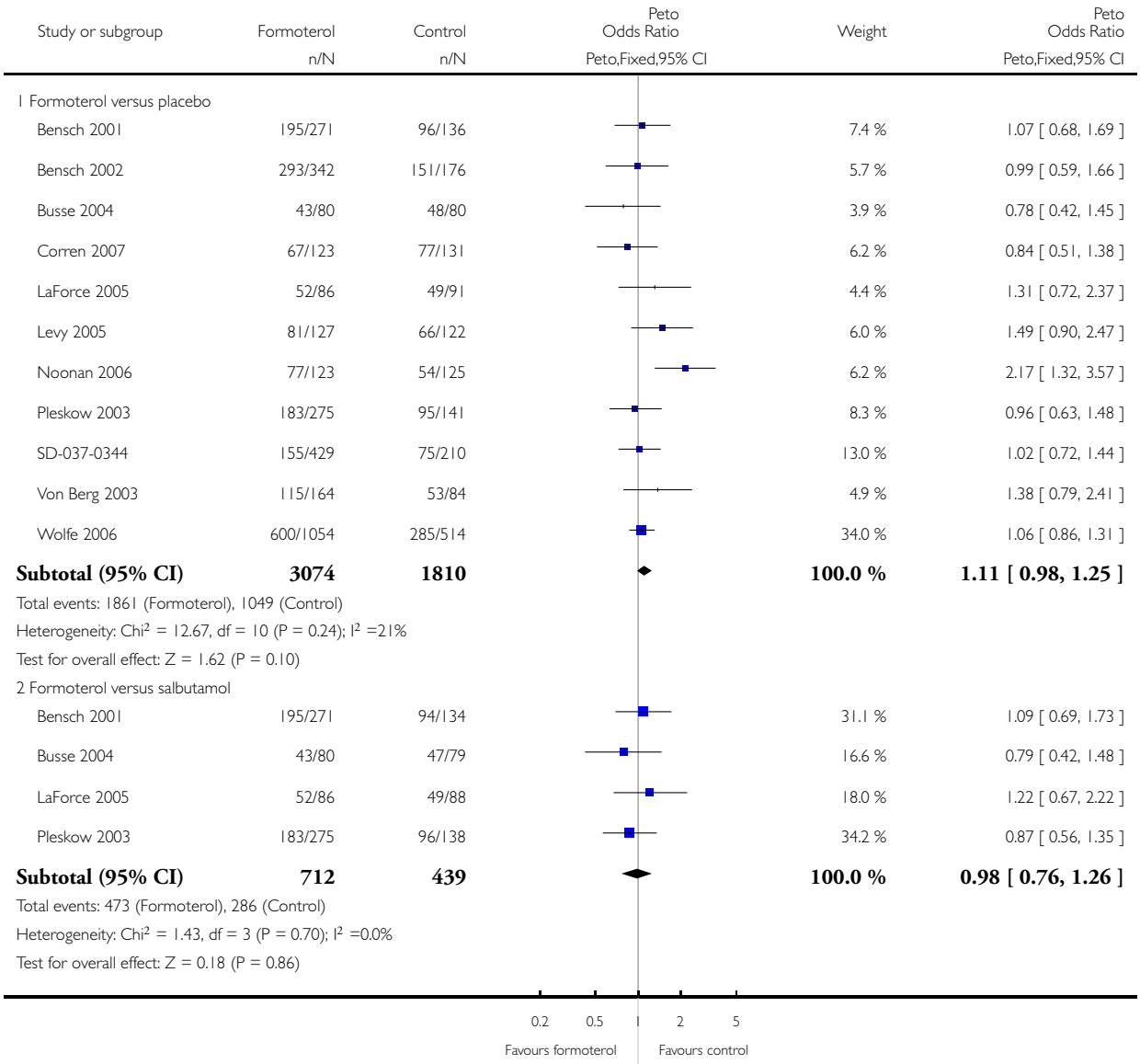
Study or subgroup	Formoterol n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
1 Formoterol versus placebo				
Bensch 2002	21/342	3/176		2.72 [1.15, 6.46]
Busse 2004	2/80	0/80		7.48 [0.46, 120.69]
Corren 2007	0/114	1/122		0.14 [0.00, 7.30]
LaForce 2005	1/86	0/91		7.83 [0.16, 395.30]
Levy 2005	1/127	0/122		7.10 [0.14, 358.29]
Steffensen 1995	0/103	2/101		0.13 [0.01, 2.11]
Von Berg 2003	6/164	1/84		2.45 [0.50, 11.95]
Subtotal (95% CI)	**1016**	**776**		**2.31 [1.17, 4.53]**
Total events: 31 (Formoterol), 7 (Control)				
Heterogeneity: Chi² = 7.53, df = 6 (P = 0.27); I² =20%				
Test for overall effect: Z = 2.43 (P = 0.015)				
2 Formoterol versus salbutamol				
Busse 2004	2/80	3/79		0.65 [0.11, 3.87]
LaForce 2005	1/86	2/88		0.52 [0.05, 5.08]
Steffensen 1995	0/103	0/100		0.0 [0.0, 0.0]
Subtotal (95% CI)	**269**	**267**		**0.60 [0.15, 2.44]**
Total events: 3 (Formoterol), 5 (Control)				
Heterogeneity: Chi² = 0.02, df = 1 (P = 0.88); I² =0.0%				
Test for overall effect: Z = 0.71 (P = 0.48)				

Analysis 17.1. Comparison 17 Adults and children all adverse events, Outcome 1 Formoterol versus placebo or salbutamol.

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

Comparison: 17 Adults and children all adverse events

Outcome: 1 Formoterol versus placebo or salbutamol

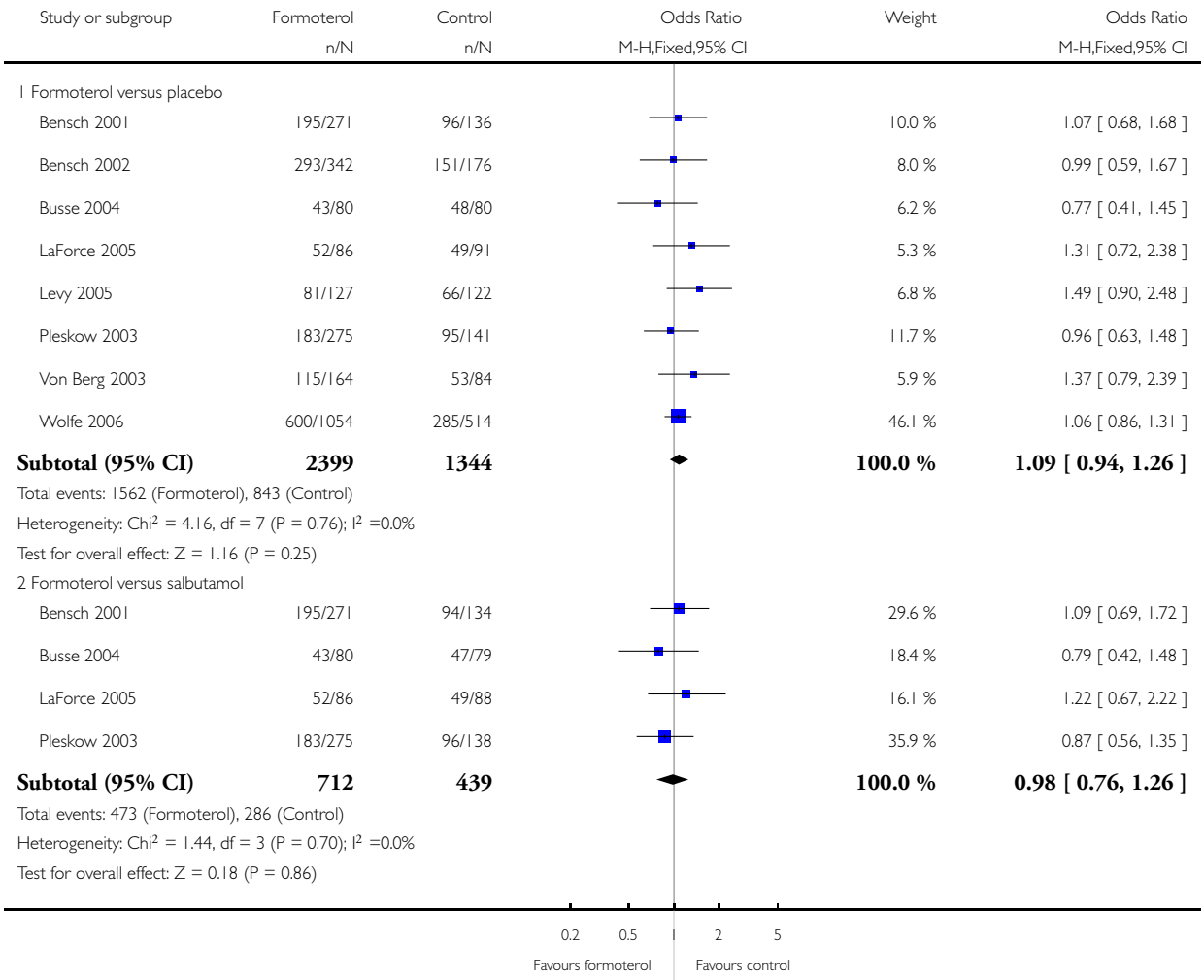


Analysis 18.1. Comparison 18 Adults and children published adverse events, Outcome 1 Formoterol versus placebo or salbutamol.

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

Comparison: 18 Adults and children published adverse events

Outcome: 1 Formoterol versus placebo or salbutamol



Analysis 19.1. Comparison 19 Adults and children all published drug-related adverse events, Outcome 1 Formoterol versus placebo or salbutamol.

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

Comparison: 19 Adults and children all published drug-related adverse events

Outcome: 1 Formoterol versus placebo or salbutamol

Study or subgroup	Formoterol n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Formoterol versus placebo					
Busse 2004	3/80	5/80		3.9 %	0.59 [0.14, 2.45]
FitzGerald 1999	13/89	9/91		10.0 %	1.55 [0.64, 3.77]
Steffensen 1995	33/103	38/101		23.9 %	0.78 [0.44, 1.39]
Wolfe 2006	121/1054	31/514		62.2 %	1.86 [1.30, 2.66]
Subtotal (95% CI)	**1326**	**786**		**100.0 %**	**1.42 [1.07, 1.88]**
Total events: 170 (Formoterol), 83 (Control)					
Heterogeneity: Chi^2 = 7.85, df = 3 (P = 0.05); I^2 =62%					
Test for overall effect: Z = 2.45 (P = 0.014)					
2 Formoterol versus salbutamol					
Busse 2004	3/80	3/79		7.7 %	0.99 [0.19, 5.02]
FitzGerald 1999	13/89	11/91		27.9 %	1.24 [0.53, 2.93]
Steffensen 1995	33/103	45/100		64.4 %	0.58 [0.33, 1.02]
Subtotal (95% CI)	**272**	**270**		**100.0 %**	**0.75 [0.48, 1.18]**
Total events: 49 (Formoterol), 59 (Control)					
Heterogeneity: Chi^2 = 2.24, df = 2 (P = 0.33); I^2 =11%					
Test for overall effect: Z = 1.26 (P = 0.21)					

Analysis 20.1. Comparison 20 Adults and children serious drug-related adverse events, Outcome 1 Formoterol versus placebo or salbutamol.

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

Comparison: 20 Adults and children serious drug-related adverse events

Outcome: 1 Formoterol versus placebo or salbutamol

Study or subgroup	Formoterol n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
1 Formoterol versus placebo				
Busse 2004	0/80	0/80		0.0 [0.0, 0.0]
LaForce 2005	0/86	0/91		0.0 [0.0, 0.0]
Levy 2005	0/127	0/122		0.0 [0.0, 0.0]
Molimard 2001	0/130	0/129		0.0 [0.0, 0.0]
Pleskow 2003	1/275	0/141		4.54 [0.07, 285.25]
van der Molen 1997	0/125	0/114		0.0 [0.0, 0.0]
Von Berg 2003	0/164	0/84		0.0 [0.0, 0.0]
Wolfe 2006	2/1054	0/514		4.43 [0.23, 84.94]
Zimmerman 2004	0/201	1/101		0.05 [0.00, 3.20]
Subtotal (95% CI)	**2242**	**1376**		**1.45 [0.18, 11.61]**
Total events: 3 (Formoterol), 1 (Control)				
Heterogeneity: Chi^2 = 3.36, df = 2 (P = 0.19); I^2 =40%				
Test for overall effect: Z = 0.35 (P = 0.73)				
2 Formoterol versus salbutamol				
Busse 2004	0/80	0/79		0.0 [0.0, 0.0]
LaForce 2005	0/86	1/88		0.14 [0.00, 6.98]
Pleskow 2003	1/275	0/138		4.49 [0.07, 286.29]
Subtotal (95% CI)	**441**	**305**		**0.71 [0.04, 12.34]**
Total events: 1 (Formoterol), 1 (Control)				
Heterogeneity: Chi^2 = 1.42, df = 1 (P = 0.23); I^2 =30%				
Test for overall effect: Z = 0.23 (P = 0.82)				

ADDITIONAL TABLES

Table 1. Study sponsors

Study ID	Sponsor
Bensch 2001	Novartis
Bensch 2002	Novartis
Busse 2004	Novartis
Corren 2007	AstraZeneca
Ekstrom 1998	AstraZeneca
Ekstrom 1998a	AstraZeneca
FitzGerald 1999	Novartis
Hekking 1990	Not reported
Kesten 1991	Novartis
Kozlik-Feldmann 1996	Not reported
LaForce 2005	Novartis
Levy 2005	Novartis
Molimard 2001	Novartis
Noonan 2006	AstraZeneca
Pleskow 2003	Novartis
SD-037-0344	AstraZeneca
Steffensen 1995	Novartis
van der Molen 1997	AstraZeneca
van Schayck 2002	Not reported
Von Berg 2003	AstraZeneca
Wolfe 2006	Novartis
Zimmerman 2004	AstraZeneca

Table 2. Proportion of participants using inhaled corticosteroids (ICS)

Study ID	Proportion of participants on ICS
Bensch 2001	51%
Bensch 2002	69%
Busse 2004	64%
Corren 2007	0% (withdrawn)
Ekstrom 1998	86%
Ekstrom 1998a	89%
FitzGerald 1999	100%
Hekking 1990	Not reported
Kesten 1991	62%
Kozlik-Feldmann 1996	0%
LaForce 2005	67%
Levy 2005	72%
Molimard 2001	100%
Noonan 2006	100%
Pleskow 2003	44%
SD-037-0344	100%
Steffensen 1995	87%
van der Molen 1997	100%
van Schayck 2002	95%
Von Berg 2003	82%
Wolfe 2006	62%
Zimmerman 2004	100%

Table 3. Intrinsic efficacy of beta-agonists

Drug	Intrinsic efficacy (%)
Isoprenaline, adrenaline	100
Fenoterol	42
Formoterol	20
Salbutamol	4.9
Salmeterol	< 2

Adapted from Hanania 2002. The authors acknowledge that it is difficult to determine the intrinsic efficacy of salmeterol given its high lipophilicity.

APPENDICES

Appendix 1. Pharmacology of beta$_2$-agonists

Beta$_2$-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 (Van Noord 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 3. The clinical significance of intrinsic efficacy remains unclear.

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 other 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 to 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 two to four 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 1), 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 one to two 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 (Jones 2001; Lipworth 2000).

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 (Hancox 1999; Wong 1990) 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 hyper responsiveness 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; Grainger 1991; Pearce 1990). 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. Sources and search methods for the Cochrane Airways Group Specialised Register (CAGR)

Electronic searches: core databases

Database	Frequency of search
MEDLINE (Ovid)	Weekly
EMBASE (Ovid)	Weekly
CENTRAL (*T he Cochrane Library*)	Quarterly
PSYCINFO (Ovid)	Monthly
CINAHL (EBSCO)	Monthly
AMED (EBSCO)	Monthly

Handsearches: core respiratory conference abstracts

Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 onwards
American Thoracic Society (ATS)	2001 onwards
Asia Pacific Society of Respirology (APSR)	2004 onwards
British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards
European Respiratory Society (ERS)	1992, 1994, 2000 onwards
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards

MEDLINE search strategy used to identify trials for the CAGR

Asthma search

1. exp Asthma/
2. asthma$.mp.
3. (antiasthma$ or anti-asthma$).mp.
4. Respiratory Sounds/
5. wheez$.mp.
6. Bronchial Spasm/
7. bronchospas$.mp.
8. (bronch$ adj3 spasm$).mp.
9. bronchoconstrict$.mp.
10. exp Bronchoconstriction/
11. (bronch$ adj3 constrict$).mp.
12. Bronchial Hyperreactivity/
13. Respiratory Hypersensitivity/
14. ((bronchial$ or respiratory or airway$ or lung$) adj3 (hypersensitiv$ or hyperreactiv$ or allerg$ or insufficiency)).mp.
15. ((dust or mite$) adj3 (allerg$ or hypersensitiv$)).mp.
16. or/1-15

Filter to identify RCTs

1. exp "clinical trial [publication type]"/
2. (randomised or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.

7. groups.ab,ti.
8. or/1-7
9. Animals/
10. Humans/
11. 9 not (9 and 10)
12. 8 not 11
The MEDLINE strategy and RCT filter are adapted to identify trials in other electronic databases

Appendix 4. 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 hospitalisation or prolongation of existing hospitalisation,
- 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."

WHAT'S NEW

Last assessed as up-to-date: 5 January 2012.

Date	Event	Description
5 January 2012	New search has been performed	No new studies found. Minor edits made and plain language summary revised
5 January 2012	New citation required but conclusions have not changed	New search carried out in January 2012 but no new studies included

HISTORY

Protocol first published: Issue 1, 2008

Review first published: Issue 4, 2008

Date	Event	Description
10 November 2008	Amended	The 'Summary of findings' tables have been reordered. Contents are unchanged. An additional reference has also been added for Corren 2007. The Primary Analysis has been changed to Peto Odds Ratio.

CONTRIBUTIONS OF AUTHORS

CJC: conception of the idea, study selection and data collection, statistical analysis and co-writing of the review.

MJC: background information (including Appendices), study selection and co-writing of the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- NHS R&D, UK.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We did not use risk difference as the primary metric for analysis of rare events, due to new advice in the latest revision of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). One of the peer reviewers also pointed out that Bradburn 2007 cautions against the use of inverse-variance and DerSimonian and Laird methods for sparse data, so for the 2009 update we used the Peto OR for the primary analysis, as no continuity correction is required for zero cells. This brings the analysis for this review in line with the other reviews in this series.

Also we investigated reporting bias by comparing published and unpublished serious adverse events, and investigating the impact of using drug-related adverse events and the combined results from serious and non-serious adverse events.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenergic beta-Agonists [*adverse effects]; Age Factors; Albuterol [adverse effects]; Asthma [*drug therapy; mortality]; Bronchodilator Agents [*adverse effects]; Chronic Disease; Ethanolamines [*adverse effects]

MeSH check words

Adult; Child; Humans