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Inhaled steroids with and without regular formoterol for asthma: serious adverse events (Review)

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[Intervention Review]

Inhaled steroids with and without regular formoterol for 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 whether regular (daily) long-acting beta$_2$-agonists (LABA) are safe when used in combination with inhaled corticosteroids (ICS). This updated Cochrane Review includes results from two large trials that recruited 23,422 adolescents and adults mandated by the US Food and Drug Administration (FDA).

Objectives

To assess the risk of mortality and non-fatal serious adverse events (SAEs) in trials that randomly assign participants with chronic asthma to regular formoterol and inhaled corticosteroids versus the same dose of inhaled corticosteroid alone.

Search methods

We identified randomised trials using the Cochrane Airways Group Specialised Register of trials. We checked websites of clinical trial registers for unpublished trial data as well as FDA submissions in relation to formoterol. The date of the most recent search was February 2019.

Selection criteria

We included randomised clinical trials (RCTs) with a parallel design involving adults, children, or both with asthma of any severity who received regular formoterol and ICS (separate or combined) treatment versus the same dose of ICS for at least 12 weeks.

Data collection and analysis

We used standard methodological procedures expected by Cochrane. We obtained unpublished data on mortality and SAEs from the sponsors of the studies. We assessed our confidence in the evidence using GRADE recommendations. The primary outcomes were all-cause mortality and all-cause non-fatal serious adverse events.

Main results

We found 42 studies eligible for inclusion and included 39 studies in the analyses: 29 studies included 35,751 adults, and 10 studies included 4035 children and adolescents. Inhaled corticosteroids included beclomethasone (daily metered dosage 200 to 800 µg), budesonide (200 to 1600 µg), fluticasone (200 to 250 µg), and mometasone (200 to 800 µg). Formoterol metered dosage ranged from 12 to 48 µg daily. Fixed

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combination ICS was used in most of the studies. We judged the risk of selection bias, performance bias, and attrition bias as low, however most studies did not report independent assessment of causation of SAEs.

Deaths

Seventeen of 18,645 adults taking formoterol and ICS and 13 of 17,106 adults taking regular ICS died of any cause. The pooled Peto odds ratio (OR) was 1.25 (95% confidence interval (CI) 0.61 to 2.56, moderate-certainty evidence), which equated to one death occurring for every 1000 adults treated with ICS alone for 26 weeks; the corresponding risk amongst adults taking formoterol and ICS was also one death (95% CI 0 to 2 deaths). No deaths were reported in the trials on children and adolescents (4035 participants) (low-certainty evidence).

In terms of asthma-related deaths, no children and adolescents died from asthma, but three of 12,777 adults in the formoterol and ICS treatment group died of asthma (both low-certainty evidence).

Non-fatal serious adverse events

A total of 401 adults experienced a non-fatal SAE of any cause on formoterol with ICS, compared to 369 adults who received regular ICS. The pooled Peto OR was 1.00 (95% CI 0.87 to 1.16, high-certainty evidence, 29 studies, 35,751 adults). For every 1000 adults treated with ICS alone for 26 weeks, 22 adults had an SAE; the corresponding risk for those on formoterol and ICS was also 22 adults (95% CI 19 to 25).

Thirty of 2491 children and adolescents experienced an SAE of any cause when receiving formoterol with ICS, compared to 13 of 1544 children and adolescents receiving ICS alone. The pooled Peto OR was 1.33 (95% CI 0.71 to 2.49, moderate-certainty evidence, 10 studies, 4035 children and adolescents). For every 1000 children and adolescents treated with ICS alone for 12.5 weeks, 8 had an non-fatal SAE; the corresponding risk amongst those on formoterol and ICS was 11 children and adolescents (95% CI 6 to 21).

Asthma-related serious adverse events

Ninety adults experienced an asthma-related non-fatal SAE with formoterol and ICS, compared to 102 with ICS alone. The pooled Peto OR was 0.86 (95% CI 0.64 to 1.14, moderate-certainty evidence, 28 studies, 35,158 adults). For every 1000 adults treated with ICS alone for 26 weeks, 6 adults had an asthma-related non-fatal SAE; the corresponding risk for those on formoterol and ICS was 5 adults (95% CI 4 to 7).

Amongst children and adolescents, 9 experienced an asthma-related non-fatal SAE with formoterol and ICS, compared to 5 on ICS alone. The pooled Peto OR was 1.18 (95% CI 0.40 to 3.51, very low-certainty evidence, 10 studies, 4035 children and adolescents). For every 1000 children and adolescents treated with ICS alone for 12.5 weeks, 3 had an asthma-related non-fatal SAE; the corresponding risk on formoterol and ICS was 4 (95% CI 1 to 11).

Authors' conclusions

We did not find a difference in the risk of death (all-cause or asthma-related) in adults taking combined formoterol and ICS versus ICS alone (moderate- to low-certainty evidence). No deaths were reported in children and adolescents. The risk of dying when taking either treatment was very low, but we cannot be certain if there is a difference in mortality when taking additional formoterol to ICS (low-certainty evidence).

We did not find a difference in the risk of non-fatal SAEs of any cause in adults (high-certainty evidence). A previous version of the review had shown a lower risk of asthma-related SAEs in adults taking combined formoterol and ICS; however, inclusion of new studies no longer shows a difference between treatments (moderate-certainty evidence).

The reported number of children and adolescents with SAEs was small, so uncertainty remains in this age group.

We included results from large studies mandated by the FDA. Clinical decisions and information provided to patients regarding regular use of formoterol and ICS need to take into account the balance between known symptomatic benefits of formoterol and ICS versus the remaining degree of uncertainty associated with its potential harmful effects.

PLAIN LANGUAGE SUMMARY

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

Review question

Is it safe to add regular formoterol to inhaled corticosteroid (ICS) for adults or children with asthma?

Background

Asthma is a disease of the lungs. Symptoms include wheezing, breathlessness, and chest tightness. Two main features of asthma are underlying inflammation and bronchoconstriction (tightening of the muscles around small tubes in the lungs). The inflammation can be treated with daily steroid inhalers. The bronchoconstriction can be treated with a beta$_2$-agonist to relax the muscles. This opens up the airways and makes it easier to breathe. Beta$_2$-agonists can be used two ways: to provide relief from symptoms of chest tightness ('short-acting beta$_2$-agonists') and to help prevent symptoms from occurring ('long-acting beta$_2$-agonists', or LABAs).

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When asthma is not controlled by daily low-dose ICS, many asthma guidelines recommend additional daily LABA, such as formoterol. We are confident that LABA improves lung function, symptoms, quality of life, and exacerbations. However, there is long-standing controversy about how safe these drugs are for people with asthma. This is what we wanted to explore in this review by focusing on rare and serious harms. These are defined as events that are life-threatening, require admission to hospital or prolongation of existing hospitalisation, or result in persistent or significant disability/incapacity or a birth defect.

Key results

We analysed data from 29 studies in 35,751 adults and 10 studies in 4035 children aged up to 17 years. The participants in the studies had a range of asthma severity, with most having been previously treated with regular ICS (over a wide range of doses). There were too few children in the studies to allow us to be certain about the effects in children.

Thirty deaths were reported in 35,751 adults. Seventeen of these deaths were reported in participants taking formoterol and ICS, and 13 deaths in participants who were taking ICS alone. Three deaths reported in adults taking formoterol and ICS were due to asthma, but there were no deaths due to asthma with ICS alone. No deaths were reported in children up to 17 years age.

The number of people experiencing serious harms of any cause was similar in adults with and without formoterol. Although there was no difference in the risk of serious harms in adults with asthma taking regular formoterol in combination with ICS compared to ICS alone, we could not confidently exclude a reduced or increased risk of events compared to taking ICS alone.

Quality of the evidence

We were moderately certain regarding the data in adults, but less certain about the effects of adding formoterol to ICS in children. Given the low number of deaths that occurred in the studies, we do not yet have enough information to be able to measure accurately the risk of adding formoterol to ICS on number of deaths.

Almost all trials were sponsored by drug manufacturers.

Other concerns were that the cause of serious adverse events (i.e. whether they were judged by the trialists to be asthma-related or not) were not independently assessed, and it may have been possible to guess which treatment group the person experiencing the adverse event was from. Although the people in the trial did not know whether they had been given a dummy drug or the active treatment, formoterol has quite a large effect on symptoms. This meant that they might have been able to guess who was taking formoterol. It was not possible for us to tell whether this occurred or not, which is why we primarily look at the all-cause events, which do not require assessment of cause.

Conclusions

We are not able to state confidently that adding formoterol to ICS carries no risk of increasing the number of deaths in comparison with ICS alone. On the other hand, we found no conclusive evidence of an increase in serious harm. Three asthma-related deaths occurred in a total of 12,777 adults treated with formoterol in combination with ICS. We found no conclusive evidence of risk of non-fatal serious harms attributed to asthma when formoterol was combined with ICS in adults.

This Plain language summary is current as of February 2019.

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SUMMARY OF FINDINGS

Summary of findings for the main comparison. Regular formoterol and ICS compared to same-dose ICS in adults with asthma

Formoterol and ICS compared to same-dose ICS for chronic asthma

Patient or population: adults with chronic asthma
Intervention: formoterol and ICS
Comparison: same-dose ICS

Setting: community; most were multicentre studies, of which 10 studies were conducted in the USA. Other multicentre studies were conducted in at least 2 to 27 countries including Argentina, Australia, Belgium, Brazil, Canada, Czech Republic, Chile, Finland, France, Germany, Hungary, Ireland, Luxembourg, Mexico, Norway, the Philippines, Poland, Spain, Thailand, and the UK. 2 single-centre studies were conducted in Japan and Russia.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with same-dose ICS	Risk with formoterol and ICS				
All-cause mortality Follow-up: 26 weeks	1 per 1000	1 per 1000 (0 to 2)	OR 1.25 (0.61 to 2.56)	35,751 (32 RCTs)	⊕⊕⊕⊖ MODERATE [1]	
All-cause non-fatal serious adverse events Follow-up: 26 weeks	22 per 1000	22 per 1000 (19 to 25)	OR 1.00 (0.87 to 1.16)	35,751 (32 RCTs)	⊕⊕⊕⊕ HIGH	The upper confidence interval of the absolute risk with formoterol and ICS resulted in 3 more adults per 1000 experiencing an SAE compared to ICS treatment alone (i.e. 25 minus 22).
Asthma mortality Follow-up: 26 weeks	No deaths	Pooled risk difference 0.0003 (−0.0007 to 0.0013)	Not estimable	24,022 (31 RCTs)	⊕⊕⊖⊖ LOW [2,3]	There were 3 deaths in the LABA + ICS treatment arm for this outcome.
Asthma-related non-fatal serious adverse events Follow-up: 26 weeks	6 per 1000	5 per 1000 (4 to 7)	OR 0.86 (0.64 to 1.14)	35,158 (30 RCTs)	⊕⊕⊕⊖ MODERATE [3]	The upper confidence interval of the absolute risk with formoterol and ICS resulted in 1 more adults per 1000 experiencing an SAE compared to ICS treatment alone (i.e. 7 minus 6).

***The risk in the intervention group** (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; **ICS:** inhaled corticosteroids; **LABA:** long-acting beta$_2$-agonist; **OR:** odds ratio; **RCT:** randomised controlled trial; **SAE:** serious adverse event

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GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1]We downgraded the evidence for this outcome by 1 due to wide upper confidence interval of the absolute risk.
[2]We downgraded the evidence for this outcome by 1 due to too few events in the ICS treatment arm.
[3]We downgraded the evidence for this outcome by 1 due to lack of independent assessment of causation of SAEs.

Summary of findings 2. Regular formoterol and ICS compared to same-dose ICS in children and adolescents with asthma

Formoterol and ICS compared to same-dose ICS for chronic asthma

Patient or population: children and adolescents with chronic asthma
Intervention: formoterol and ICS
Comparison: same-dose ICS

Setting: community; all were multicentre studies, with 4 studies conducted in the USA and 1 study in the UK. Other studies were conducted in at least 7 countries including Argentina, Australia, Belgium, Brazil, Bulgaria, Czech Republic, Denmark, France, Germany, Hungary, India, Mexico, Poland, Romania, Russian Federation, South Africa, Spain, Switzerland, and Ukraine.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with same-dose ICS	Risk with formoterol and ICS				
All-cause mortality Follow-up: 12.5 weeks	No deaths	No deaths	Pooled risk difference 0.0000 (95% CI −0.0034 to 0.0034)	4035 (10 RCTs)	⊕⊕⊝⊝ LOW [1]	
All-cause non-fatal serious adverse events Follow-up: 12.5 weeks	8 per 1000	11 per 1000 (6 to 21)	OR 1.33 (0.71 to 2.49)	4035 (10 RCTs)	⊕⊕⊕⊝ MODERATE [2]	The upper confidence interval of the absolute risk with formoterol and ICS resulted in 13 more children and adolescents per 1000 experiencing an SAE compared to ICS alone (i.e. 21 minus 8).
Asthma-related mortality Follow-up: 12.5 weeks	No deaths	No deaths	Pooled risk difference 0.0000 (95% CI −0.0034 to 0.0034)	4035 (10 RCTs)	⊕⊕⊝⊝ LOW [1]	

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Asthma-related non-fatal serious adverse events Follow-up: 12.5 weeks	3 per 1000	4 per 1000 (1 to 11)	OR 1.18 (0.40 to 3.51)	4035 (10 RCTs)	⊕⊝⊝⊝ VERY LOW [2, 3, 4]	The upper confidence interval of the absolute risk with formoterol and ICS resulted in 8 more children and adolescents per 1000 experiencing an SAE compared to ICS alone (i.e. 11 minus 3).

*__The risk in the intervention group__ (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; **ICS:** inhaled corticosteroids; **OR:** odds ratio; **RCT:** randomised controlled trial; **SAE:** serious adverse event

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1]We downgraded the evidence for this outcome by 2 due to no deaths and uncertainty of treatment.
[2]We downgraded the evidence for this outcome by 1 due to wide confidence interval.
[3]We downgraded the evidence for this outcome by 1 due to lack of independent assessment of causation of SAEs.
[4]We downgraded the evidence for this outcome by 1 due to unexplained heterogeneity between trial results.

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BACKGROUND

Description of the condition

When asthma is not controlled by low-dose inhaled corticosteroids (ICS) alone, many asthma guidelines recommend the use of additional long-acting beta$_2$-agonists (LABA). Several Cochrane Reviews have addressed the efficacy of LABA in addition to ICS, Ducharme 2010b; Ni Chroinin 2009a, in comparison with placebo (Walters 2007), short-acting beta$_2$-agonists (SABA) (Walters 2002), and leukotriene-receptor antagonists (LTRA) (Ducharme 2011a). The efficacy of LABA compared to increased doses of ICS has also been examined (Ducharme 2010a). The beneficial effects of LABA on lung function, symptoms, quality of life, and exacerbations requiring oral corticosteroids (OCS) have been demonstrated.

Description of the intervention

Two LABAs are currently available for the treatment of asthma: salmeterol and formoterol (also known as eformoterol). These two drugs have shown differences in speed of onset and receptor activity and are used in different ways: salmeterol has a slower onset of action than salbutamol (Beach 1992), and is therefore unsuitable for use as a reliever, whereas formoterol in combination with ICS can be used for maintenance and relief of symptoms (MART). 'The Fenoterol Story' is a reminder that not all beta$_2$-agonists may carry the same risks (Pearce 2007), so in view of the potential differences in adverse effects between salmeterol and formoterol, we have considered the two drugs separately.

How the intervention might work

Much debate has focused on the interaction between ICS and LABA in relation to serious adverse events (SAEs) since the publication of SMART 2006. This study did not randomly assign participants to ICS, nevertheless a subgroup analysis of the results was carried out on the basis of ICS use at baseline. It is tempting to find reassurance from the fact that no statistically significant increase in asthma-related mortality was observed in the subgroup using ICS, but this is not the correct way to test for interaction (Altman 2003), and no assessment was carried out during the trial in relation to the actual use of ICS during the course of the study.

Concern remains that the symptomatic benefit derived from treatment with LABAs might lead to underestimation of attack severity in acute asthma, and could lead to an increase in asthma-related deaths. Furthermore, regular treatment with beta$_2$-agonists can lead to tolerance of their bronchodilator effects, and this phenomenon might be more marked with longer-acting as opposed to shorter-acting compounds (Lipworth 1997). A number of molecular mechanisms have been proposed to explain the possible detrimental effects for people taking beta$_2$-agonists long term, including receptor down-regulation and desensitisation (Giembycz 2006)

Why it is important to do this review

There has been a long-standing controversy over the regular use of beta$_2$-agonists in asthma, which is ongoing. Sears 1986 suggested that excessive use of SABA might have contributed directly or indirectly to an increase in asthma deaths in New Zealand between 1960 and 1980. The authors comment that "most deaths were associated with poor assessment, underestimation of severity and inappropriate treatment (over-reliance on bronchodilators and under-use of systemic corticosteroids), and delays in obtaining help".

Counfounding by severity has been shown by Sears 2009 in data from the RELIEF study, where the rate of asthma-related SAEs was significantly higher in both arms of the study amongst participants taking ICS in comparison with those not taking ICS. This is a serious threat to any conclusions drawn from observational data when the interaction between ICS and formoterol is assessed. Consequently, there is a need to systematically review all available data from controlled trials that randomly assigned participants to regular formoterol in combination with ICS, and to consider all SAEs (fatal and non-fatal), whether or not these are deemed by the investigators to be related to trial medication.

Two systematic reviews have addressed the impact of LABA on all-cause mortality and SAEs. Cates 2008 evaluated salmeterol, and Cates 2012 evaluated formoterol. Both reviews considered LABA that were randomly assigned without additional ICS and described increased risks of non-fatal SAEs.

A review comparing regular salmeterol randomly assigned in combination with ICS (in a single inhaler or in separate inhalers) versus ICS alone has recently been updated (Cates 2018), and an overview of the safety of regular formoterol or salmeterol in children has been published (Cates 2012a).

The focus of this review is on regular formoterol randomly assigned in combination with ICS (in a single inhaler or in separate inhalers) compared with ICS alone. Because of the difficulty involved in deciding whether adverse events are asthma-related, this review focused on studies that captured mortality and SAEs and records both all-cause outcomes and those considered by trial investigators to be asthma-related events.

OBJECTIVES

To assess the risks of mortality and non-fatal SAEs in trials that randomly assign participants with chronic asthma to regular formoterol and inhaled corticosteroid versus the same dose of inhaled corticosteroid alone.

METHODS

Criteria for considering studies for this review

Types of studies

We included parallel-design randomised controlled trials (RCTs), with or without blinding.

Types of participants

We included participants with a clinical diagnosis of asthma of any age group, unrestricted by disease severity or previous or current treatment. We excluded studies on acute asthma and exercise-induced bronchospasm.

Types of interventions

We included studies that compared ICS and formoterol with ICS alone. We included studies where the treatments were taken regularly once or twice daily for a period of ≥ 12 weeks at any dose and delivered by any single or separate

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devices (i.e. chlorofluorocarbon metred-dose inhaler (CFC-MDI), hydrofluoroalkane metred-dose inhaler (HFA-MDI), or dry powder inhaler (DPI)). We included studies where the comparison groups took the same dose and type of inhaled corticosteroid. Co-intervention with leukotriene-receptor antagonists (LTRA), cromones, or theophylline was allowed as long as they were not part of the randomly assigned intervention and were therefore not systematically different between groups.

We excluded studies that randomly assigned participants to formoterol and ICS for intermittent use as a reliever or studies that compared different doses of formoterol or different delivery devices or propellants without a placebo arm. We also excluded studies in which ICS were used in all participants as background treatment (rather than as a randomised intervention).

Types of outcome measures

Primary outcomes

- All-cause mortality.
- All-cause non-fatal SAEs.

Secondary outcomes

- Asthma-related mortality.
- Asthma-related non-fatal SAEs.
- Respiratory-related mortality.
- Respiratory-related non-fatal SAEs.
- Cardiovascular-related mortality.
- Cardiovascular-related non-fatal SAEs.
- Asthma-related non-fatal life-threatening events (intubation or admission to intensive care).
- Respiratory-related non-fatal life-threatening events (intubation or admission to intensive care).

We did not subgroup outcomes according to whether the trial investigators considered them to be related to trial medication.

For the definition of a non-fatal SAE, see Appendix 1.

Search methods for identification of studies

Electronic searches

The previously published version included searches up to August 2012 (see Appendix 2). We updated the search for this version from 2011 to 18 February 2019.

We identified studies from the Cochrane Airways Trials Register (Cochrane Airways 2019), which is maintained by the Information Specialist for the Group. The Cochrane Airways Trials Register contains studies identified from several sources:

- monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL), through the Cochrane Register of Studies;
- weekly searches of MEDLINE Ovid SP 2011 to 18 February 2019;
- weekly searches of Embase Ovid SP 2011 to 18 February 2019;
- monthly searches of PsycINFO Ovid SP 2011 to 18 February 2019;
- monthly searches of CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature) 2011 to 18 February 2019;
- monthly searches of AMED EBSCO (Allied and Complementary Medicine) all years to date;
- handsearches of the proceedings of major respiratory conferences.

Studies contained in the Trials Register are identified through search strategies based on the scope of Cochrane Airways. Details of these strategies, as well as a list of handsearched conference proceedings, are provided in Appendix 3. The search strategy used to identify studies for this review is presented in Appendix 4.

We also searched the following trials registries:

- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov/);
- World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch/).

We searched the Cochrane Airways Trials Register and additional sources to 18 February 2019, with no restriction on language or type of publication.

Searching other resources

We checked the reference lists of all primary studies and review articles for additional references. We checked websites of clinical trial registers for unpublished trial data. We searched relevant manufacturers' websites for study information. We also checked US Food and Drug Administration (FDA) submissions in relation to formoterol. We searched for errata or retractions from included studies published in full text on PubMed (www.ncbi.nlm.nih.gov/pubmed) on 8 April 2019.

Data collection and analysis

Selection of studies

Two review authors (SJ, CJC) independently screened the titles and abstracts of the search results and coded them as 'retrieved' (eligible or potentially eligible/unclear) or 'did not retrieve'. We retrieved the full-text study reports of all potentially eligible studies, and two review authors (SJ, CJC) independently screened them for inclusion, recording the reasons for exclusion of ineligible studies. Any disagreements were resolved through discussion. We identified and excluded duplicates and collated multiple reports of the same study so that each study, rather than each report, was the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table (Moher 2009).

Data extraction and management

For the current update, we used Covidence to extract data and assess risk of bias for each included study (Covidence systematic review software).

We extracted data on characteristics of included studies (methods, participants, interventions, outcomes) and results of the included studies. We contacted sponsors of the included studies for unpublished adverse event data and searched the sponsor's website for further details of adverse events. All-cause SAEs (fatal and non-fatal) were recorded, and in view of the difficulty involved in deciding whether events were asthma-related, details of the cause of death and of SAEs were noted when available. The definition of 'serious adverse events' used in a particular trial was

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recorded, and further information was sought if this was not clear (particularly in relation to hospital admissions and SAEs).

- Methods: study design, total duration of study, details of any 'run-in' period, number of study centres and location, study setting, withdrawals, and date of study.
- Participants: N, mean age, severity of condition, baseline lung function, inclusion criteria and exclusion criteria.
- Interventions: intervention, comparison, concomitant medications, and excluded medications.
- Outcomes: primary and secondary outcomes specified and collected, and time points reported.
- Notes: funding for studies and notable conflicts of interest of trial authors.

Two review authors (SJ, CJC) independently extracted outcome data from the included studies. We noted in the 'Characteristics of included studies' table if outcome data were not reported in a useable way. Any disagreements were resolved by consensus. One review author (SJ) transferred data into the Review Manager 5 file (RevMan 2014). We double-checked that data were entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (CJC) spot-checked study characteristics for accuracy against the study report.

Assessment of risk of bias in included studies

Two review authors (SJ, CJC) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (with assistance from Susan Hansen for the original version of the review) (Higgins 2011). Any disagreements were resolved by discussion. We assessed risk of bias according to the following domains:

- random sequence generation;
- allocation concealment;
- blinding of participants and personnel;
- blinding of outcome assessment;
- incomplete outcome data;
- selective outcome reporting (we considered studies to be at high risk of bias if independent assessment of causation of SAEs was lacking);
- other bias.

We judged each potential source of bias as high, low, or unclear and provided a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. We summarised the 'Risk of bias' judgements across different studies for each of the domains listed. We considered blinding separately for different key outcomes where necessary. Where information on risk of bias related to unpublished data or correspondence with trialists, we noted this in the 'Risk of bias' table.

When considering treatment effects, we took into account the risk of bias for the studies that contributed to that outcome.

Measures of treatment effect

The outcomes used in this review were dichotomous. We recorded the number of participants with one or more outcome events by allocated treated group.

We undertook meta-analyses only where this was meaningful, that is if the treatments, participants, and the underlying clinical question were similar enough for pooling to make sense.

Where multiple trial arms were reported in a single study, we included only the relevant arms. If two comparisons (e.g. low-dose ICS/formoterol versus ICS and high-dose ICS/formoterol versus ICS) were combined in the same meta-analysis, we combined the active arms or halved the control group in order to avoid double-counting.

We used intention-to-treat or 'full analysis set' analyses where they were reported (i.e. analyses where data had been imputed for participants who were randomly assigned but did not complete the study) instead of completer or per-protocol analyses.

Unit of analysis issues

We confined our analysis to participants with one or more SAEs, rather than focusing on the number of events that occurred (as the latter is not independent when one participant experiences multiple events, and a single SAE may be recorded under several different categories).

Dealing with missing data

We contacted investigators or study sponsors in order to verify key study characteristics and to obtain missing numerical outcome data where possible (e.g. when a study was identified as an abstract only). Where this was not possible, and the missing data were thought to introduce serious bias, we took this into consideration in the GRADE assessment for affected outcomes.

Assessment of heterogeneity

We used the I^2 statistic to measure heterogeneity amongst the studies in each analysis employing the following criteria (Higgins 2011):

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

In the case of substantial heterogeneity, we reported it and explored the possible causes by prespecified subgroup analysis.

Assessment of reporting biases

We obtained full data on all-cause mortality and SAEs. Where data for asthma-related SAEs were not reported, we judged studies as 'high risk', and 'unclear risk' if the information provided by the authors or sponsors was insufficient. Upon pooling of more than 10 studies, we created and examined a funnel plot to explore possible small-study and publication biases.

Data synthesis

The outcomes of this review were dichotomous, and we recorded the numbers of participants with at least one outcome event by allocated treated group. We calculated Peto odds ratios (ORs) and risk differences (RDs). The Peto OR is advantageous when events are rare, as no adjustment for zero cells is required (Bradburn 2007). In view of the low number of events and the high proportion of zero cells, we considered this specific property to be more important than potential problems with unbalanced treatment arms and large

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effect sizes associated with this method. The primary analysis of results for SAE outcomes was conducted in Review Manager 5 using the Peto method, and the Mantel-Haenszel method was used as a sensitivity analysis. We used a random-effects model and performed a sensitivity analysis with a fixed-effect model if required.

Subgroup analysis and investigation of heterogeneity

We undertook subgroup analyses on the basis of participant age (adults versus children) and the dose of formoterol used (usual dose versus high dose). We also carried out subgroup analyses comparing the different types of ICS now included in this review, and had sufficient data to divide budesonide into high dose (800 µg daily) and moderate dose (400 µg or less daily) in adults. We made subgroup comparisons using tests for interaction (Altman 2003). We were unable to carry out planned subgroups based on asthma severity (see Differences between protocol and review).

Sensitivity analysis

We carried out sensitivity analyses to assess the impact of the method used to combine study events (RD, Peto OR, and Mantel-Haenszel OR). We included the degree of bias protection as part of the sensitivity analysis (with an emphasis on independent outcome assessment for the asthma-related events). We also included a post hoc sensitivity analysis excluding the results from studies in which formoterol and ICS were administered in separate inhalers.

'Summary of findings' tables

We assessed the certainty of the evidence for all-cause mortality, all-cause non-fatal SAEs, and asthma-related SAEs. Assessments were conducted according to recommendations put forth by the GRADE Working Group and are presented in Summary of findings for the main comparison for adults Summary of findings 2 for children and adolescents for key outcomes (all-cause mortality, asthma-related mortality, all-cause non-fatal SAEs, and asthma-related SAEs).

We created our 'Summary of findings' tables using the following outcomes: all-cause mortality, all-cause non-fatal SAEs, asthma-related mortality, and asthma-related non-fatal SAEs. We used the five GRADE considerations (risk of bias, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence relating to the studies that contributed data for the prespecified outcomes. We used the methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), employing GRADEpro GDT software (GRADEpro GDT). We justified all decisions to downgrade the certainty of evidence using footnotes and made comments to aid the reader's understanding of the review where necessary.

RESULTS

Description of studies

Results of the search

We included a total of 27 trials from the previous version of this review (21 trials included in the 2008 update, and a further six trials from the 2012 update search) (Cates 2012). The current update covers the period from 2011 to 2019. We identified a further 454 abstracts, of which 48 were considered as potentially relevant to this review. Full-text assessment led to the inclusion of 33 studies that met the inclusion criteria. Fifteen of the 33 studies were identified as new trials (Corren 2013; EudraCT 2010-020602-14-DE; Matsunaga 2013; Murphy 2015; Nathan 2012; NCT01475032; Paggiaro 2016; Pearlman 2013; Pearlman 2017; Pertseva 2013; Peters 2016; Ploszczuk 2014; Samson 2012; Stirbulov 2012; Weinstein 2019). The remaining 18 studies included 16 additional references for the 15 new trials (13 conference abstracts, two ClinicalTrials.gov references, and one further publication for Ploszczuk 2014), and two ongoing trials (Ongoing studies),

Twelve of the 15 trials included adults taking regular formoterol in combination with either beclomethasone, budesonide, fluticasone, or mometasone (Corren 2013; EudraCT 2010-020602-14-DE; Matsunaga 2013; Murphy 2015; Nathan 2012; Paggiaro 2016; Pearlman 2013; Pertseva 2013; Peters 2016; Samson 2012; Stirbulov 2012; Weinstein 2019). The remaining three trials of formoterol in combination with either budesonide or fluticasone involved children (NCT01475032; Pearlman 2017; Ploszczuk 2014).

Three of the trials in adults did not report outcome data, and although they met the inclusion criteria, they were not included in the analyses (Paggiaro 2016; Samson 2012; Stirbulov 2012).

With the studies from the previous updates and current update, we have included a total of 42 trials (Characteristics of included studies), of which 39 are included in the analyses (Figure 1).

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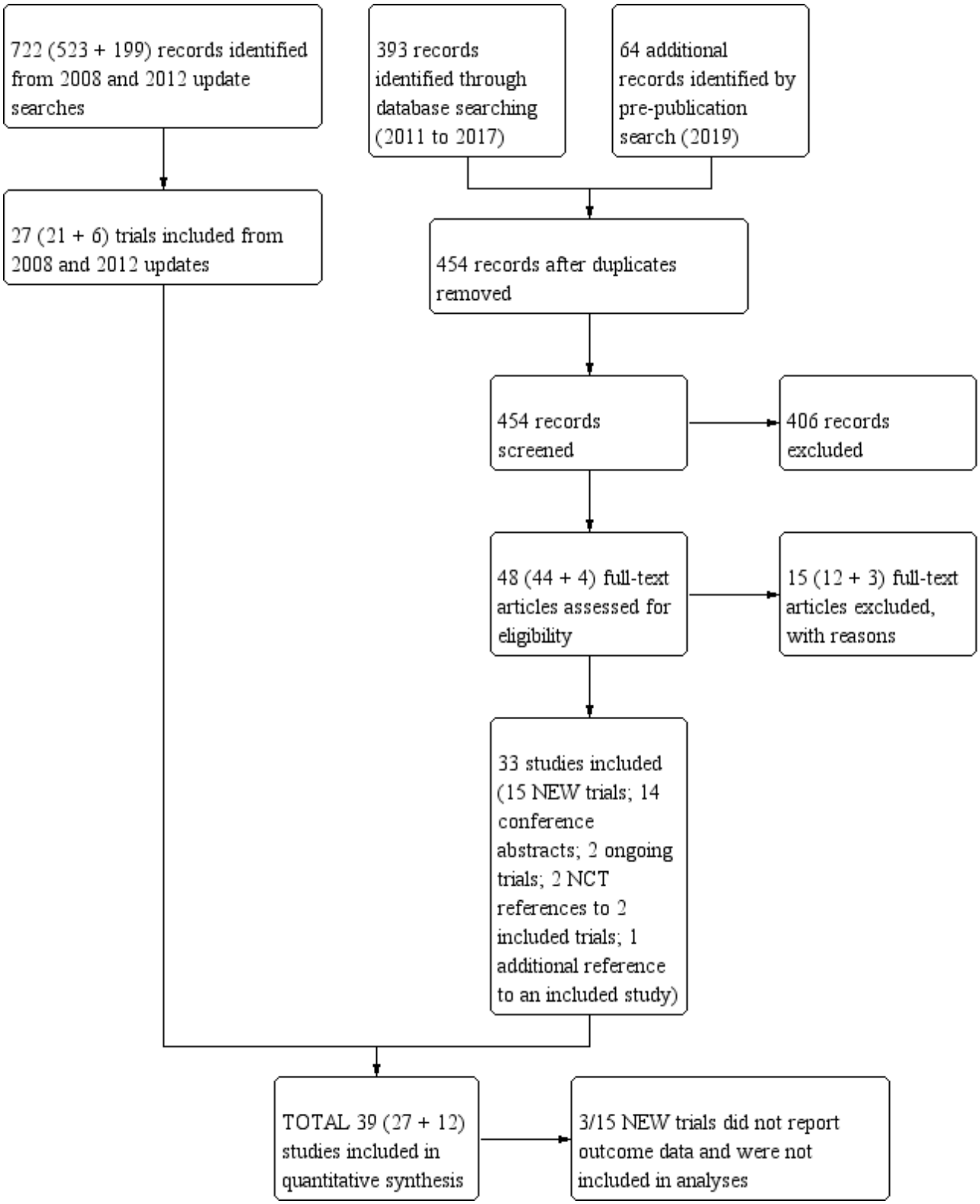
Figure 1. Study flow diagram: review update.



Included studies

The 42 studies included in this review are described in detail in Characteristics of included studies, and a summary of the daily metered dose of beclomethasone, budesonide, fluticasone, or mometasone in addition to formoterol used in each trial is provided in Table 1 for adults and Table 2 for children. To avoid confusion, all delivered doses in these tables have been converted to an equivalent metered dose (so budesonide/formoterol (Symbicort)

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320/9 µg is a delivered dose that is equivalent to a metered dose of budesonide 400 µg and formoterol 12 µg).

Table 1 and Table 2 also indicate whether each study randomly assigned participants to once- or twice-daily formoterol; used combined or separate inhalers; and delivered the medication using dry powder inhaler (DPI) or pressurised metred-dose inhalers (pMDIs). Some trials had more than two arms and so featured more than one option in each of these cases. Because OPTIMA (O'Byrne 2001), FACET (Pauwels 1997), and Peters 2016 randomly assigned participants to higher and lower doses of budesonide, each has been considered as two separate comparisons.

All the trials on beclomethasone and formoterol were sponsored by Chiesi Farmaceutica (EudraCT 2010-020602-14-DE; NCT01475032; Paggiaro 2016); trials on budesonide and formoterol were sponsored or supported by AstraZeneca, Ache Laboratorios Farmaceuticos, the Japanese Society for the Promotion of Science, and Medical University of Lodz (Brown 2012; Buhl 2003; Chuchalin 2002; Corren 2007; D5896C00001; Jenkins 2006; Kuna 2006; Matsunaga 2013; Morice 2007; Morice 2008; Murphy 2015; Noonan 2006; O'Byrne 2001; Pauwels 1997; Pearlman 2017; Peters 2008; Pohunek 2006; Price 2002; SD-039-0714; SD-039-0718; SD-039-0719; SD-039-0725; SD-039-0726; Stirbulov 2012; Tal 2002; Zetterstrom 2001); and all the trials on mometasone and formoterol were sponsored by Merck or Schering-Plough (Meltzer 2012; Nathan 2010; Weinstein 2010; Weinstein 2019). Trials on fluticasone and formoterol were sponsored by Mundipharma Research Ltd, Skyepharma, and Skyepharma/Abbott Respiratory LLC (Corren 2013; Nathan 2010; Pearlman 2013; Pertseva 2013; Ploszczuk 2014).

Adults

We included 29 trials with a total of 37,984 adults (aged 12 years and over) (Brown 2012; Buhl 2003; Chuchalin 2002; Corren 2007; Corren 2013; D5896C00001; EudraCT 2010-020602-14-DE; Jenkins 2006; Kuna 2006; Matsunaga 2013; Meltzer 2012; Morice 2007; Murphy 2015; Nathan 2010; Nathan 2012; Noonan 2006; O'Byrne 2001; Paggiaro 2016; Pauwels 1997; Pearlman 2013; Pertseva 2013; Peters 2008; Peters 2016; Price 2002; Samson 2012; SD-039-0714; SD-039-0726; Spector 2012; Stirbulov 2012; Weinstein 2010; Weinstein 2019; Zangrilli 2011; Zetterstrom 2001). Eleven of these trials enrolled adults aged 18 years and over (Buhl 2003; Chuchalin 2002; Kuna 2006; Matsunaga 2013; O'Byrne 2001; Paggiaro 2016; Pauwels 1997; Samson 2012; Stirbulov 2012; Weinstein 2010; Zetterstrom 2001).

Participants mostly had forced expiratory volume in 1 second (FEV_1) < 80% predicted. The mean age of participants was 34 years (so although small numbers of adolescents may have been included, we have reported these as adult studies). None of these studies reported separate results for adolescents, so all participants in these studies have been analysed as adults.

The weighted mean duration of the adult trials was 26 weeks. The daily metered dose of formoterol used ranged from 12 to 24 µg, with the exception of Jenkins 2006 and Peters 2008, who used 48 µg daily (which remains within the licensed daily dosage range). The daily metered doses of beclomethasone were 800 µg; budesonide ranged from 200 to 1600 µg; fluticasone ranged from 200 to 500 µg; and mometasone from 200 to 800 µg (see Table 1).

Children and adolescents

We included 10 trials in children and adolescents, which involved 4035 participants in the following age ranges: Morice 2008, 6 to 11 years old; NCT01475032, 2 to 11; Pearlman 2017, 6 to 12; Ploszczuk 2014, 5 to 12; Pohunek 2006, 4 to 11; SD-039-0714, 11 to 17; SD-039-0718, 6 to 15; SD-039-0719, 6 to 11; SD-039-0725, 6 to 15; and Tal 2002, 4 to 17. In all studies, the mean age of participants was younger than 18 years and mostly had FEV_1 < 80% predicted.

The weighted mean duration of studies of children and adolescents was 12.5 weeks. The daily metered dose of formoterol was 12 to 24 µg. The daily metered dose of budesonide was 200 to 400 µg, and fluticasone daily dose was 200 µg (see Table 2).

Excluded studies

We excluded 74 studies with reasons described in Characteristics of excluded studies.

Risk of bias in included studies

An overview of the risk of bias in individual studies is provided in Figure 2; support for judgements in individual studies are shown in Characteristics of included studies.

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

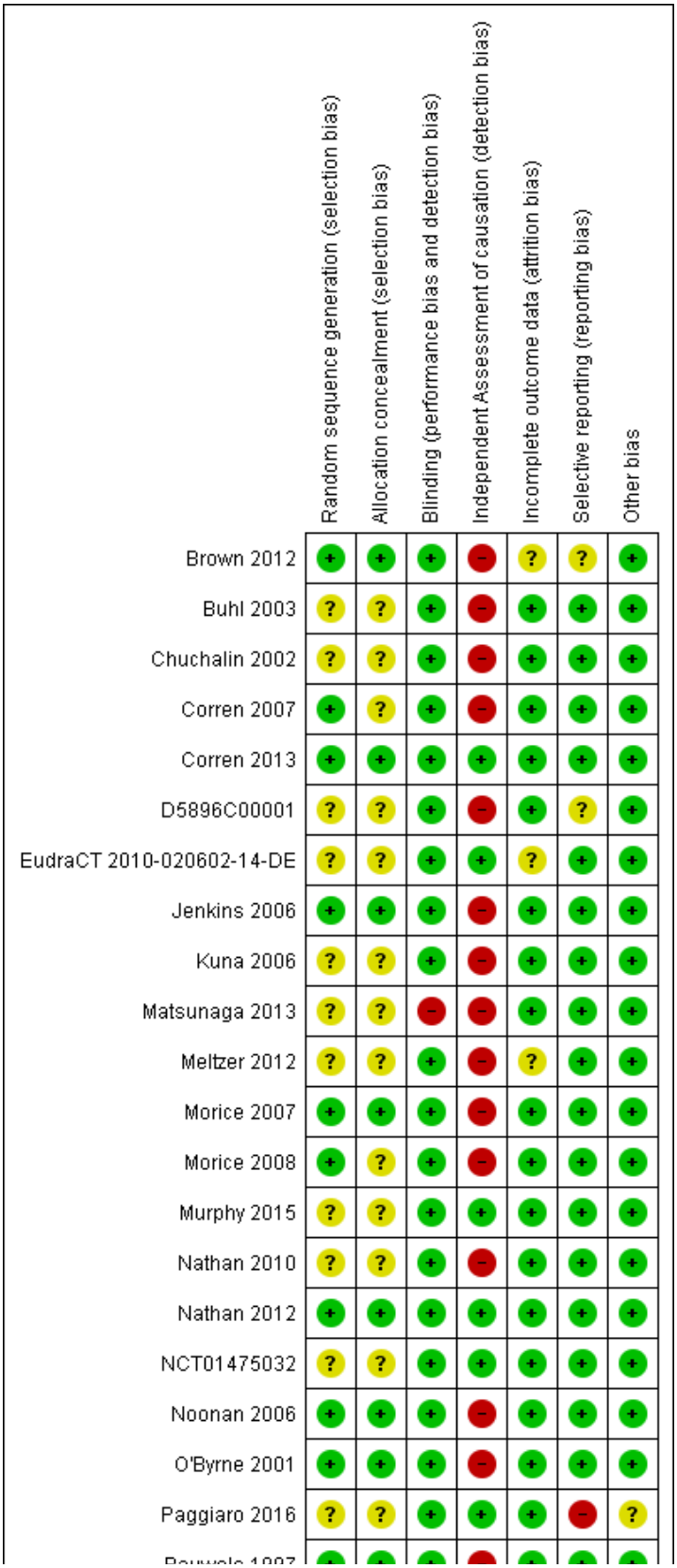

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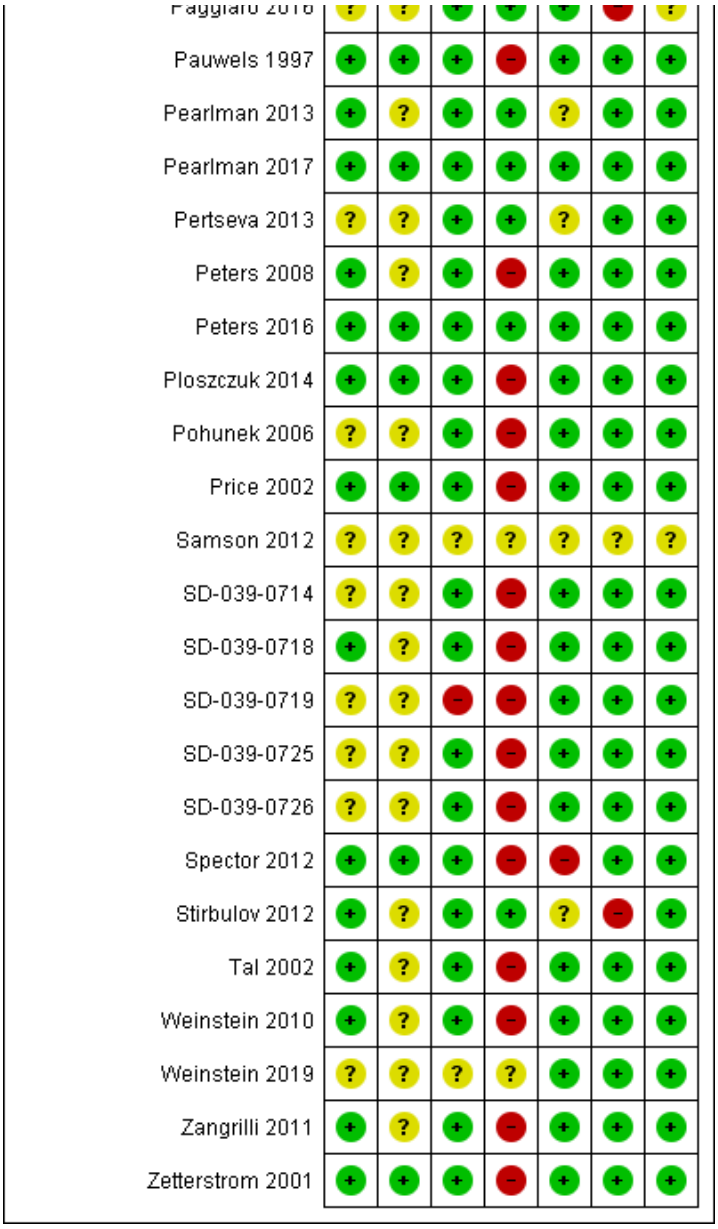
Figure 2. (Continued)



Allocation

We assessed 23 studies as at low risk of bias for random sequence generation and 15 studies as at low risk of bias for allocation concealment. We found limited information available from paper publications or web reports on sequence generation or allocation concealment, but have considered that this is unlikely to be a source of bias because the studies were sponsored, and standard methodology would have been used to minimise the risk of selection bias. We therefore judged the risk of selection bias as low, although sequence generation and allocation concealment are marked as unclear in many of the studies in Figure 2.

Blinding

All of the studies were double-blind with the exception of Matsunaga 2013 and SD-039-0719, both of which were open-label studies. We regarded the overall risk of performance and detection bias as low for the all-cause events.

Independent outcome assessment (detection bias)

We were concerned that bias might have been introduced in the attribution of asthma as the cause of serious events, as this was not independently assessed in some of the included studies. Although the trials were double-blind, formoterol can have a big impact on asthma symptoms, and those who decided on the cause of the events may have guessed which treatment was being given.

Incomplete outcome data

The rate of withdrawals and dropouts was clearly reported and was generally less than 20% for randomly assigned participants; these rates were similar in the arms of each study. However, Spector 2012

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reported more withdrawals on budesonide alone (34% compared with 24% on combination treatment), so we judged this study to be at high risk of attrition bias.

Selective reporting

Data were obtained from or provided by the sponsor for fatal and non-fatal SAEs by treatment group and causation for all studies, except for Paggiaro 2016; Samson 2012; Stirbulov 2012, which did not include details of either all-cause or asthma-related SAEs.

Other potential sources of bias

The majority of included studies were sponsored by manufacturers of combination products, but we did not regard sponsorship as necessarily increasing the risk of bias when studies were well designed.

Effects of interventions

See: **Summary of findings for the main comparison** Regular formoterol and ICS compared to same-dose ICS in adults with asthma; **Summary of findings 2** Regular formoterol and ICS compared to same-dose ICS in children and adolescents with asthma

Primary outcomes

All-cause mortality

Adults

We included 29 studies in the analysis (participants = 35,751). Three studies compared low- and high-dose formoterol plus ICS with ICS alone (O'Byrne 2001; Pauwels 1997; Peters 2016). In the analysis, each treatment dose from the three studies was reported separately (resulting in 32 estimates of treatment effect), and the number of participants in the ICS only treatment group was halved (when necessary) to avoid double-counting.

Seventeen deaths were reported in 18,645 participants taking formoterol with ICS, and 13 deaths occurred out of 17,106 participants taking ICS alone. These trials were combined with the use of the Peto odds ratio (as no continuity correction for zero cells is required). The Peto OR of all-cause mortality with formoterol was 1.25 (95% confidence interval (CI) 0.61 to 2.56; 29 studies; 35, 751 participants ; I^2 = 0%; Figure 3; Analysis 1.1; Table 3). This means that for every 1000 adults treated for 26 weeks, one death occurred on ICS alone, and the corresponding risk for formoterol and ICS was also one death (95% CI 0 to 2). We assessed this evidence as of moderate certainty because only 30 deaths occurred in total across all of the trials (Summary of findings for the main comparison). We were, therefore, unable to conclude with high certainty that regular formoterol with ICS is as safe as regular ICS alone.

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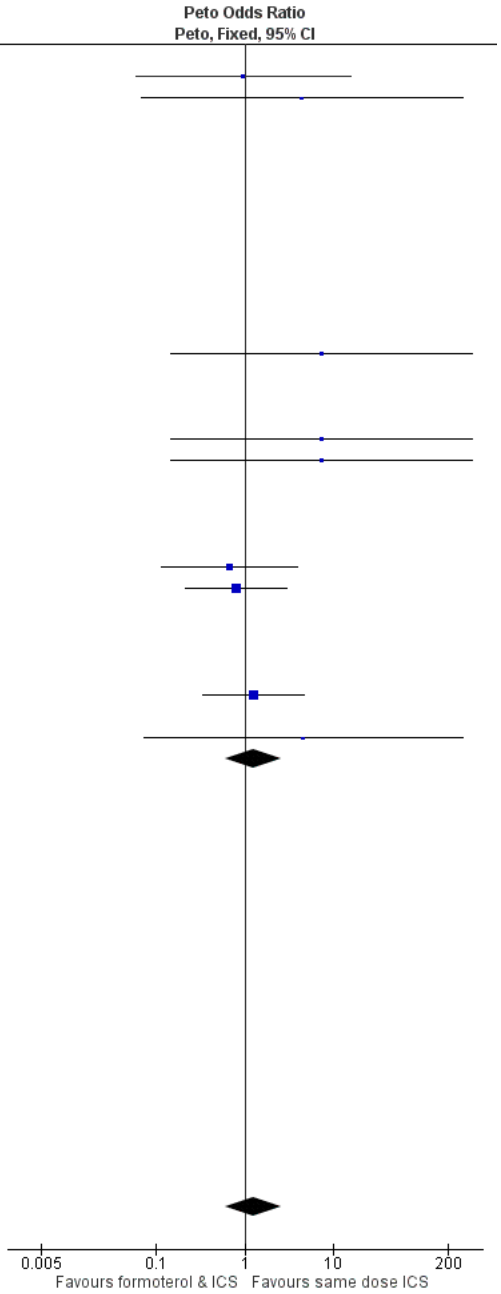
Figure 3. Forest plot of comparison: 1 Formoterol and ICS versus same-dose ICS, outcome: 1.1 All-cause mortality.

Study or Subgroup	Formoterol and ICS Events	Formoterol and ICS Total	Same dose ICS Events	Same dose ICS Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.1.1 Adults						
Brown 2012	1	377	1	364	6.7%	0.97 [0.06, 15.47]
Buhl 2003	1	352	0	171	3.0%	4.42 [0.07, 288.27]
Chuchalin 2002	0	111	0	114		Not estimable
Corren 2007	0	123	0	121		Not estimable
Corren 2013	0	110	0	113		Not estimable
D5896C00001	0	312	0	153		Not estimable
EudraCT 2010-020602-14-DE	0	192	0	184		Not estimable
Jenkins 2006	0	341	0	115		Not estimable
Kuna 2006	0	409	0	207		Not estimable
Matsunaga 2013	0	15	0	15		Not estimable
Meltzer 2012	0	182	0	188		Not estimable
Morice 2007	0	462	0	217		Not estimable
Murphy 2015	0	71	0	143		Not estimable
Nathan 2010	1	191	0	192	3.4%	7.43 [0.15, 374.34]
Nathan 2012	0	115	0	117		Not estimable
Noonan 2006	0	239	0	109		Not estimable
O'Byrne 2001 (1)	0	315	0	312		Not estimable
O'Byrne 2001 (2)	1	554	0	550	3.4%	7.34 [0.15, 369.72]
Pauwels 1997 (3)	1	215	0	214	3.4%	7.35 [0.15, 370.66]
Pauwels 1997 (4)	0	210	0	213		Not estimable
Pearlman 2013	0	119	0	119		Not estimable
Pertseva 2013	0	146	0	292		Not estimable
Peters 2008	0	443	0	133		Not estimable
Peters 2016 (5)	2	1645	3	1646	16.8%	0.67 [0.12, 3.87]
Peters 2016 (6)	4	4201	5	4201	30.2%	0.80 [0.22, 2.96]
Price 2002	0	250	0	255		Not estimable
SD-039-0726	0	301	0	145		Not estimable
Spector 2012	0	156	0	155		Not estimable
Weinstein 2010	0	255	0	240		Not estimable
Weinstein 2019	5	5868	4	5861	30.2%	1.25 [0.34, 4.61]
Zangrilli 2011	0	127	0	123		Not estimable
Zetterstrom 2001	1	238	0	124	3.0%	4.58 [0.07, 284.60]
Subtotal (95% CI)		**18645**		**17106**	**100.0%**	**1.25 [0.61, 2.56]**
Total events	17		13			
Heterogeneity: Chi² = 4.06, df = 8 (P = 0.85); I² = 0%						
Test for overall effect: Z = 0.60 (P = 0.55)						
1.1.2 Children and adolescents						
Morice 2008	0	415	0	207		Not estimable
NCT01475032	0	421	0	213		Not estimable
Pearlman 2017	0	183	0	90		Not estimable
Ploszczuk 2014	0	168	0	172		Not estimable
Pohunek 2006	0	417	0	213		Not estimable
SD-039-0714	0	136	0	134		Not estimable
SD-039-0718	0	128	0	145		Not estimable
SD-039-0719	0	123	0	63		Not estimable
SD-039-0725	0	352	0	169		Not estimable
Tal 2002	0	148	0	138		Not estimable
Subtotal (95% CI)		**2491**		**1544**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**21136**		**18650**	**100.0%**	**1.25 [0.61, 2.56]**
Total events	17		13			
Heterogeneity: Chi² = 4.06, df = 8 (P = 0.85); I² = 0%						
Test for overall effect: Z = 0.60 (P = 0.55)						
Test for subgroup differences: Not applicable						



Footnotes
(1) 800 µg budesonide +12 µg formoterol versus 800 µg budesonide
(2) 400 µg budesonide + 12 µg formoterol versus 400 µg budesonide
(3) 400 µg budesonide + 12 µg formoterol twice daily (9 µg delivered dose) versus 400 µg budesonide
(4) 100 µg budesonide + 12 µg formoterol twice daily (9 µg delivered dose) versus 100 µg budesonide
(5) 400 µg budesonide + 24 µg formoterol versus 400 µg budesonide daily
(6) 800 µg budesonide + 24 µg formoterol versus 800 µg budesonide daily

Reports on the cause of each death are documented in Table 4.

Children and adolescents

No deaths were reported in trials on children and adolescents treated with formoterol and ICS or ICS alone (Figure 3; Analysis 1.1). As it was not possible to calculate the OR from the data, we used the pooled risk difference (RD) to assess the data (RD 0.0000, 95% CI −0.0034 to 0.0034; 10 studies; 4035 participants) (Table 5). This means that for every 1000 children treated with formoterol and ICS for 12.5 weeks, the 95% CI was compatible with a possible increase or decrease of three deaths. We assessed this evidence as of low certainty because no deaths were reported across the trials (Summary of findings 2; Figure 3). We were unable to conclude that regular formoterol with ICS is as safe as regular ICS alone in terms

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of mortality, but the fact that there were no deaths is reassuring in terms of low mortality risks in trials on children in both groups.

The test for subgroup interaction between adults and children was not possible as there were no deaths in children.

All-cause non-fatal serious adverse events

A non-fatal SAE is generally defined as an event that falls into any of the following categories.

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

This is further explained in Appendix 1, and AstraZeneca has confirmed that this definition was used in its included trials (even though this often was not made explicit in the paper reports).

Adults

We included 29 studies in the analysis (35,751 participants). Three studies compared low- and high-dose formoterol plus ICS with a placebo treatment (O'Byrne 2001; Pauwels 1997; Peters 2016). In the analysis, each treatment dose from the three studies was reported separately (resulting in 32 estimates of treatment effect).

The number of adults experiencing one or more non-fatal SAEs was very similar when formoterol was randomly assigned with ICS in comparison with ICS alone. One or more non-fatal SAEs occurred in 401 out of 18,645 (2.1%) participants on regular formoterol with ICS and in 369 out of 17,106 (2.1%) participants on ICS alone. The Peto OR was 1.00 (95% CI 0.87 to 1.16; 29 studies; 35,751 participants; $I^2 = 0\%$; Figure 4; Analysis 1.2). For every 1000 adults treated for 26 weeks, 22 on ICS alone experienced an SAE; the corresponding risk for formoterol and ICS was also 22 (95% CI 19 to 25; Summary of findings for the main comparison). We assessed this evidence as of high certainty. The 95% CI for the absolute risk with formoterol and ICS indicates that, at most, three extra or three less adults per 1000 people may experience a non-fatal SAE compared to ICS alone.

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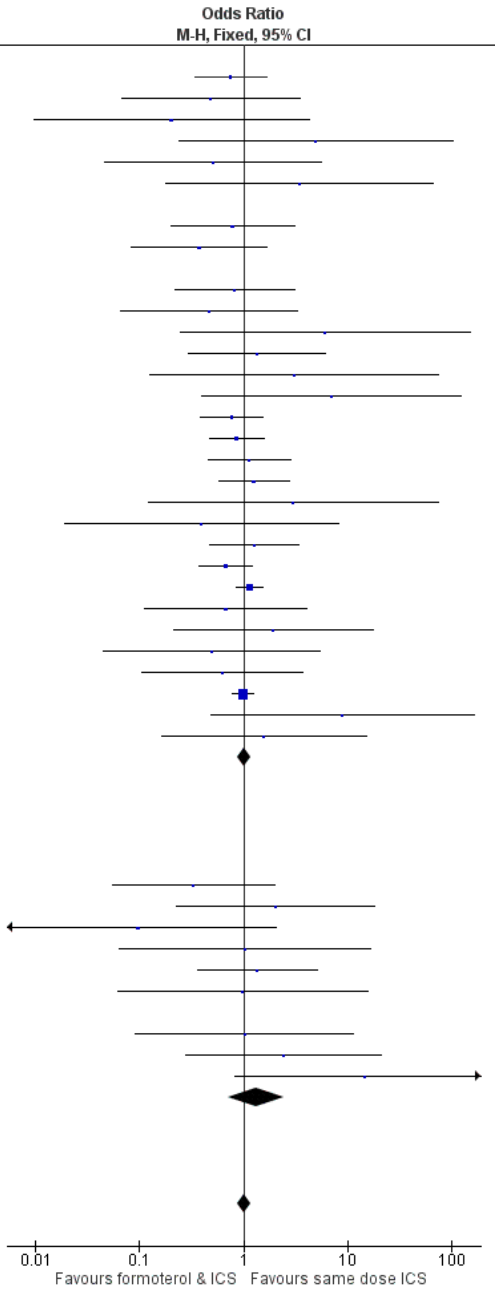
Figure 4. Forest plot of comparison: 1 Formoterol and ICS versus same-dose ICS (Peto OR), outcome: 1.2 All-cause non-fatal serious adverse events.

Study or Subgroup	Formoterol and ICS Events	Formoterol and ICS Total	Same dose ICS Events	Same dose ICS Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.2.1 Adults						
Brown 2012	11	377	14	364	3.6%	0.75 [0.34, 1.68]
Buhl 2003	2	352	2	171	0.7%	0.48 [0.07, 3.46]
Chuchalin 2002	0	111	2	114	0.6%	0.20 [0.01, 4.25]
Corren 2007	2	123	0	121	0.1%	5.00 [0.24, 105.24]
Corren 2013	1	110	2	113	0.5%	0.51 [0.05, 5.70]
D5896C00001	3	312	0	153	0.2%	3.47 [0.18, 67.64]
EudraCT 2010-020602-14-DE	0	192	0	184		Not estimable
Jenkins 2006	7	341	3	115	1.1%	0.78 [0.20, 3.08]
Kuna 2006	3	409	4	207	1.4%	0.38 [0.08, 1.69]
Matsunaga 2013	0	15	0	15		Not estimable
Meltzer 2012	4	182	5	188	1.2%	0.82 [0.22, 3.11]
Morice 2007	2	462	2	217	0.7%	0.47 [0.07, 3.34]
Murphy 2015	1	71	0	143	0.1%	6.11 [0.25, 151.81]
Nathan 2010	4	191	3	192	0.8%	1.35 [0.30, 6.10]
Nathan 2012	1	115	0	117	0.1%	3.08 [0.12, 76.36]
Noonan 2006	7	239	0	109	0.2%	7.06 [0.40, 124.81]
O'Byrne 2001 (1)	15	315	19	312	4.7%	0.77 [0.38, 1.55]
O'Byrne 2001 (2)	20	554	23	550	5.7%	0.86 [0.47, 1.58]
Pauwels 1997 (3)	10	210	9	213	2.2%	1.13 [0.45, 2.85]
Pauwels 1997 (4)	15	215	12	214	2.9%	1.26 [0.58, 2.76]
Pearlman 2013	1	119	0	119	0.1%	3.03 [0.12, 75.02]
Pertseva 2013	0	146	2	292	0.4%	0.40 [0.02, 8.31]
Peters 2008	21	443	5	133	1.9%	1.27 [0.47, 3.45]
Peters 2016 (5)	19	1645	28	1646	7.1%	0.68 [0.38, 1.21]
Peters 2016 (6)	100	4201	87	4201	21.9%	1.15 [0.86, 1.54]
Price 2002	2	250	3	255	0.8%	0.68 [0.11, 4.09]
SD-039-0726	4	301	1	145	0.3%	1.94 [0.21, 17.51]
Spector 2012	1	156	2	155	0.5%	0.49 [0.04, 5.50]
Weinstein 2010	2	255	3	240	0.8%	0.62 [0.10, 3.77]
Weinstein 2019	136	5868	137	5861	34.5%	0.99 [0.78, 1.26]
Zangrilli 2011	4	127	0	123	0.1%	9.00 [0.48, 168.95]
Zetterstrom 2001	3	238	1	124	0.3%	1.57 [0.16, 15.25]
Subtotal (95% CI)		**18645**		**17106**	**95.5%**	**1.00 [0.87, 1.16]**
Total events	401		369			
Heterogeneity: Chi² = 18.47, df = 29 (P = 0.93); I² = 0%						
Test for overall effect: Z = 0.05 (P = 0.96)						
1.2.2 Children and adolescents						
Morice 2008	2	415	3	207	1.0%	0.33 [0.05, 1.99]
NCT01475032	4	421	1	213	0.3%	2.03 [0.23, 18.31]
Pearlman 2017	0	183	2	90	0.9%	0.10 [0.00, 2.03]
Ploszczuk 2014	1	168	1	172	0.3%	1.02 [0.06, 16.51]
Pohunek 2006	8	417	3	213	1.0%	1.37 [0.36, 5.21]
SD-039-0714	1	136	1	134	0.3%	0.99 [0.06, 15.91]
SD-039-0718	0	128	0	145		Not estimable
SD-039-0719	2	123	1	63	0.3%	1.02 [0.09, 11.52]
SD-039-0725	5	352	1	169	0.3%	2.42 [0.28, 20.88]
Tal 2002	7	148	0	138	0.1%	14.68 [0.83, 259.54]
Subtotal (95% CI)		**2491**		**1544**	**4.5%**	**1.33 [0.71, 2.49]**
Total events	30		13			
Heterogeneity: Chi² = 8.41, df = 8 (P = 0.39); I² = 5%						
Test for overall effect: Z = 0.88 (P = 0.38)						
Total (95% CI)		**21136**		**18650**	**100.0%**	**1.02 [0.89, 1.17]**
Total events	431		382			
Heterogeneity: Chi² = 26.90, df = 38 (P = 0.91); I² = 0%						
Test for overall effect: Z = 0.26 (P = 0.80)						
Test for subgroup differences: Chi² = 0.72, df = 1 (P = 0.40), I² = 0%						



Footnotes
(1) 800 µg budesonide +12 µg formoterol versus 800 µg budesonide
(2) 400 µg budesonide + 12 µg formoterol versus 400 µg budesonide
(3) 100 µg budesonide + 12 µg formoterol twice daily (9 µg delivered dose) versus 100 µg budesonide
(4) 400 µg budesonide + 12 µg formoterol twice daily (9 µg delivered dose) versus 400 µg budesonide
(5) 400 µg budesonide + 24 µg formoterol versus 400 µg budesonide daily
(6) 800 µg budesonide + 24 µg formoterol versus 800 µg budesonide daily

Children and adolescents

More children and adolescents randomised to formoterol and ICS reported non-fatal SAEs, but the OR was not statistically significant. Non-fatal SAEs were reported amongst 30 out of 2491 children and adolescents (1.2%) on regular formoterol and ICS compared to 13 out of 1544 (0.8%) children and adolescents randomised to ICS alone.

The OR was 1.33 (95% CI 0.71 to 2.49; 10 studies; 4035 participants; ; I^2 = 5%; Analysis 1.2). For every 1000 children and adolescents treated for 12.5 weeks, 8 children experienced an SAE on ICS alone; the corresponding risk on formoterol and ICS was 11 children and

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adolescents (95% CI 6 to 21). We assessed this evidence as of moderate certainty because the 95% CI showed that there were up to 13 more, or two less children and adolescents on formoterol and ICS who may suffer an SAE in comparison with 8 per 1000 on ICS alone (Summary of findings 2).

The test for subgroup interaction between adults and children and adolescents did not find a significant impact of age on treatment effect during analysis as Peto OR (test for subgroup differences: $Chi^2 = 0.72$, df = 1, P = 0.40, $I^2 = 0\%$; see Figure 4; Analysis 1.2).

Secondary outcomes

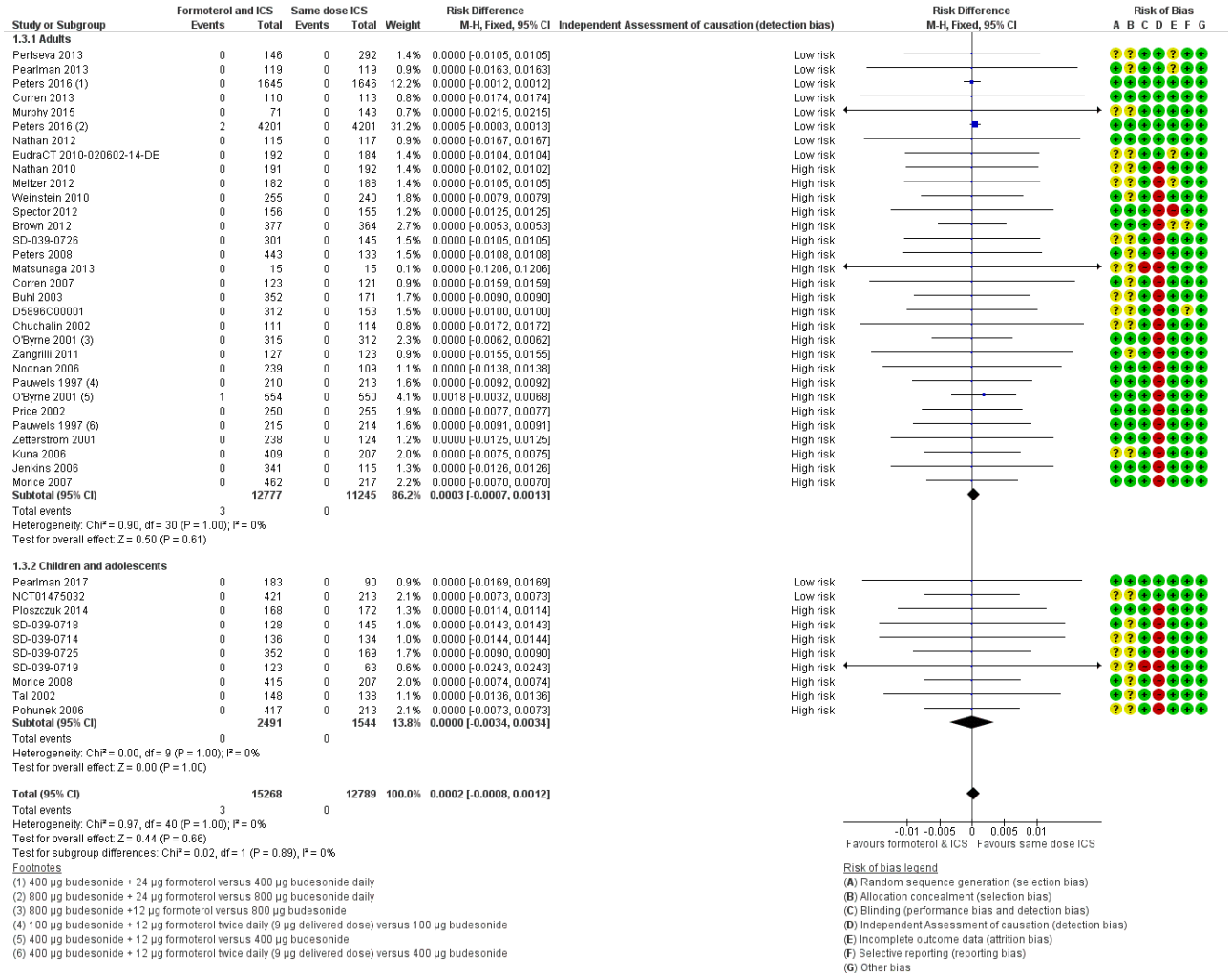
Asthma-related mortality

Adults

Twenty-eight studies involving 24,022 adults reported the number of asthma-related deaths. One study did not report this outcome and was not included in the analysis (Meltzer 2012). Three studies compared low- and high-dose formoterol plus ICS with a placebo treatment (O'Byrne 2001; Pauwels 1997; Peters 2016). In the analysis, each treatment dose from the three studies was reported separately (resulting in 31 estimates of treatment effect).

Although it was not originally reported as an asthma-related death in the trial report, one death in O'Byrne 2001 (OPTIMA) was subsequently attributed to status asthmaticus and septic shock in a subsequent meta-analysis (Sears 2009). The full report on the cause of death provided by the sponsors stated: "One of the deaths occurred in a 35 year old female after an 8 day hospitalisation for a severe asthma attack leading to intubation, ventilation, and nosocomial pneumonia with septic shock". Two deaths occurred in Peters 2016, which were also attributed to asthma in the high-dose budesonide/formoterol arm (Figure 5; Analysis 1.3; Table 4). There were, therefore, three asthma-related deaths in the formoterol and ICS treatment arm across all of the studies. We analysed the data using the pooled RD (as most studies had no deaths in either arm); the pooled RD was 0.0003 (95% CI −0.0007 to 0.0013; 28 studies; 24,022 participants; $I^2 = 0\%$) at 26 weeks. This means that for every 1000 adults, there was a maximum of one more death potentially attributed to formoterol and ICS compared with ICS alone (Summary of findings for the main comparison). We assessed this evidence as of low certainty because there were only a total of three deaths due to asthma and because of imprecision. We were, therefore, unable to determine with certainty whether formoterol with ICS is as safe as regular ICS alone.

Figure 5. Forest plot of comparison: 1 Formoterol and ICS versus same-dose ICS (Peto OR), outcome: 1.3 Asthma mortality.



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Children and adolescents

No asthma-related deaths occurred amongst 4035 children and adolescents either on formoterol and ICS or ICS alone at 12.5 weeks. We analysed the data using the pooled RD, which was 0.0000 (95% CI −0.0034 to 0.0034) (Figure 5; Analysis 1.3; Table 4). We assessed this evidence as of low certainty because there were no deaths from asthma in children and adolescents (Summary of findings 2).

The test for subgroup interaction between adults and children and adolescents did not find a significant impact of age on treatment effect during analysis as RD (test for subgroup differences: Chi^2 = 0.02, df = 1, P = 0.89, I^2 = 0%).

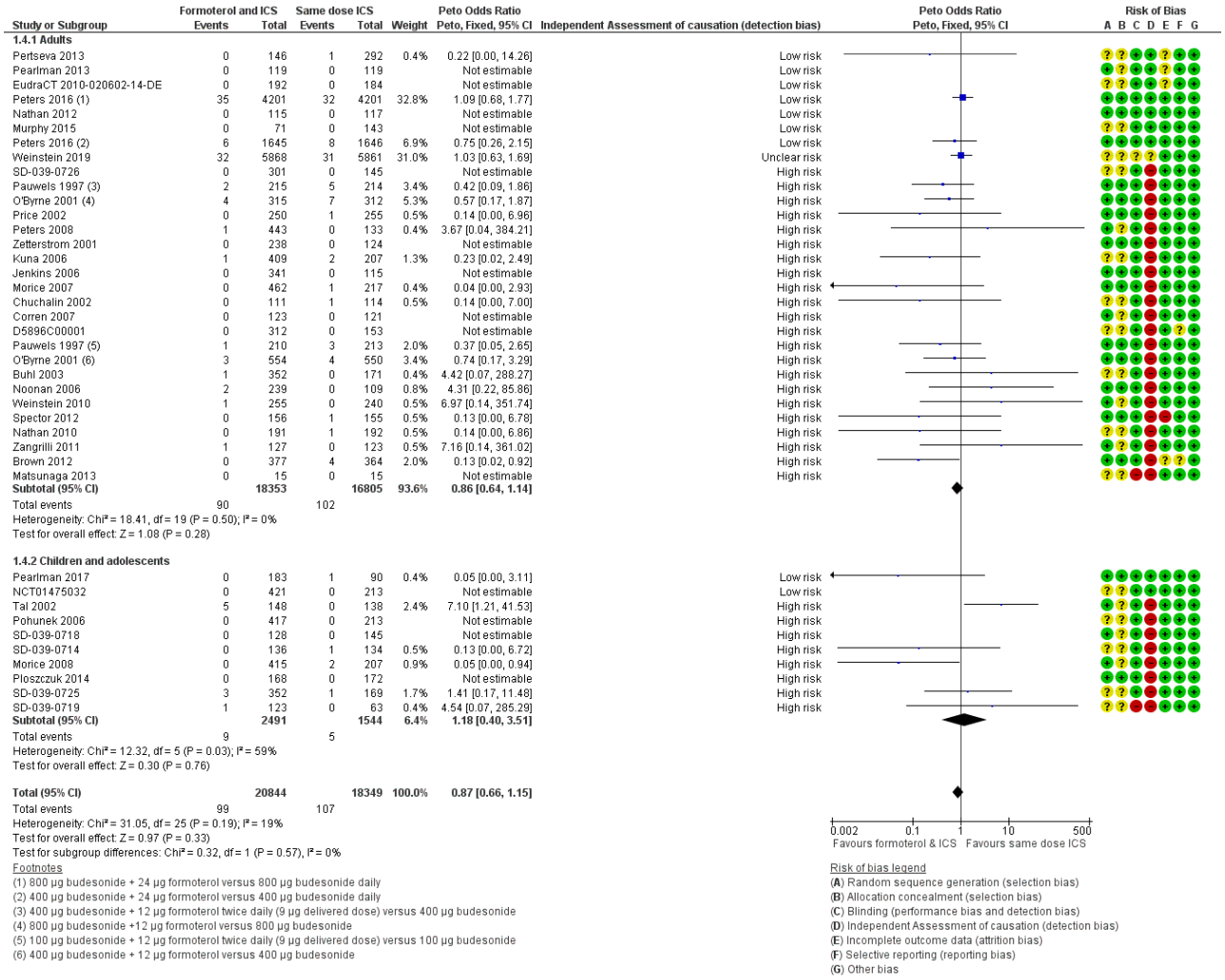
Asthma-related non-fatal serious adverse events

Adults

We included 27 studies involving 35,158 adults in the analysis. Two studies did not report this outcome and were not included in the analysis (Corren 2013; Meltzer 2012). Three studies compared low- and high-dose formoterol plus ICS with a placebo treatment (O'Byrne 2001; Pauwels 1997; Peters 2016). In the analysis, each treatment dose from the three studies was reported separately (resulting in 30 estimates of treatment effect).

The number of adults experiencing one or more asthma-related non-fatal SAEs was lower in participants randomised to receive formoterol and ICS compared to those receiving ICS alone. However, the difference was not statistically significant when analysed as either the Peto OR or the RD. A total of 90 out of 18,353 (0.49%) participants on regular formoterol and ICS and 102 out of 16,805 (0.6%) participants on ICS alone suffered an asthma-related SAE. The Peto OR was 0.86 (95% CI 0.64 to 1.14; 27 studies; 35,158 participants; I^2 = 0%; Figure 6; Analysis 1.4). This means that for every 1000 adults treated for 26 weeks, six experienced an asthma-related non-fatal SAE on ICS alone; the corresponding risk on formoterol and ICS was five adults (95% CI 4 to 7). We assessed this evidence as of moderate certainty due to the lack of independent assessment of causation of SAEs in most of the studies (see Summary of findings for the main comparison and sensitivity analysis below).

Figure 6. Forest plot of comparison: 1 Formoterol and ICS versus same-dose ICS, outcome: 1.4 Asthma-related non-fatal serious adverse events.



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Children and adolescents

In trials in participants who were younger than 18 years of age, the results were again more heterogeneous. Nine young people out of 2491 (0.36%) on regular formoterol and ICS and five out of 1544 (0.32%) on ICS alone suffered an asthma-related SAE. The confidence interval around the increased odds of SAEs related to asthma was wide and not statistically significant (Peto OR 1.18, 95% CI 0.40 to 3.51; 10 studies; 4035 participants; I^2 = 59%; Figure 6; Analysis 1.4). The pooled RD was 0.0006 (95% CI −0.0046 to 0.0057; Table 5; Analysis 2.4). There were three children and adolescents per 1000 on ICS alone with a serious adverse event related to asthma over 12.5 weeks, whilst we would expect four per 1000 on combination therapy (95% CI 1 to 11 per 1000). We assessed this evidence as of very low certainty because of the wide upper confidence interval of the absolute risk in the formoterol and ICS treatment arm; lack of independent assessment of causation of SAEs; and unexplained heterogeneity between trial results (Summary of findings 2).

The test for subgroup interaction between adults and children and adolescents did not find a significant impact of age on treatment effect during analysis as Peto OR (test for subgroup differences: Chi^2 = 0.32, df = 1, P = 0.57, I^2 = 0%).

Other secondary outcomes

We did not identify data for other proposed secondary outcomes (e.g. respiratory-related mortality, respiratory-related non-fatal SAEs, cardiovascular-related mortality, cardiovascular-related non-fatal SAEs, or respiratory-related non-fatal life-threatening events) either because it was not possible to obtain outcome data or the outcome was not measured in the study.

Weinstein 2019 reported asthma-related hospitalisations (defined as a stay of 24 hours or longer in a hospital, emergency department, or equivalent urgent care facility) in 39 out of 5868 adults on formoterol and ICS, and 32 out of 5861 adults on ICS alone at 26 weeks. The hazard ratio for the time to first serious asthma outcome on ICS and formoterol compared to ICS alone was 1.22 (95% CI 0.76 to 1.94).

One intubation (ICS-only group; O'Byrne 2001) was reported. Weinstein 2019 reported no asthma-related intubations at 26 weeks of ICS and formoterol or ICS alone.

Sensitivity analyses

Risk of bias

No deaths occurred in adults or children and adolescents in the unblinded studies (Matsunaga 2013; SD-039-0719), so exclusion of this study resulted in no difference in mortality outcomes. When these studies were excluded for non-fatal SAEs, the Peto OR in adults did not change; however, in children and adolescents the Peto OR increased to 1.40 (95% CI 0.73 to 2.68, I^2 = 45%). A funnel plot did not suggest obvious asymmetry related to publication bias (Figure 7).

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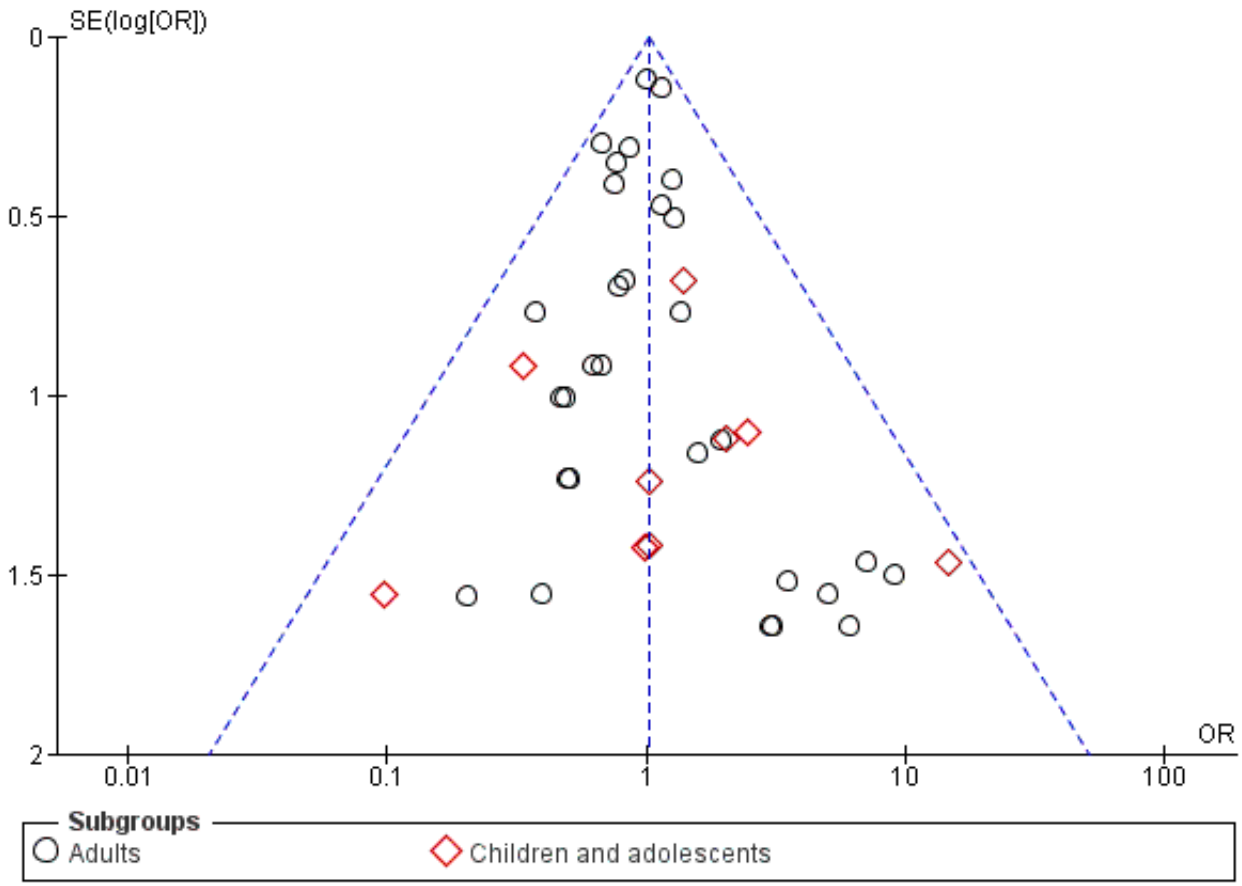
Figure 7. Funnel plot of comparison: 1 Formoterol and ICS versus same-dose ICS (Peto OR), outcome: 1.2 All-cause non-fatal serious adverse events.



In adults, when we considered those studies with independent assessment of causation there was little difference in asthma mortality (RD 0.0003, 95% CI −0.0006 to 0.0012; 8 studies; 13,414 participants; $I^2 = 0\%$) in comparison to the result from all studies (RD 0.0003, 95% CI −0.0007 to 0.0013; 28 studies; 24,022 participants ; $I^2 = 0\%$) (Analysis 3.1). However, considering only the studies with independent outcome assessment moved the impact on non-fatal asthma-related SAEs towards the null (Peto OR 1.01, 95% CI 0.65 to 1.56; 7 studies; 13,191 participants; $I^2 = 0\%$) compared to the result from all the studies (Peto OR 0.86, 95% CI 0.64 to 1.14; 27 studies; 35,158 participants; $I^2 = 0\%$) (Analysis 3.2).

There were not enough events in children and adolescents to carry out sensitivity analysis on detection bias for the asthma-related outcomes.

Restricting results to combined inhalers only

We considered the data for non-fatal SAEs for sensitivity analysis by removing studies in which adults or children and adolescents were given separate inhalers. There were no great changes in results of the analysis in either adults or children and adolescents when compared to the full data set (Table 6).

Methods of analysis

The analysis results were not sensitive to effect measure or choice of model. The primary outcomes were also analysed using Mantel-Haenszel fixed-effect and random-effects models. The result of a fixed-effect model for mortality was OR 1.17 (95% CI 0.60 to 2.29; Analysis 4.1). This method uses a correction for zero cells, which means that the pooled OR is smaller than the Peto OR, because the addition of 0.5 to all cells when the arms have similar numbers randomly assigned will generate an OR of 3 when only one event is reported. When outcomes are very sparse (as for mortality), the results are entirely dependent on the size of the zero cell adjustment and whether the treatment arms are balanced.

For all-cause SAEs in adults , the Mantel-Haenszel fixed-effect (OR 1.00, 95% CI 0.87 to 1.16) and random-effects models (OR 0.99, 95% CI 0.86 to 1.14) yielded results identical to those obtained by the Peto method. As for asthma-related SAEs in adults, the Mantel-Haenszel fixed-effect (OR 0.85, 95% CI 0.65 to 1.12) and random-effects models (OR 0.88, 95% CI 0.66 to 1.16) provided results that were very similar to those obtained when the Peto model was used. Analyses were also carried out using the risk difference for following outcomes: all-cause mortality, all-cause non-fatal SAEs, and asthma-related non-fatal SAEs (see Table 5).

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Dose of formoterol

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

Subgroup analyses

The studies did not show a difference in all-cause SAEs in adults between subgroups when they were classified according to the ICS type that was used (see Analysis 5.1). This was the only outcome with sufficient data to justify subgroup analysis on the basis of ICS type and dose of budesonide.

Although the results for adults and children and adolescents showed opposite directions of effect for non-fatal SAEs (both all-cause and asthma-related), the confidence intervals were wide and the test for interaction did not show a significant interaction of treatment effect and age.

DISCUSSION

Summary of main results

The CIs for all-cause mortality in adults indicate that for every 1000 patients treated with regular formoterol and ICS in comparison with ICS alone, we can expect between one more and one less death in adults given formoterol in addition to ICS over an average of 26 weeks of treatment. The pooled Peto OR for adults was 1.25 (95% CI 0.61 to 2.56; moderate-certainty evidence) and could not be calculated for children and adolescents because no deaths in this group were reported (low-certainty evidence) (Summary of findings for the main comparison; Summary of findings 2).

Regarding non-fatal SAEs in adults, for every 1000 adults treated for 26 weeks, 22 on ICS alone experienced an SAE; the corresponding risk for formoterol and ICS was 22 adults (95% CI 19 to 25). The Peto OR was 1.00 (95% CI 0.87 to 1.16; high-certainty evidence) (Summary of findings for the main comparison).

In children and adolescents, for every 1000 children and adolescents treated for 12.5 weeks, 8 experienced an SAE on ICS alone; the corresponding risk on formoterol and ICS was 11 children and adolescents (95% CI 6 to 21; moderate-certainty evidence) (Summary of findings 2).

Overall completeness and applicability of evidence

The studies mainly recruited adults (mostly with FEV_1 < 80% predicted) randomised to different licenced doses of formoterol and ICS for about 22 weeks (Table 1; Summary of findings for the main comparison). The smaller number of studies in children and adolescents (mostly with FEV_1 < 80% predicted) up to 18 years were of shorter duration, with studies lasting up to 12 weeks (Table 1; Summary of findings 2).

With the addition of new studies resulting from the 2019 update search, the number of adults in this review has increased to 37,984, and the number of children and adolescents has increased to 4035. Uncertainty remains over the risks to children and adolescents of taking formoterol in addition to ICS, as there were either no events or the number of events for all outcomes was small. Regarding the adult data, overall there were more participants due to the inclusion of two large studies identified from the 2019 update (Peters 2016; Weinstein 2019). The inclusion of the results from these two studies in this 2019 review update has resulted in better precision of the overall analyses. However, we were unable to conclude with high certainty that formoterol and ICS is as safe as taking ICS alone.

Further investigation of the evidence in a funnel plot suggested that there was no publication bias that could have contributed to the uncertain result (Figure 7). Three additional new adult trials were included in the review but not in the analyses as they did not report any data for outcomes investigated in this review (Paggiaro 2016; Samson 2012; Stirbulov 2012).

Most of the new trials were multicentre studies recruiting participants from the USA, South America, and Europe. One new trial was a single-centre study recruiting participants in Japan (Matsunaga 2013); two trials included in the 2012 update focused on African-American adults (Brown 2012; Spector 2012); and one trial studied Hispanic adults (Zangrilli 2011), so the diversity of ethnic groups represented is now greater. However, there remains very little in the way of separate data on adolescent participants recruited in any of the adult or adolescent trials. This is in spite of the fact that separate data on adolescents was to be reported in large trials initiated by the FDA (Chowdhury 2011).

Certainty of the evidence

We assessed the risk of bias for all of the included studies (Summary of findings for the main comparison; Summary of findings 2). Almost all of the studies were double-blind, and although allocation concealment was not well reported, it was likely to have been adequate, as all trials were sponsored or supported by product manufacturers. Lack of blinding of participants or care providers or outcome assessors was an issue in some studies, and these were downgraded accordingly. Because the trials were carried out for regulatory purposes, the collection of SAE data would have been assessed with the use of uniform definitions across studies.

For asthma-related events, we judged the risk of bias to be increased if studies did not undertake independent assessment of the causation of events, which may have introduced bias if the investigators had a high threshold for classifying events as asthma-related. However, we would have expected such a bias to decrease any differences observed in asthma-related events.

The level of heterogeneity within the subgroup of paediatric trials was significant (I^2 = 59%) for asthma-related non-fatal SAEs, and could not be easily explained. Even with the addition of three studies from the 2019 update, it remains unclear whether taking formoterol was beneficial or harmful, as the CIs from two studies did not overlap (Morice 2008; Tal 2002), and the direction of effect from these two studies showed benefit, Morice 2008, and harm, Tal 2002.

We rated the certainty of the evidence as high to low for adult evidence (Summary of findings for the main comparison). For outcomes that were rated as moderate or low certainty, we downgraded by one point due to a wide upper confidence interval of the absolute risk, too few events in the ICS treatment arm, or lack of independent assessment of causation of SAEs. We rated the certainty of the evidence for outcomes reported in children and adolescents as moderate to very low (Summary of findings 2). The evidence for all-cause mortality was downgraded by two

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points due to no deaths and uncertainty of the treatment. Other outcomes were downgraded by one point due to wide confidence intervals, lack of independent assessment of causation of SAEs, or unexplained heterogeneity between trials.

Addition of new trials

The 2019 update of this review included five new trials that examined the combination of formoterol and fluticasone in 1856 adults, Corren 2013; Nathan 2012; Pearlman 2013; Pertseva 2013, and 512 children (Ploszczuk 2014). Although the number of participants in the included studies was sufficient, not enough events were observed to determine the safety of this combination compared to other combinations of ICS and formoterol in both children and adolescents and adults. Two new trials were also included that compared beclomethasone and formoterol in adults (EudraCT 2010-020602-14-DE; Paggiaro 2016). It was not possible to make any inferences regarding treatment with beclomethasone plus formoterol, as no events were observed in one trial (EudraCT 2010-020602-14-DE), and one trial did not report safety outcomes in their publication (Paggiaro 2016). We identified six new additional studies for the combination of budesonide and formoterol compared with budesonide alone in both adults and children (Matsunaga 2013; Murphy 2015; NCT01475032; Pearlman 2017; Peters 2016; Stirbulov 2012). Of the adult results, Stirbulov 2012 was not included in the analysis because the outcomes were not reported in the publication.

A large trial with 11,729 participants that was ongoing at the time of the 2012 update has now been included in the 2019 update for the comparison of combined formoterol and mometasone versus mometasone alone in adults (Weinstein 2019), however despite the addition of the new evidence, we were unable to determine with high certainty that ICS and formoterol are safe to use when compared to ICS alone.

Potential biases in the review process

Selection of the best method to combine studies with rare events is contentious when event rates are low, not least because of the corrections required to calculate ORs with zero events (Sweeting 2004). It became apparent in the course of the review that the pooled ORs were heavily dependent on the zero adjustment used in the Mantel-Haenszel and inverse variance methods, therefore we used the Peto OR and RDs to report the results of this review. The imbalance between trial arms is never greater than two to one, therefore the likely bias with use of the Peto OR is small (Sweeting 2004).

Similarly, the included studies were influenced by the decision to restrict the review to trials that randomly assigned participants to formoterol plus ICS (i.e. excluding trials that randomised people to formoterol or placebo but who were taking background ICS). This decision reduces the risk of bias that can arise when participants discontinue their usual inhaled steroid medication if they feel better while receiving the randomly assigned treatment. This presupposes a similar risk of SAEs when formoterol and budesonide are delivered via a single inhaler, and when formoterol is introduced to ICS therapy via a separate inhaler, when both are randomly assigned treatments in a controlled trial.

Agreements and disagreements with other studies or reviews

Mortality

More deaths reported in the Cochrane Review of trials comparing formoterol with placebo (Cates 2012), and the present review comparing formoterol with ICS versus the same dose of ICS, occurred in participants who were randomly assigned to formoterol (with or without ICS; Table 4), although either result may have happened by chance. This is a cause for concern because although it may seem that many of the deaths were not related to asthma, it is often difficult to be sure of the exact cause of death, and the classification of cause of death is not straightforward. For example, the participant who died during the OPTIMA trial, O'Byrne 2001, was recorded by authors as dying from septic shock but was listed in Sears 2009 as dying from status asthmaticus and septic shock, whereas the 13-year-old boy who died in Von Berg 2003 is listed in Sears 2009 as dying of respiratory failure, although the initial article reported that the cause of death was subarachnoid haemorrhage. Sears 2009 does not report all-cause mortality in the subgroup of trials in participants receiving regular formoterol and maintenance ICS; the primary analysis on all-cause mortality included the RELIEF study, which allowed regular LABA in both arms and was therefore not included in this review. The adjusted all-cause mortality risk ratio in Sears 2009 is 1.79 (95% CI 0.80 to 4.00) when studies with any baseline ICS are considered; the conditional logistic regression was adjusted for trial effect (data on file provided by AstraZeneca).

Only three asthma-related deaths were reported in adults in this review, but the overview of Sears 2009 identified two additional asthma-related deaths from the AstraZeneca database of trials in which participants were receiving maintenance ICS; all three deaths occurred in participants who had been randomly assigned to regular formoterol.

Six additional deaths were reported when formoterol and ICS were compared with higher doses of ICS, three in each arm (Jaeschke 2008).

We have concluded that although the precision has become greater with addition of two large trials (Peters 2016 and Weinstein 2019), we agree with the conclusion of Sears 2009 that it is still insufficient to conclude that there is no increased mortality with formoterol use in conjunction with ICS.

All-cause non-fatal serious adverse events

Information derived from trials in children and adolescents in this review is insufficient to permit a determination as to whether the increased risk of non-fatal SAEs found with formoterol alone in Cates 2012 (Peto OR 2.48, 95% CI 1.27 to 4.83) is abolished by the addition of ICS (Peto OR 1.33, 95% CI 0.71 to 2.49), as overlap in CIs leads to negative test findings for interaction (test for subgroup differences: $Chi^2 = 8.41$, df = 8, P = 0.39, $I^2 = 5\%$) (Figure 4). This is discussed more fully in the overview of the safety of regular formoterol or salmeterol in children (Cates 2012a), and is in agreement with the findings of McMahon 2011, who reported a significant association between younger age and increased risk of all-cause non-fatal SAEs with formoterol or salmeterol monotherapy, but no significant age association with combination inhalers.

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AUTHORS' CONCLUSIONS

Implications for practice

In this update, we have included results from two large studies and now have data from a total of 35,751 adults and 4035 children and adolescents with asthma. Despite the increased precision of estimates as a result of the increased number of participants from the inclusion of new studies, we are still not able to reassure people with asthma that regular use of inhaled corticosteroids (ICS) with formoterol carries no increased risk of mortality compared with ICS alone in adults (moderate-certainty evidence) or children and adolescents (low-quality evidence). On the other hand, we found high-certainty evidence of a similar rate of serious adverse events (SAEs) between therapies in adults. In addition, there were only three asthma-related deaths from a total of 24,022 adults taking formoterol (low-certainty evidence).

In children and adolescents, the number of events was too small to determine whether the increase in all-cause non-fatal SAEs previously found in those taking regular formoterol alone was abolished by the additional use of ICS (moderate-certainty evidence). However, the overall incidence of SAEs was lower in children and adolescents than adults.

We were not able to identify studies to address the trade-offs between mortality risks and quality of life of combined formoterol and ICS compared with ICS alone (see Appendix 5). Clinical decisions and information provided to patients regarding regular use of formoterol must take into account the balance between known symptomatic benefits of formoterol and the degree of uncertainty associated with its potential harmful effects.

Implications for research

We investigated mortality and SAEs as outcomes of interest for those taking combined formoterol and ICS. For the next update of this review, a dose response analysis of combined formoterol and ICS (e.g. 12 µg versus 6 µg formoterol) and the frequency of associated SAEs will help to inform those prescribing inhalers. In addition, an analysis of outcomes after once-daily versus twice-daily combined formoterol and ICS would also be useful information for prescribers.

Future research should clearly specify the number of participants with fatal and non-fatal SAEs by treatment group and cause. We await publication of the separate results from adolescents included in the new trials. We identified two ongoing trials, one that has completed and an ongoing study recruiting over 2000 participants, which we will assess for eligibility when data become available (NCT02554786; NCT02741271). As the trials included in this review were of mostly short duration, further trials should have a long enough duration to observe fatal and non-fatal SAEs.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Brown 2012

Methods	**Study Design**: a randomised, double-blind, parallel-group study over 52 weeks in 122 centres in the USA, between February 2007 and November 2009. 2-week single-blind run-in on budesonide 320 µg twice daily.
Participants	**Population**: 742 African-American adults (aged 12 years and over) with asthma (ATS definition). **Baseline Characteristics**: mean age 37 years. FEV_1 78% predicted. Concomitant ICS used by all participants (± LABA). **Inclusion Criteria**: stable asthma for ≥ 6 months. FEV_1 % predicted risk ≥ 50%, bronchodilator reversibility ≥ 12% in FEV_1 or 0.2 L. **Exclusion Criteria**: smoking history of greater than 10 pack-years, use of OCS within 30 days or beta-blockers (including eye drops) during the study. Pregnancy, breastfeeding, or malignancy in the past 5 years.
Interventions	• Budesonide/formoterol 160/9 µg twice daily. • Budesonide 160 µg twice daily. Delivery was pMDI.
Outcomes	Safety variables included asthma exacerbations (oral/systemic corticosteroid use or an asthma-related hospitalisation or emergency room/urgent care visit) and AEs. No published data found on asthma-related non-fatal SAEs, so we used hospitalisation for asthma exacerbation as a proxy measure.
Notes	Sponsored by AstraZeneca.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation occurred with the use of computer-generated sequential allocation; approximately equal distribution of participants per treatment group at each site was ensured by the use of balanced blocks.

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Brown 2012 *(Continued)*

Allocation concealment (selection bias)	Low risk	Allocation concealment was maintained by packaging the study medications identically, with the exception of the computer-generated randomisation number.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind.
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number of reported withdrawals reasonably balanced, but high proportions of total: • 149/377 (intervention group); • 125/365 (control group).
Selective reporting (reporting bias)	Unclear risk	No reporting of asthma-related SAEs, so there may be high risk for this outcome.
Other bias	Low risk	Sponsorship was not regarded as increasing the risk of bias as the study was well designed.

Buhl 2003

Methods	**Study Design**: a randomised, double-blind, double-dummy, active-controlled, multicentre, parallel-group study over 12 weeks from October 1999 to June 2000 at 56 centres in 9 countries: Argentina (5), Belgium (5), the Czech Republic (14), Germany (6), Mexico (4), Russia (6), Spain (5), the Netherlands (7), and the UK (4). Run-in 2 weeks on budesonide 200 µg twice daily.
Participants	**Population**: 523 adults (18 to 78 years) with moderate persistent asthma. **Baseline Characteristics**: mean age 44 years. FEV_1 77% predicted. Concomitant ICS used by all participants (400 to 1000 µg/day), and condition not fully controlled on this dose. **Inclusion Criteria**: outpatients aged 18 years and older with perennial asthma (ATS) with a minimum duration of 6 months. Used any ICS at a constant daily dose of 400 to 1000 µg for ≥ 30 days before entry and still had suboptimal asthma control. FEV_1 % predicted between 60% and 90%, bronchodilator reversibility by an increase of ≥ 12% in FEV_1 over baseline at 15 minutes after inhalation of a SABA. **Exclusion Criteria**: use of oral, parenteral, or rectal glucocorticosteroids within 30 days before visit 1, seasonal asthma, significant respiratory infection within 30 days of visit 1, severe cardiovascular disorder or any other significant disease or disorder, pregnant or planning a pregnancy, breastfeeding, or not using acceptable contraceptives, or not surgically sterile, hypersensitivity to study drugs, and tobacco smokers or previous smokers if greater than 10 pack-years.
Interventions	• Budesonide/formoterol 320/9 µg daily. • Budesonide/formoterol 160/4.5 µg twice daily. • Budesonide 400 µg daily (equivalent daily dose of budesonide). Delivery was DPI.
Outcomes	The primary efficacy variable was morning PEF (L/min).

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Buhl 2003 *(Continued)*

	Paper reports 5 SAEs: 1 in the once-daily budesonide/formoterol group and 2 each in the other groups. 1 death due to cardiac arrest and 4 other events were reported. (No details given by treatment group in article or in web report.) Jaeschke 2008 reports 1 death on combined treatment and 2 participants with non-fatal SAE on combined treatment and 2 on budesonide. 1 SAE on budesonide/formoterol was asthma-related.
Notes	Sponsored by AstraZeneca.

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) All outcomes	Low risk	Double-blind.
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	480 of 523 (92%) completed the study.
Selective reporting (reporting bias)	Low risk	SAE data not attributable to treatment groups in article but obtained from Jaeschke 2008.
Other bias	Low risk	Sponsorship was not regarded as increasing the risk of bias as the study was well designed.

Chuchalin 2002

Methods	**Study Design**: a randomised, double-blind, parallel-group study over 12 weeks in Russia. Run-in 2 weeks.
Participants	**Population**: 333 adults (18 to 66 years) with mild to moderate asthma. **Baseline Characteristics**: mean age 45 years. FEV_1 unknown % predicted. Concomitant ICS used by no participants. **Inclusion Criteria**: diagnosed ≥ 6 months. FEV_1 % predicted between 50% and 85%, bronchodilator reversibility ≥ 15% in FEV_1 over baseline after inhalation of terbutaline. Female participants to be post-menopausal or surgically sterile or using medically approved contraceptive measures. **Exclusion Criteria**: smoking history of greater than 10 pack-years, current or recent users of inhaled, oral, or parenteral corticosteroids, oral leukotriene antagonists, nedocromil sodium or sodium cromoglycate, beta-blockers (including eye drops).
Interventions	• Budesonide/formoterol 200/9 µg twice daily.

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Chuchalin 2002 *(Continued)*

	• Budesonide 200 µg twice daily. Delivery was DPI.
Outcomes	The primary efficacy variable was change in PEF in the morning before any study medication was taken. Article reports no deaths and 2 SAEs (aggravated asthma and hypertension) in the budesonide-only group that required hospitalisation.
Notes	Supported by AstraZeneca.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported.
Allocation concealment (selection bias)	Unclear risk	"Allocated a randomised number (identifying which of the three treatments they would receive) in consecutive order, per centre, at the second visit."
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind.
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	316 of 338 (93%) completed the study.
Selective reporting (reporting bias)	Low risk	SAE data reported in the article.
Other bias	Low risk	Sponsorship was not regarded as increasing the risk of bias as the study was well designed.

Corren 2007

Methods	**Study Design**: 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. 123 randomly assigned to budesonide/formoterol and 121 to budesonide. The web report also includes 13 children in these treatment groups aged 6 to 11 years, but they were not separately analysed. **Baseline Characteristics**: mean age 36 years. FEV_1 75% predicted. Concomitant ICS used by all participants at baseline but withdrawn for the formoterol and placebo arms of this study. **Inclusion Criteria**: mild to moderate persistent asthma for ≥ 6 months, treated with ICS for ≥ 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 the run-in period. Bronchodilator reversibility of ≥ 12%

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Corren 2007 *(Continued)*

	and 0.20 L in FEV_1 over baseline within 15 to 30 minutes after administration of salbutamol 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, or a > 10 pack-year smoking history at screening. Pregnant or breastfeeding.
Interventions	• Budesonide/formoterol (Symbicort) 160/9 µg twice daily. • Budesonide 160 µg twice daily. The Symbicort and budesonide arms of this study are included in this review. Delivery was DPI.
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 SAEs in the budesonide/formoterol group (lobar pneumonia and facial bone fracture) were reported in the article. No cardiac-related SAEs were reported in any group. No deaths occurred in any group (website data). Jaeschke 2008 reports no asthma-related SAEs.
Notes	Study sponsored by AstraZeneca.

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) All outcomes	Low risk	Double-dummy. Participants received both a pMDI and a DPI containing active treatment or placebo of the alternative active treatment as appropriate.
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	18 of 123 discontinued on budesonide/formoterol and 18 of 121 on budesonide.
Selective reporting (reporting bias)	Low risk	SAEs reported in paper publication.
Other bias	Low risk	Sponsorship was not regarded as increasing the risk of bias as the study was well designed.

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Corren 2013

Methods	**Study Design:** a randomised, double-blind, placebo- and active-controlled, multicentre, stratified, parallel-group study over 12 weeks from July 2006 to April 2008. 78 centres in North America. Run-in 14 to 17 days on 100 or 200 µg fluticasone.
Participants	**Population**: 557 adolescents and adults (12 to 82 years) with asthma. **Baseline Characteristics:** mean age 43 years. FEV_1 predicted 65%. Concominant ICS used by all participants. **Inclusion Criteria**: 12 years of age and older, history of asthma for ≥ 12 months, documented use of inhaled ICS for ≥ 4 weeks prior to screening, FEV_1 40% to 80% predicted at screening and baseline. Documented reversibility of 15% within 12 months of screening visit or at screening visit (15% increase from pre-FEV_1 levels following salbutamol inhalation or nebulised salbutamol administration). **Exclusion criteria**: life-threatening asthma within past year or during run-in period, history of systemic ICS medication within 3 months before screening, history of omalizumab use within past 6 months, history of LTRA use within past week, current evidence/history of significant disease or abnormality (uncontrolled hypertension, CHD, CHF, cardiac dysrhythmia), upper or lower respiratory infection within 4 weeks prior to screening or during run-in period.
Interventions	• Fluticasone/formoterol 250/10 µg twice daily + placebo. • Fluticasone/formoterol 100/10 µg twice daily + placebo. • Formoterol 10 µg twice daily + placebo. • Fluticasone 250 µg twice daily + placebo. • Placebo twice daily. Delivery was HFA pMDI.
Outcomes	The primary efficacy endpoint was the mean change of PEFR in the morning and evening from baseline to week 12. There was 1 SAE in the fluticasone/formoterol 250/10 µg twice-daily + placebo group and 2 SAEs in the fluticasone 250 µg twice-daily + placebo group. No deaths occurred in any group, and no asthma-related SAEs were reported.
Notes	Study sponsored by SkyePharma AG.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation according to minimisation with biased coin assignment.
Allocation concealment (selection bias)	Low risk	An interactive voice response system was used for participant enrolment and treatment allocation.
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding was maintained throughout the study with the use of dummy placebo inhalers.
Independent Assessment of causation (detection bias) Asthma-related events	Low risk	All investigators, personnel at the study site, and representatives involved in monitoring, data management, and any other aspect of the trial, including sponsor personnel, were blinded throughout the study.
Incomplete outcome data (attrition bias)	Low risk	< 20% missing data.

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Corren 2013 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	Asthma SAEs were not reported.
Other bias	Low risk	Sponsorship was not regarded as increasing the risk of bias as the study was well designed.

D5896C00001

Methods	**Study Design**: a randomised, double-blind, single-dummy, active-controlled, multicentre, parallel-group study over 12 weeks from October 2003 to February 2005 at 143 centres in the USA. Run-in 4 to 5 weeks on single-blind budesonide/formoterol (Symbicort) pMDI.
Participants	**Population**: 619 adolescents and adults (12 to 79 years) with asthma. **Baseline Characteristics**: mean age 35 years. FEV_1 76% predicted. Concomitant ICS used by all participants. **Inclusion Criteria**: participants ≥ 12 years of age, had a documented clinical diagnosis of asthma for ≥ 6 months before screening and were in stable condition. Should have received maintenance asthma treatment with ICS for ≥ 4 weeks before the screening visit. FEV_1 % predicted between 60% and 90% measured ≥ 24 hours after the last dose of LABA and 6 hours after the last dose of SABA.
Interventions	• Budesonide/formoterol 160/4.5 µg, 2 inhalations once daily. • Budesonide/formoterol 80/4.5 µg, 2 inhalations once daily (data from this arm not used). • Budesonide/formoterol 80/4.5 µg, 2 inhalations twice daily. • Budesonide 160 µg, 2 inhalations once daily. Delivery was pMDI.
Outcomes	Primary variable: evening predose FEV_1. No full paper publication for this study. Web report indicated 2 SAEs on budesonide/formoterol 160/4.5 twice daily, with a participant who had an MI on the day after the treatment was discontinued. No deaths occurred. No data on asthma SAEs were found in the original review, but 2012 update includes report by Kerwin (no asthma-related SAEs in the study arms included in this review).
Notes	Sponsored by AstraZeneca.

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) All outcomes	Low risk	Double-blind. To maintain blinding with the twice-daily dosing regimen, all participants randomly assigned to receive once-daily dosing were to take the active treatment in the evening and a matched placebo device in the morning.

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D5896C00001 *(Continued)*

Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	12% dropout in each arm.
Selective reporting (reporting bias)	Unclear risk	No asthma-related SAE data found.
Other bias	Low risk	Sponsorship was not regarded as increasing the risk of bias as the study was well designed.

EudraCT 2010-020602-14-DE

Methods	**Study Design**: a randomised, double-blind, double-dummy, 2-arm parallel multinational group study over 12 weeks at 57 centres in 9 European countries including Bulgaria, Czech Republic, France, Germany, Hungary, Italy, Poland, Russia, and the UK. Run-in 2 weeks (on usual ICS).
Participants	**Population**: 376 adults (18 years of age and over) with persistent asthma. **Baseline Characteristics**: majority of participants were aged 18 to 64 (85%), with 15% aged ≥ 65 years. Concominant ICS used by all participants. **Inclusion Criteria**: male or female aged ≥ 18 years, FEV_1 ≥ 40% and < 80% of person's predicted normal value and an absolute value of ≥ 0.9 L, after appropriate washout from bronchodilators at screening and at the end of the run-in period, positive response to the reversibility test at screening, defined as change in FEV_1 ≥ 12% and ≥ 200 mL over baseline, within 30 minutes after administration of 400 µg of salbutamol pMDI.
Interventions	• Beclomethasone/formoterol 200/6 µg, 4 inhalations daily (total 800/24 µg). • Beclomethasone 100 µg, 8 inhalations daily (total 800 µg). Delivery was pMDI.
Outcomes	The primary efficacy variable was change in morning PEF. Adverse events were recorded as secondary measures.
Notes	Chiesi Farmaceutici S.p.A.

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) All outcomes	Low risk	Participants and care providers were blinded.

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EudraCT 2010-020602-14-DE *(Continued)*

Independent Assessment of causation (detection bias) Asthma-related events	Low risk	Not reported, but assumed outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported.
Selective reporting (reporting bias)	Low risk	None.
Other bias	Low risk	Sponsorship was not regarded as increasing the risk of bias as the study was well designed.

Jenkins 2006

Methods	**Study Design:** a randomised, double-blind, double-dummy, reference-controlled, multicentre, parallel-group study over 24 weeks from July 2001 to June 2002 at 54 centres in 6 countries: Australia (11), Austria (6), Czech Republic (15), France (9), Poland (8), and Spain (5). Run-in 2 weeks (on usual ICS).
Participants	**Population**: 456 adolescents and adults (12 to 79 years) with persistent symptomatic asthma. **Baseline Characteristics**: mean age 46 years. FEV_1 66% predicted. Concomitant ICS used by all participants. **Inclusion Criteria**: outpatients aged 12 years and older with a diagnosis of asthma (≥ 6 months), FEV_1 % predicted between 40% and 85% and bronchodilator reversibility by an increase of ≥ 15% in FEV_1 over baseline after inhalation of a bronchodilator. For patients aged 18 years and older, an increase in baseline FEV_1 of ≥ 200 mL 15 to 30 minutes postbronchodilator was required at study entry (visit 1). All participants had used ICS for ≥ 4 months at a constant daily dose of ≥ 750 µg for ≥ 4 weeks before study entry. **Exclusion Criteria**: deterioration of asthma resulting in a change in asthma therapy. Total asthma symptom score had to be > 1 on a scale of 0 to 6 for ≥ 4 of the last 7 days of run-in. The total asthma symptom score was the sum of daytime and nighttime asthma symptom scores, each measured on a scale of 0 to 3 (where 0 = no symptoms and 3 = unable to perform usual activities (or to sleep because of asthma)).
Interventions	• Budesonide/formoterol 320/9 µg, 2 inhalations twice daily + placebo twice daily. • Budesonide 400 µg, 2 inhalations twice daily/formoterol 9 µg, 2 inhalations twice daily + placebo twice daily. • Budesonide 400 µg, 2 inhalations twice daily + placebo twice daily. This was the treatment for the first 12 weeks, then group 3 was split between the first 2 treatments. Delivery was DPI.
Outcomes	The primary efficacy variable was morning PEF as registered daily on diary cards. Article reports 5 participants with SAE on budesonide/formoterol and 2 on budesonide. 1 death occurred in the budesonide/formoterol group from pulmonary embolism, but as this was after 17 weeks, when there was no budesonide control arm, this was not included in the meta-analysis. Data from AstraZeneca show 7 participants with SAE on budesonide/formoterol and 3 on budesonide in the first 12 weeks of the study. This has been used in the meta-analysis. It is not clear why the article reports different numbers.

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Jenkins 2006 *(Continued)*

Notes	Sponsored by AstraZeneca.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Individual treatment codes were computer generated in balanced blocks of 8 at AstraZeneca R&D, Lund, Sweden.
Allocation concealment (selection bias)	Low risk	Codes were then assigned to participants and were kept in sealed envelopes until data analysis.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind.
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	400 of 456 (88%) completed the study.
Selective reporting (reporting bias)	Low risk	SAE data in article, but they did not match final data from sponsors.
Other bias	Low risk	Sponsorship was not regarded as increasing the risk of bias as the study was well designed.

Kuna 2006

Methods	**Study Design:** a randomised, double-blind, double-dummy, active-controlled, multicentre, parallel-group study over 12 weeks from November 1999 to July 2000 at 60 centres in 8 countries: Finland (5), Germany (17), Mexico (4), New Zealand (3), Norway (6), Poland (7), Russia (5), and Sweden (13). Run-in 2 weeks in which all participants received budesonide 200 µg daily (half the previous average dose).
Participants	**Population**: 616 adults (18 to 80 years) with mild to moderate persistent asthma. **Baseline Characteristics**: mean age 45 years. FEV_1 78.5% predicted. Concomitant ICS used by all participants. **Inclusion Criteria**: diagnosis of asthma (6 months minimum duration of asthma) that was not optimally controlled despite a daily ICS dose of 200 to 500 µg for ≥ 30 days before study entry. FEV_1 % predicted of 60% to 90%, ≥ 12% bronchodilator reversibility in FEV_1 after inhalation of either 1 mg of terbutaline or 0.4 mg salbutamol. **Exclusion Criteria**: used any systemic corticosteroids within the previous 30 days; seasonal asthma (defined as asthma exacerbated by seasonal increases in aero allergens); respiratory infection in the 4 weeks before study entry; a severe cardiovascular disorder or any other significant disease; used beta-blocker therapy (including eye drops) or had a history of heavy smoking (≥ 10 pack-years); women of childbearing potential who were pregnant or who failed to use acceptable contraceptive measures.
Interventions	• Budesonide/formoterol 80/4.5 µg, 2 inhalations once daily. • Budesonide/formoterol 80/4.5 µg twice daily.

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Kuna 2006 *(Continued)*

	• Budesonide 200 µg once daily. Delivery was DPI, and all study arms received equivalent delivered dose of 160 µg budesonide daily.
Outcomes	The primary variable was morning PEF. "Seven serious adverse events were reported: two in the once-daily BDF group, one in the twice-daily BDF group and four in the budesonide group." Although the 3 asthma SAEs were not described by treatment group in the article or the web report, Jaeschke 2008 indicates 1 on budesonide/formoterol and 2 events on budesonide, with 1 hospitalisation for asthma in each group. No mortality.
Notes	Sponsored by AstraZeneca.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	Low risk	To ensure treatment blinding, a double-dummy design was used so that participants received 4 successively numbered Turbuhalers, with the corresponding placebo inhalers identical in appearance to those containing the active medication.
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	555 of 616 (90%) completed the study.
Selective reporting (reporting bias)	Low risk	SAEs reported in paper by treatment group.
Other bias	Low risk	Sponsorship was not regarded as increasing the risk of bias as the study was well designed.

Matsunaga 2013

Methods	**Study Design**: randomised, parallel-group study.
Participants	**Population**: 36 adults (aged 20 years and over) with partly controlled or uncontrolled asthma. **Baseline Characteristics**: mean age 32 years. FEV_1 86% predicted. No use of corticosteroids prior to study. **Inclusion Criteria**: age 20 years or older, asthma classified according to GINA, asthma control defined by ACQ criteria (well controlled: 0.75 and inadequately controlled: > 1.5). **Exclusion Criteria**: smoking history, asthma exacerbation, systemic steroid treatment during 8 weeks prior to study, poor adherence to treatment, other pulmonary disease.

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Matsunaga 2013 *(Continued)*

Interventions	• Budesonide/formoterol 160/4.5 µg twice daily. • Budesonide 160 µg twice daily. Delivery was not reported.
Outcomes	No all-cause mortality or asthma-related mortality. No all-cause SAE or asthma-related SAE in study.
Notes	Sponsored by the Japanese Society for the Promotion of Science.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Reported as randomised, but method of randomisation not reported.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding (performance bias and detection bias) All outcomes	High risk	The study was open-label.
Independent Assessment of causation (detection bias) Asthma-related events	High risk	The study was open-label.
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 20% missing data.
Selective reporting (reporting bias)	Low risk	None.
Other bias	Low risk	Sponsored by the Japanese Society for the Promotion of Science.

Meltzer 2012

Methods	**Study Design**: randomised, multicentre, double-blind, double-dummy, placebo-controlled, parallel-group study over 26 weeks at 172 sites worldwide. Run-in 2 weeks mometasone furoate100 µg twice daily.
Participants	**Population**: 370 adults (in the arms that were eligible for this review) (aged 12 years and over) with asthma (generally moderate uncontrolled asthma). **Baseline Characteristics**: mean age 38 years. FEV_1 75% predicted. Concomitant ICS used by all participants for ≥ 12 weeks (with or without LABA). **Inclusion Criteria**: asthma for ≥ 12 months and on a stable ICS regimen for ≥ 12 weeks. FEV_1 60% to 85% predicted, bronchodilator reversibility ≥ 12% in FEV_1 or 0.2 L; alternatively PEF variability over 20%. **Exclusion Criteria**: unstable asthma, smoking history greater than 10 pack-years, past history or present evidence of oropharyngeal candidiasis.

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Meltzer 2012 *(Continued)*

Interventions	• Mometasone furoate/formoterol 100/10 µg twice daily. • Mometasone furoate 100 µg twice daily. Delivery was pMDI (the placebo and formoterol arms in this trial were not considered for this review).
Outcomes	All-cause SAE data not reported by treatment group in article, but data kindly provided by the authors: 4 adults with SAE on mometasone furoate/formoterol and 5 with SAE on mometasone (1 on formoterol and 1 on placebo). No hospital admissions for asthma exacerbation, so no asthma-related SAEs (confirmed by authors).
Notes	Sponsored by Merck Sharp & Dohme.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, double-dummy.
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	36 of 182 discontinued on combination and 41/188 on mometasone furoate alone, but imbalance was noted for treatment failure (2% and 7%, respectively).
Selective reporting (reporting bias)	Low risk	SAE details obtained from authors.
Other bias	Low risk	Sponsorship was not regarded as increasing the risk of bias as the study was well designed.

Morice 2007

Methods	**Study Design**: a randomised, double-blind, double-dummy, parallel-group study over 12 weeks from April 2002 to February 2003 at 62 centres in Brazil (7), Bulgaria (5), Canada (9), Hungary (9), Mexico (7), the Philippines (6), Thailand (5), and the UK (14). Run-in 2 weeks on pre-study ICS, but LABA was withdrawn from the 15% previously treated with LABA and ICS.
Participants	**Population**: 680 adolescents and adults (12 to 79 years) with asthma. **Baseline Characteristics**: mean age 40 years. FEV_1 70% predicted. Concomitant ICS used previously by all participants (mean dose 770 µg/day). **Inclusion Criteria**: 12 years of age and older with asthma for ≥ 6 months, who were inadequately controlled on ICS alone, FEV_1 % predicted between 50% and 90%, bronchodilator reversibility by an increase of ≥ 12% in FEV_1 after inhalation of terbutaline 1 mg, a history of daily ICS use (stable dose of 500

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Morice 2007 *(Continued)*

	to 1600 µg/day within 30 days before enrolment) for ≥ 3 months. Symptoms must have been present on ≥ 4 of the last 7 days of run-in. **Exclusion Criteria**: not defined.
Interventions	• Budesonide 200 µg, 2 inhalations twice daily (treatment 1). • Budesonide/formoterol 160/4.5 µg, 2 inhalations twice daily (treatment 2). • Budesonide/formoterol 160/4.5 µg, 2 inhalations twice daily (treatment 3). All delivered the same daily dose of budesonide. Delivery was CFC pMDI for budesonide only (treatment 1). Delivery was either DPI or HFA pMDI for combined budesonide/formoterol (treatment 2 and 3).
Outcomes	The primary efficacy endpoint was the change in morning PEF from baseline (mean of the last 10 days of run-in) to the mean value over the 12-week treatment period. Article reports: "No deaths occurred. Four participants experienced serious adverse events, two in the budesonide group (joint dislocation, asthma) and two in BDF pMDI (menorrhagia, increased liver enzymes)."
Notes	Sponsored by AstraZeneca.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned sequentially in blocks of 6 using a computer-generated randomisation schedule.
Allocation concealment (selection bias)	Low risk	Eligible participants were consecutively allocated the lowest available randomisation code. In view of double-dummy design, this is considered satisfactory.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, double-dummy. To maintain blinding, each participant also received a placebo device.
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	600 of 680 (88%) completed the study.
Selective reporting (reporting bias)	Low risk	Full SAE data available from article by treatment group and cause.
Other bias	Low risk	Sponsorship was not regarded as increasing the risk of bias as the study was well designed.

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Morice 2008

Methods	**Study Design**: a randomised, double-blind, double-dummy, parallel-group study over 12 weeks from June 2002 to May 2003 at 53 centres in Argentina (4), Brazil (6), Denmark (14), Hong Kong (1), Mexico (6), Poland (4), Slovakia (12), and Taiwan (6). Run-in 2 weeks on previous ICS dose (but previous LABA may have been withdrawn; not made clear in the article).
Participants	**Population**: 622 children (6 to 11 years) with symptomatic asthma. **Baseline Characteristics**: mean age 8 years. FEV_1 82% predicted. Concomitant ICS used by all participants (375 to 100 µg daily). **Inclusion Criteria**: paediatric outpatients (6 to 11 years) with asthma and a history of clinically important exercise-induced bronchoconstriction, daily use of 375 to 1000 µg of ICS, PEF ≥ 50% of predicted normal value (pre-bronchodilator). Had to have a total asthma symptom score (nighttime plus daytime) of ≥ 1 on ≥ 4 of the last 7 days of the run-in period and a mean morning PEF during the last 7 days of the run-in period of 50% to 85% of postbronchodilatory PEF, measured at visit 1 (enrolment). **Exclusion Criteria**: inability to use DPI and PFM.
Interventions	• Budesonide 100 µg, 2 inhalations twice daily (treatment 1). • Budesonide/formoterol 80/4.5 µg, 2 inhalations twice daily (treatment 2). • Budesonide/formoterol 80/4.5 µg, 2 inhalations (treatment 3) Dose of budesonide was equivalent in each arm (100 metered dose equivalent to 160 delivered doses). Delivery was pMDI for budesonide only and budesonide/formoterol (treatment 3). Delivery was DPI for budesonide/formoterol (treatment 2).
Outcomes	The primary efficacy endpoint was the change in morning PEF from baseline (mean of the last 10 days of run-in) to the mean value over the 12-week treatment period. Article reports: "Five patients reported serious adverse events: 3 in budesonide group (asthma aggravation (2), nervousness), 2 budesonide/formoterol DPI (acute sinusitis, migraine). No deaths were reported."
Notes	Sponsored by AstraZeneca.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned sequentially in blocks of 6 using a computer-generated randomisation schedule.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind (all participants used a placebo inhaler and an active inhaler).
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed.
Incomplete outcome data (attrition bias)	Low risk	583 of 622 (94%) completed the study.

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Morice 2008 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	SAEs reported by treatment group and cause in paper.
Other bias	Low risk	Sponsorship was not regarded as increasing the risk of bias as the study was well designed.

Murphy 2015

Methods	**Study Design:** randomised, multicentre, double-blind, parallel-group study over 12 weeks in the USA, Bulgaria, and Hungary. Run-in period was 2 weeks prior to randomisation, during which LABAs were discontinued and participants were treated with BUD actuation counter pMDI 160 µg, 2 inhalations twice daily.
Participants	**Population:** 214 adolescents and adults (aged 12 years and over) with asthma requiring daily medium- to high-dose ICS for ≥ 3 months. **Baseline Characteristics:** mean age 42.7 years, mean FEV_1 (L) at baseline was 2.13 (SD 0.56). **Inclusion Criteria:** male or females, 12 years and above, clinical diagnosis of asthma according to the ATS definition ≥ 6 months, pre-bronchodilator FEV_1 ≥ 45% and ≤ 85% of predicted normal, reversible airway obstruction, documented daily use of ICS for ≥ 3 months. **Exclusion Criteria:** history of life-threatening asthma, defined for this protocol as an asthma episode that required intubation or was associated with hypercapnia, respiratory arrest, or hypoxic seizures during the 2 years prior to visit 2, hospitalised during previous 6 months for asthma, required emergency treatment more than once during previous 6 months for an asthma-related condition, intake of oral, rectal, or parenteral glucocorticosteroid within 30 days of enrolment, respiratory infection affecting the asthma within 30 days.
Interventions	• Budesonide/formoterol 2 x 160/4.5 µg twice daily (total 640/18 µg per day) (2 of the budesonide/formoterol arms were combined). • Budesonide 2 x 160 µg twice daily (640 µg per day). Delivery was BAI or pMDI for combined treatment. Delivery was pMDI for budesonide only.
Outcomes	The primary efficacy variable was mean change in pre- and postdose FEV_1 from baseline to 12 weeks.
Notes	The study was sponsored by AstraZeneca.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported, but assumed randomisation as this was a sponsored study.
Allocation concealment (selection bias)	Unclear risk	Not reported, but assumed randomisation as this was a sponsored study.
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and care providers were blinded.

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Murphy 2015 *(Continued)*

Independent Assessment of causation (detection bias) Asthma-related events	Low risk	Assumed that outcome assessors were blinded because the study was sponsored.
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 20% missing data.
Selective reporting (reporting bias)	Low risk	None.
Other bias	Low risk	Sponsorship was not regarded as increasing the risk of bias as the study was well designed.

Nathan 2010

Methods	**Study Design**: randomised, multicentre, double-blind, double-dummy, placebo-controlled, parallel-group study over 26 weeks at 152 sites worldwide. Run-in 2 or 3 weeks mometasone furoate 200 µg twice daily.
Participants	**Population**: 383 adults (in the arms that were eligible for this review) (aged 12 years or older) with asthma (generally moderate uncontrolled asthma). **Baseline Characteristics**: mean age 42 years. FEV_1 73% predicted. Concomitant ICS used by all participants for ≥ 12 weeks (with or without LABA). **Inclusion Criteria**: asthma for ≥ 12 months and on a stable medium-dose ICS regimen for ≥ 12 weeks. FEV_1 60% to 85% predicted, bronchodilator reversibility ≥ 12% in FEV_1 or 0.2 L; alternatively PEF variability over 20%. **Exclusion Criteria**: unstable asthma, smoking history greater than 10 pack-years, past history or present evidence of oropharyngeal candidiasis.
Interventions	• Mometasone furoate/formoterol 200/10 µg twice daily. • Mometasone furoate 200 µg twice daily. Delivery was pMDI (the placebo and formoterol arms in this trial were not considered for this review).
Outcomes	To evaluate the safety and tolerability of the study drugs, clinical assessment and review of laboratory data included monitoring of AEs and SAEs. We found no specific reporting of deaths in the trial reports, but the FDA report detailed that "in P04334, a 53-year-old female (Patient 0012/Site 12) on mometasone furoate/formoterol 200/10 twice daily died from metastatic uterine leiomyosarcoma".
Notes	Sponsored by Merck & Co.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details.

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Nathan 2010 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, double-dummy.
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	18% and 17% withdrawals on combination and mometasone furoate.
Selective reporting (reporting bias)	Low risk	Full SAE data obtained from publications and FDA report.
Other bias	Low risk	Sponsorship was not regarded as increasing the risk of bias as the study was well designed.

Nathan 2012

Methods	**Study Design**: randomised, double-blind, placebo- and active-controlled, parallel-group study over 12 weeks at 59 centres in North America and Europe. Run-in 14 ± 3 days with pMDI 50 µg twice daily fluticasone as maintenance therapy for participants with ICS use prior to screening. Run-in time for those with no prior ICS was 14 to 28 days in which they did not receive any maintenance therapy.
Participants	**Population**: 459 adolescents and adults (aged 12 years and over) with mild to moderate asthma. Fluticasone propionate/formoterol 115 participants, fluticasone 117 participants (placebo group and formoterol-only group not included in this review). **Baseline Characteristics**: mean age 38 years, FEV_1 73% predicted. Concominant ICS used by nearly half of the participants. **Inclusion Criteria**: history of asthma for 12 months, documented ICS use for ≥ 4 weeks prior to screening (ICS-requiring participants), no history of ICS medication for ≥ 12 weeks prior to screening (non-ICS-requiring participants), FEV_1 60% to 85% at screening, reversibility 15% within 12 months of screening. **Exclusion Criteria**: Life-threatening asthma within 12 months or during run-in period, systemic corticosteroid use within 3 months prior to screening, omalizumab use within 6 months, LTRA use within 1 week of study, evidence or history of other clinically significant uncontrolled conditions (hypertension, CHD, CHF, MI, cardiac dysrhythmia), upper or lower respiratory infection 4 weeks prior to screening or during run-in, COPD, CF, or bronchiectasis, HIV-positive status, smoking history (10 pack-years), current smoking, alcohol, substance abuse, confined in institution.
Interventions	• Fluticasone propionate/formoterol 50 µg/5 µg, 2 inhalations twice daily (total 200/20 µg). • Fluticasone propionate 50 µg, 2 inhalations twice daily (total 200 µg). • Formoterol 5 µg, 2 inhalations twice daily (total 20 µg) (not included in this review). • Placebo, 2 inhalations twice daily. Delivery was HFA pMDI for fluticasone propionate/formoterol (treatment 1). Delivery was pMDI for all other treatments.

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Nathan 2012 *(Continued)*

Outcomes	The co-primary efficacy endpoints were mean change in FEV_1 from baseline to predose at week 12, mean change in FEV_1 from predose at baseline to 2 hours postdose at week 12, and discontinuation due to lack of efficacy. No deaths were reported in the study (all-cause or asthma-related). 1 SAE (all-cause) was reported in the fluticasone propionate/formoterol arm (right-sided renal colic), which was not considered to be treatment related. There were no asthma-related SAEs.
Notes	Sponsored by SkyePharma AG.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was achieved using minimisation with biased coin assignment.
Allocation concealment (selection bias)	Low risk	An interactive voice response system was used to conceal allocation.
Blinding (performance bias and detection bias) All outcomes	Low risk	Dummy placebo and intervention inhalers were identical.
Independent Assessment of causation (detection bias) Asthma-related events	Low risk	Investigators, study site personnel, and representatives involved in monitoring and data management were blinded. Study sponsors were also blinded throughout the study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 20% missing data.
Selective reporting (reporting bias)	Low risk	None.
Other bias	Low risk	Sponsorship was not regarded as increasing the risk of bias as the study was well designed.

NCT01475032

Methods	**Study Design**: randomised, multicentre, multinational, double-blind, double-dummy, parallel-group study over 12 weeks. All participants had a run-in period of 2 weeks of 100 µg beclomethasone.
Participants	**Population**: 638 children (aged 5 to < 12 years) with partially controlled asthma (GINA). **Baseline Characteristics**: age 5 to < 12 years (5 to 8 years = 288/683; 9 to 12 years = 339/638). **Inclusion Criteria**: children (aged ≥ 5 and < 12 years), partially controlled asthma, symptomatic asthmatic patients treated with BDP up to 400 µg or equivalent, FEV_1 ≥ 60% and ≤ 95% of predicted normal values. **Exclusion Criteria**: 2 or more admissions to hospital for asthma exacerbation in the past 12 months or any admission to intensive care ever, occurrence of acute asthma exacerbations or lower respiratory tract infections in the 4 weeks before study entry, history of near-fatal asthma, history of cystic fibrosis,

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NCT01475032 *(Continued)*

	bronchiectasis, or primary ciliary dyskinesia, diagnosis of restrictive lung disease, patients treated with systemic corticosteroids.
Interventions	• Beclomethasone/formoterol 50/6 µg pMDI, 2 inhalations twice daily (total 200/24 µg per day) (treatment A) plus (treatment B) beclomethasone/formoterol 2 inhalations 50/6 µg twice daily (total 200/24 µg per day). • Beclomethasone 50 µg, 2 inhalations twice daily (total 200 µg per day) (treatment C). Delivery was pMDI.
Outcomes	The co-primary efficacy variables were change in FEV_1 from baseline to end of treatment (12 weeks) and change in morning PEF from baseline to end of treatment (12 weeks). No deaths were reported in the study. 4 participants in the combined beclomethasone/formoterol arm had SAEs compared to 1 participant in the beclomethasone-only arm. There were no asthma-related SAEs.
Notes	The study was sponsored by Chiesi Farmaceutici S.p.A.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported, but assumed randomisation as this was a sponsored study.
Allocation concealment (selection bias)	Unclear risk	Not reported, but assumed randomisation as this was a sponsored study.
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and care providers were blinded.
Independent Assessment of causation (detection bias) Asthma-related events	Low risk	Outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 20% missing data.
Selective reporting (reporting bias)	Low risk	None.
Other bias	Low risk	Sponsorship was not regarded as increasing the risk of bias as the study was well designed.

Noonan 2006

Methods	**Study Design**: 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 on single-blind budesonide 80 µg, 2 inhalations twice daily.
Participants	**Population**: 596 adolescents and adults (12 to 87 years) with moderate to severe persistent asthma. budesonide+formoterol (pMDI) 124 participants, budesonide (pMDI) + formoterol (DPI) 115 participants, budesonide (pMDI) 109 participants.

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Noonan 2006 *(Continued)*

	Baseline Characteristics: mean age 41 years. FEV_1 67% predicted. Concomitant ICS used by all participants. **Inclusion Criteria**: moderate to severe persistent asthma treated long term 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 ≥ 12% and 0.20 L from the pre-salbutamol baseline value within 15 to 30 min 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	• Budesonide 160 µg twice daily (treatment1). • Budesonide/formoterol 160/9 µg pMDI twice daily (treatment 2). • Budesonide pMDI and formoterol DPI 160/9 µg twice daily (treatment 3). Delivery was pMDI for budesonide only. Delivery was pMDI for combined budesonide/formoterol (treatment 2). Delivery was pMDI for budesonide and DPI for formoterol in (treatment 3).
Outcomes	The co-primary efficacy variables were baseline-adjusted average 12-hour FEV_1 and predose FEV_1. "Nine subjects had SAEs during double-blind treatment: 4 on budesonide/formoterol pMDI (asthma -2, URTI and ECG T wave inversion), 2 in the formoterol group and 3 in the budesonide + formoterol group (small intestine obstruction, abdominal injury, pneumonia)." Web data found on AstraZeneca clinical trials website SD-039-0717.
Notes	Sponsored by AstraZeneca. Jaeschke 2008 excluded this study as it included more than 20% dropouts.

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.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind.
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	23% withdrawals in combined arms and 28% in budesonide arm.
Selective reporting (reporting bias)	Low risk	Full SAE data on website.
Other bias	Low risk	Sponsorship was not regarded as increasing the risk of bias as the study was well designed.

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O'Byrne 2001

Methods	**Study Design:** a randomised, double-blind, parallel-group study over 12 months from January 1998 to February 2000 at 198 centres in 17 countries. Run-in 1 month.
Participants	**Population**: 1970 adults (18 to 76 years) with mild asthma (Group A 698) and mild to moderate asthma (Group B 1272). **Baseline Characteristics**: (Group A) mean age 31 years. FEV_1 90% predicted. Concomitant ICS used by no participants. (Group B) mean age 37 years. FEV_1 87% predicted. Concomitant ICS used by all participants. **Inclusion Criteria**: 12 years of age and older. Diagnosis of stable asthma, according to the ATS. (Group A) had used no ICS for ≥ 3 months, pre-bronchodilator FEV_1 % predicted ≥ 70% at visit 1. 15-minute postbronchodilator FEV_1 % predicted of ≥ 80% at visit 1 (2 × 0.5 mg Bricanyl Turbuhaler). (Group B) taking no more than 400 µg of inhaled budesonide or its equivalent for ≥ 3 months, pre-bronchodilator FEV_1 % predicted ≥ 50% at visit 1. 15-minute postbronchodilator FEV_1 % predicted ≥ 70% at visit 1 (2 x 0.5 mg Bricanyl Turbuhaler). **Exclusion Criteria**: use of OCS within 3 months before visit 1, beta-blocker therapy (eye drops included). Pregnant or lactating women or women not using acceptable contraceptives as judged by the investigator, participants with a history of smoking greater than 15 pack-years.
Interventions	(This report relates to participants given 200 µg budesonide twice daily (1) or 400 µg budesonide twice daily (2)): (Group A) • Budesonide 200 µg (1). • Budesonide/formoterol 200/4.5 µg (1). Placebo arm from Group A was not included in this review. (Group B) • Budesonide 200 µg. • Budesonide/formoterol 200/4.5 µg. • Budesonide 400 µg (2). • Budesonide/formoterol 400/4.5 µg (2). Delivery was by Turbuhaler.
Outcomes	Primary variable was time to first severe asthma exacerbation, expressed as the risk for a first severe exacerbation, and rate (proportion) of poorly controlled days. SAEs are not mentioned at all in the article publication, and the web report (SD-037-0345) gives only total numbers of participants with SAEs for Groups A and B (with no indication of treatment group). AstraZeneca has provided a breakdown of all-cause SAEs and asthma-related SAEs (AstraZeneca data on file 2008). 1 death was not reported in the article but was mentioned in the web report as probably due to "septic shock" in Group A. Sears 2009 indicates that the death was also related to status asthmaticus and occurred in a participant who was taking budesonide/formoterol combination treatment. The full report of the death from the sponsors is as follows: "One of the deaths occurred in a 35 year old female after an 8-day hospitalisation for a severe asthma attack leading to intubation, ventilation, and nosocomial pneumonia with septic shock".

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O'Byrne 2001 *(Continued)*

Notes	Sponsored by AstraZeneca.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers.
Allocation concealment (selection bias)	Low risk	Opaque, consecutively numbered envelopes containing assignment.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind. Identical placebo.
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	81% in Group A and 87% in Group B completed the study.
Selective reporting (reporting bias)	Low risk	SAE data provided by sponsors and found from other sources.
Other bias	Low risk	Sponsorship was not regarded as increasing the risk of bias as the study was well designed.

Paggiaro 2016

Methods	**Study Design:** a randomised, double-blind, double-dummy, multicentre, multinational, 2-arm parallel-group study over 12 weeks across 9 European countries (Bulgaria, Czech Republic, France, Germany, Hungary, Italy, Poland, Russia, and the UK). Run-in 2 weeks on extrafine beclomethasone 800 µg daily.
Participants	**Population:** 376 adults (aged 18 years and over) with persistent, not optimally controlled asthma. **Baseline Characteristics:** adults with a mean age of 49.3 years, FEV_1 64.5% predicted normal value. **Inclusion Criteria:** Male or female patients aged > 18 years, persistent asthma not optimally controlled (based on GINA 2010 asthma control parameters), on high doses of ICS or medium dose of ICS + LABA at a stable dose for ≥ 4 weeks prior to screening. FEV_1 ≥ 40% and < 80% of predicted for the patient normal value and ≥ 0.9 L. Documented positive response to the reversibility test, defined as change in FEV_1 ≥ 12% and ≥ 200 mL over baseline, within 30 minutes after administration of 400 µg of salbutamol pMDI. At screening and at the end of the run-in period, patients with inadequately controlled asthma according to GINA 2010 and with a score on the ACQ > 0.75. **Exclusion Criteria:** history of near-fatal asthma or of a past hospitalisation for asthma in ICU or of frequent exacerbations (3 or more asthma exacerbations/year). Hospitalisation, ED admission, or use of systemic steroids (more than 3 days) for asthma exacerbation in the 4 weeks prior to screening visit and during the run-in period. Symptomatic infection of the lower airways in the 4 weeks before the screening visit. Current or ex-smokers with total cumulative exposure equal to or more than 5 pack-years and/or having stopped smoking 1 year or less prior to screening visit.

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Paggiaro 2016 *(Continued)*

	Patients with a clinically significant abnormality at 12-lead ECG or presenting a QTcB interval value in ECG > 450 ms in males or > 470 ms in females).
Interventions	• Beclomethasone/formoterol 200 µg/6 µg, 2 inhalations twice daily (total 800/24 µg/day). • Beclomethasone 100 µg, 4 inhalations twice daily (total 800 µg/day). Delivery was pMDI.
Outcomes	Primary outcome measures included change from baseline to end of treatment (12 weeks) of PEF. Treatment effect AEs were recorded, however the number of participants with events was not reported for each treatment group.
Notes	The authors have been contacted, awaiting response.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sponsored study, assumed that there is low risk of bias.
Allocation concealment (selection bias)	Unclear risk	Sponsored study, assumed that there is low risk of bias.
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and care providers were unaware of treatment allocation.
Independent Assessment of causation (detection bias) Asthma-related events	Low risk	Outcome assessors were unaware of treatment allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low attrition in the study.
Selective reporting (reporting bias)	High risk	Safety outcome data were not sufficiently reported.
Other bias	Unclear risk	Insufficient information to make a judgement.

Pauwels 1997

Methods	**Study Design**: a randomised, double-blind, multicentre, parallel-group study over 12 months at 71 centres in 9 countries: Belgium, Canada, the Netherlands, Israel, Italy, Luxembourg, Norway, Spain, and the UK. Run-in 4 weeks on 800 µg twice daily.
Participants	**Population**: 852 adults (18 to 70 years) with persistent symptomatic asthma. **Baseline Characteristics**: mean age 42 years. FEV_1 76% predicted. Concomitant ICS used by all participants (mean dose 820 µg/day). **Inclusion Criteria**: 18 to 70 years old, who had asthma for ≥ 6 months and had been treated with an ICS for ≥ 3 months. FEV_1 % predicted ≥ 50%, bronchodilator reversibility by an increase of ≥ 15% in FEV_1 over baseline after inhalation of 1 mg of terbutaline. Stable asthma during run-in and compliant with treatment.

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Pauwels 1997 *(Continued)*

	Exclusion Criteria: 3 or more courses of OCS or had been hospitalised for asthma during the previous 6 months. Taking more than 2000 µg of beclomethasone or 1600 µg of budesonide daily by pMDI, 800 µg of budesonide daily by Turbuhaler DPI or 800 µg of fluticasone daily.
Interventions	This study reported (1) low-dose budesonide (100 µg twice daily) and (2) high-dose budesonide (400 µg twice daily). • Budesonide 100 µg twice daily + placebo (1). • Budesonide/formoterol 100 µg/12 µg twice daily (9 µg delivered dose) (1). • Budesonide 400 µg twice daily + placebo (2). • Budesonide/formoterol 400 µg/12 µg twice daily (9 µg delivered dose) (2). Delivery was DPI.
Outcomes	2 primary outcome variables, the rate of severe exacerbations and the rate of mild exacerbations, according to treatment group. SAE data (all-cause and asthma-related) provided by AstraZeneca from data on file 2008. No SAE data provided in the paper publication, except asthma admissions, but the sponsors have provided data on file for the numbers of participants with all-cause and asthma-related SAEs.
Notes	Sponsored by AstraZeneca.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation schedule (Ducharme 2010b).
Allocation concealment (selection bias)	Low risk	Participants were randomly assigned to treatment groups in balanced blocks of 4 at each centre.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind.
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	694 of 852 (81%) completed the study.
Selective reporting (reporting bias)	Low risk	SAE data provided by sponsors.
Other bias	Low risk	Sponsorship was not regarded as increasing the risk of bias as the study was well designed.

Pearlman 2013

Methods	**Study Design**: randomised, double-blind, active-controlled, parallel-group, stratified study over 12 weeks at 43 centres in North America from June 2006 to January 2008. Run-in 14 days (± 3 days) flutica-

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Pearlman 2013 *(Continued)*

	sone 50 µg pMDI twice daily for those who required ICS, and 14 to 28 days for those not requiring ICS at screening.
Participants	**Population**: 357 adolescents and adults (12 to 79 years) with mild to moderate asthma. **Baseline Characteristics**: mean age 37 years, FEV_1 73% predicted, concomitant ICS use by more than half of the participants. **Inclusion Criteria**: 12 months' asthma history, documented ICS use for steroid-requiring participants (≥ 4 weeks prior to screening), no ICS use for ≥ 12 weeks for non-steroid-requiring participants. Documented reversibility 15% within 12 months of screening, symptoms of asthma during run-in. **Exclusion Criteria**: life-threatening asthma within past 12 months or during run-in, ICS use within 3 months before screening, omalizumab use within 6 months, LTRA use within past week, current or past history of clinically significant disease (uncontrolled hypertension, CHD, CHF, MI, cardiac dysrhythmia), upper or lower respiratory infection within 4 weeks of screening or during run-in, COPD, CF, or bronchiectasis, HIV-positive status, smoking history (10 pack-years), current smoking history within 12 months of screening, current or history of alcohol or substance abuse within 12 months of screening, those confined in institution.
Interventions	• Fluticasone propionate/formoterol fumarate 50/5 µg, 2 inhalations twice daily (total 200/20 µg per day). • Fluticasone propionate 50 µg, 2 inhalations twice daily (total 200 µg per day). • Formoterol fumarate 5 µg, 2 inhalations twice daily (total 20 µg per day) (data not used in this review). Delivery was HFA pMDI.
Outcomes	The 2 co-primary outcomes were mean FEV_1 change from morning predose at baseline to morning predose at 12 weeks, and mean FEV_1 change from morning predose at baseline to 2-hour postdose at 12 weeks. No deaths were reported in the study. 1 participant in the fluticasone/formoterol arm (attempted suicide) and 1 participant in the fluticasone arm (torn cartilage in right knee) had an all-cause SAE, but these events were not considered to be related to the study medication. There were no asthma-related SAEs.
Notes	The study was sponsored by Skyepharma.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation method not reported, assumed as the trial was pharma sponsored.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported.
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and care providers were blinded.
Independent Assessment of causation (detection bias) Asthma-related events	Low risk	Assumed that outcome assessors were blinded because the study was sponsored.
Incomplete outcome data (attrition bias)	Unclear risk	Not reported.

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Pearlman 2013 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	None.
Other bias	Low risk	Sponsorship was not regarded as increasing the risk of bias as the study was well designed.

Pearlman 2017

Methods	**Study Design**: a randomised, double-blind, parallel-group, multicentre study over 12 weeks performed from April 2014 through April 2016 at 88 sites in the USA, Mexico, Panama, and Slovakia. Run-in of 7 to 28 days on low-dose ICS (budesonide DPI 90 µg x 1 inhalation twice daily (80 µg delivered dose)).
Participants	**Population**: 279 children (aged 6 to < 12 years) with asthma. **Baseline Characteristics**: mean age 9 years, asthma duration 5.9 years, concomitant use of ICS by all participants (medium use by 90% of participants), FEV_1 74% predicted. **Inclusion Criteria**: ATS diagnosis of asthma ≥ 6 months prior to study start, FEV_1 60% to 100% predicted normal, demonstrated reversibility of clinic FEV_1 of ≥ 12% from pre-salbutamol level within 15 to 30 minutes after administration of a standard dose of salbutamol. **Exclusion Criteria**: hospitalised ≥ once or required emergency treatment more than once for an asthma-related condition during the 6 months prior to visit 1, required treatment with systemic corticosteroids (e.g. oral, parenteral, or rectal) for any reason within the 6 weeks prior to visit 1.
Interventions	• Budesonide/formoterol 80/2.25 µg, 2 inhalations twice daily (total 320/9 µg per day). • Budesonide/formoterol 80/4.5 µg, 2 inhalations twice daily (total 320/18 µg per day). • Budesonide 80 µg, 2 inhalations twice daily (320 µg per day). Delivery was pMDI.
Outcomes	The primary efficacy variable was the change from baseline predose clinic FEV_1 (value at randomisation, week 0) to the 1-hour postdose clinic FEV_1 at week 12. No deaths were reported in the study. 1 participant had an all-cause SAE (acute lymphocytic leukaemia) in the ICS-only arm, and 1 participant reported an asthma-related SAE (asthma exacerbation) in the ICS only arm.
Notes	The study was sponsored by AstraZeneca, LP.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratified randomisation method was followed.
Allocation concealment (selection bias)	Low risk	An interactive voice response system/interactive web response system was used to allocate participants.
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and care providers were blinded.

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Pearlman 2017 *(Continued)*

Independent Assessment of causation (detection bias) Asthma-related events	Low risk	Outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 20% missing data.
Selective reporting (reporting bias)	Low risk	None.
Other bias	Low risk	Sponsorship was not regarded as increasing the risk of bias as the study was well designed.

Pertseva 2013

Methods	**Study Design**: a randomised, double-blind, active-controlled, parallel-group, stratified, multicentre study over 12 weeks at 68 sites in Europe, South America, and the USA (Argentina, Chile, Hungary, Mexico, Peru, Poland, Romania, South Africa, Ukraine, the USA). All participants had a run-in period of 14 ± 3 days of 100 or 200 µg fluticasone/day.
Participants	**Population**: 483 adolescents and adults with moderate to severe asthma. **Baseline Characteristics**: mean age 42 years, 13% of participants were adolescents, FEV_1 % predicted 63.5%, concomitant ICS use by all participants. **Inclusion Criteria**: ≥ 12 years at screening, history of asthma for 12 months prior to screening, documented use of ICS for ≥ 4 weeks prior to screening, requiring ICS, FEV_1 of 40% to 80% of predicted normal values at both screening and baseline visits, documented reversibility within 12 months of screening, defined as a ≥ 15%. **Exclusion Criteria**: life-threatening asthma within past year or during run-in period, history of systemic (oral or injectable) corticosteroid medication within 3 months before screening, upper or lower respiratory infection within 4 weeks prior to screening or during run-in period, COPD, CF, bronchiectasis, smoking history (10 pack-years), current smoking history within 12 months prior to screening, previous exposure to Flutiform.
Interventions	• Fluticasone/formoterol (SKP) 125/5 µg, 2 inhalations twice daily (total 500/20 µg per day). • Fluticasone (GSK) 125 µg, 2 inhalations twice daily (total 500 µg per day). • Fluticasone (SKP) 125 µg, 2 inhalations twice daily (total 500 µg per day). Delivery was pMDI.
Outcomes	The 2 co-primary efficacy variables measured were mean FEV_1 change from predose at baseline to 2 hours' post dose at 12 weeks, and PEFR. No deaths occurred in the study. There were no all-cause SAEs. Asthma-related SAEs occurred in all 3 arms (1 participant in the fluticasone/formoterol arm, 2 participants in the GSK fluticasone arm, and 1 participant in the SKP fluticasone arm).
Notes	The study was sponsored by Skyepharma and Abbott Respiratory LLC.

Risk of bias

Bias	Authors' judgement	Support for judgement

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Pertseva 2013 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Randomisation method not reported, assumed as the trial was sponsored by a pharmaceutical company.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported.
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and care providers were blinded.
Independent Assessment of causation (detection bias) Asthma-related events	Low risk	Assumed that outcome assessors were blinded because the study was sponsored.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported.
Selective reporting (reporting bias)	Low risk	None.
Other bias	Low risk	Sponsorship was not regarded as increasing the risk of bias as the study was well designed.

Peters 2008

Methods	**Study Design**: a randomised, double-blind, single-dummy, multicentre, phase III, parallel-group study over 52 weeks from August 2003 to February 2005 at 77 centres in the USA. Run-in 2 weeks on budesonide 320 µg twice daily (LABA discontinued).
Participants	**Population**: 708 adults (12 to 81 years) with moderate to severe persistent asthma. **Baseline Characteristics**: mean age 40 years. FEV_1 72% predicted. Concomitant ICS used by all participants (mean daily dose around 500 µg). **Inclusion Criteria**: 12 years of age and older with a documented clinical diagnosis of moderate to severe asthma for ≥ 6 months before screening, received maintenance asthma treatment with a stable dose of ICS for ≥ 4 weeks before the screening visit. FEV_1 % predicted of ≥ 45%, bronchodilator reversibility by an increase of ≥ 12% in FEV_1 and ≥ 0.20 L from baseline within 15 to 30 minutes after administration of a fast-acting $beta_2$-agonist or have a documented history of this level of reversibility after administration of a fast-acting $beta_2$-agonist whilst using ICS within 1 year of screening. Requiring 2 asthma controller medications or with a history of ≥ 2 asthma-related nighttime awakenings or ≥ 3 uses of rescue medication within the week before screening. Required to be non-smokers, with a less than 20-pack-year smoking history. **Exclusion Criteria**: had a significant disease or disorder (e.g. cardiovascular, pulmonary (other than asthma), hepatic, renal) that, in the opinion of the investigator, could put the participant at risk or influence the results of the study. In addition, those treated with systemic corticosteroids within 30 days before screening or during the period between screening and randomisation were excluded.
Interventions	• Budesonide/formoterol 640/18 µg twice daily. • Budesonide/formoterol 320/9 µg twice daily (this arm was not used in the analysis for this review). • Budesonide 640 µg twice daily.

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Peters 2008 *(Continued)*

	Delivery was pMDI.
Outcomes	Because this study was a safety study, no single variable was considered primary. However, spirometry (predose and 2-hour postdose FEV_1) was conducted at each study visit to detect any untoward decreases in lung function over the 52-week period. Web report indicates 21 participants with SAE on budesonide/formoterol 640/18 µg twice daily and 5 on budesonide 640 µg twice daily. No deaths in the study. Article reports 1 asthma SAE in the budesonide/formoterol 640/18 µg twice-daily group.
Notes	Sponsored by AstraZeneca (SD-039-0728).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly assigned using a 3:1:1 overall randomisation scheme and a computer-generated allocation schedule.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind.
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	579 of 708 (82%) completed the study.
Selective reporting (reporting bias)	Low risk	SAE data available from paper and web report.
Other bias	Low risk	Sponsorship was not regarded as increasing the risk of bias as the study was well designed.

Peters 2016

Methods	**Study Design**: randomised, double-blind, active-controlled, multicentre, parallel-group study over 26 weeks in various countries (Argentina, Brazil, Bulgaria, Chile, Colombia, Czech Republic, France, Germany, India, Italy, Mexico, Panama, Peru, Philippines, Poland, Puerto Rico, Republic of Korea, Romania, Russian Federation, Slovakia, South Africa, Thailand, Ukraine, the UK, the USA, Vietnam). No report of run-in ICS.
Participants	**Population**: 11,693 adolescents and adults (aged 12 to ≥ 65 years) with persistent asthma and receiving daily medication. **Baseline Characteristics**: mean age 43 years, concomitant ICS use by most participants. **Inclusion Criteria**: ≥ 12 years of age, documented clinical diagnosis of asthma for ≥ 1 year prior to visit 2, history of ≥ 1 asthma exacerbation (including: requiring systemic corticosteroids between 4 and 12

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Peters 2016 *(Continued)*

	months prior to randomisation, asthma-related hospitalisation between 4 and 12 months prior to randomisation, current use of ICS, ICS/LABA combination or ICS/LTRA combination, or ICS + other maintenance therapy for ≥ 4 weeks prior to randomisation, LTRA as monotherapy at stable dose for ≥ 4 weeks prior to randomisation, daily SABA 4 weeks prior to randomisation (if ≥ 1.5 on ACQ). **Exclusion Criteria**: history of life-threatening asthma, treatment with systemic corticosteroids (tablets, suspensions, or injectable) for any reason within 4 weeks prior to visit 2, ongoing exacerbation requiring treatment with systemic corticosteroids, asthma exacerbation within 4 weeks of randomisation or more than 4 separate exacerbations in the 12 months preceding randomisation or more than 2 hospitalisations for treatment of asthma in the 12 months preceding randomisation, respiratory infection or other viral/bacterial illness, or is recovering from such an illness at the time of visit 2, asthma symptoms that persisted throughout the day on 2 consecutive days, PEF ≥ 50% of predicted normal, malignancy in past 5 years, any significant disease or disorder that would risk patient participation or influence results of study.
Interventions	• Budesonide/formoterol 160/4.5 µg, 2 inhalations twice daily (total (640/18 µg per day). • Budesonide/formoterol 80/4.5 µg, 2 inhalations twice daily (total 320/18 µg per day). • Budesonide 160 µg, 2 inhalations twice daily (total 640 µg per day). • Budesonide 80 µg, 2 inhalations twice daily (total 160 µg per day). Budesonide/formoterol 160/4.5 µg, 2 inhalations twice daily versus budesonide 160 µg, 2 inhalations twice daily. Budesonide/formoterol 80/4.5 µg, 2 inhalations twice daily versus budesonide 80 µg, 2 inhalations twice daily. Delivery was pMDI.
Outcomes	The primary objective was to evaluate the risk of asthma-related SAEs (defined as a composite of asthma-related deaths, intubations, and hospitalisations), with the first serious asthma-related event as the primary endpoint. Safety assessments were limited to SAEs (including death from any cause), discontinuations resulting from adverse events, and discontinuations resulting from exacerbations. For budesonide/formoterol, 2 inhalations 160/4.5 µg twice daily versus budesonide, 2 inhalations 160 µg twice daily: There were 4 deaths in the budesonide/formoterol arm and 5 deaths in the budesonide arm. There were 2 asthma-related deaths in the budesonide/formoterol arm. There were 104 adults with all-cause SAEs in the budesonide/formoterol arm and 92 in the budesonide arm. Asthma-related SAEs occurred in 37 participants in the budesonide/formoterol arm and 32 in the budesonide arm. For budesonide/formoterol, 2 inhalations 80/4.5 µg twice daily versus 2 inhalations budesonide 80 µg twice daily: There were 2 deaths in the budesonide/formoterol arm and 3 deaths in the budesonide arm. There were no asthma-related deaths in either treatment arm. All-cause SAEs occurred in 19 participants in the budesonide/formoterol arm and 28 participants in the budesonide arm. In the budesonide/formoterol arm 6 participants had an asthma-related SAE, and in the budesonide arm 8 participants had an asthma-related SAE.
Notes	The study was sponsored by AstraZeneca.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was stratified according to dose level of ICS on the basis of asthma control and prior asthma therapy.

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Peters 2016 *(Continued)*

Allocation concealment (selection bias)	Low risk	Not reported, but assumed done because study is sponsored.
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and care providers were blinded to formoterol (but not to dose of budesonide).
Independent Assessment of causation (detection bias) Asthma-related events	Low risk	Independent blind assessment of safety outcomes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 20% missing data.
Selective reporting (reporting bias)	Low risk	None.
Other bias	Low risk	Sponsorship was not regarded as increasing the risk of bias as the study was well designed.

Ploszczuk 2014

Methods	**Study Design**: randomised, double-blind, parallel-group, multicentre study over 12 weeks from March 2012 to November 2013 across multiple sites (Bulgaria, Czech Republic, Hungary, India, Poland, Romania, Russian Federation, Ukraine). Run-in 2 to 4 weeks of ICS.
Participants	**Population:** 512 children (aged 5 to < 12 years) with asthma. **Baseline Characteristics:** 66% males, 33% females included in the study. **Inclusion Criteria:** male and female children aged 5 to < 12 years who had a known history of moderate to severe persistent reversible asthma for ≥ 6 months prior to screening visit, FEV_1 of ≥ 60% to ≤ 90% predicted during the screening period followed by appropriate withholding of asthma medications (no LABA within 12 hours with or without SABA within 6 hours of PFT; no ICS on the day of screening), documented reversibility of ≥ 15% FEV_1 in the screening period, current ICS use at stable dose for ≥ 4 weeks prior to screening, inadequate asthma control on ICS alone at ≤ 500 µg fluticasone equivalents per day or controlled asthma on ICS-LABA combination at ICS dose ≤ 200 µg fluticasone equivalents per day, demonstrated satisfactory pMDI and spacer technique, perform adequate spirometry, willing and able to add information in electronic diary with parent or guardian's help, attend all study visits, willing and able to substitute pre-study inhaler medication for entire study duration, if female postmenarche, a urine pregnancy test may be undertaken at discretion of the investigator and parents/legal representative (test must be negative), written informed consent and assent obtained as per national law. **Exclusion Criteria:** near-fatal or life-threatening asthma within the past year (including intubation), hospitalisation or emergency visit for asthma within the past 6 months, history of systemic (injectable/oral) corticosteroid medication within 1 month of screening visit, current or prior non-response or partial response only to ICS-LABA combination, evidence of clinically unstable disease (determined by medical history, clinical laboratory tests, physical examination), clinically significant upper and lower respiratory infection within 4 weeks before screening, significant non-reversible active pulmonary disease, known HIV-positive status, current smoking history within 12 months before screening, current alcohol/substance abuse within 12 months before screening, beta-blocking agents, tricyclic antidepressants, monoamine oxidase inhibitors, astemizole (Hismanal), quinidine-type antiarrhythmics, or potent CYP 3A4 inhibitors such as ketoconazole within 1 week prior to screening, current use of medications that could affect outcome of study, hypersensitivity/idiosyncratic reaction to test

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Ploszczuk 2014 *(Continued)*

	medication/components, had an investigational medicinal product within 30 days of screening, current participation on a clinical study.
Interventions	• Fluticasone propionate/formoterol 100/10 µg twice daily (total 200/20 µg per day). • Fluticasone propionate 100 µg twice daily (total 200 µg per day). • Fluticasone propionate/salmeterol 100/50 µg twice daily (total 200/100 µg per day) (this arm was not used in the analysis of this review). Delivery was pMDI.
Outcomes	The primary efficacy variables measured were change from baseline of predose to 2-hour postdose FEV_1 over 12 weeks. Safety and tolerability profiles were reported to be similar in all treatment groups, but data were not reported.
Notes	The study was sponsored by Mundipharma Research Ltd. This is a conference abstract that was also published in another journal (Ploszczuk 2014). The trial was published on ClinicalTrials.gov and EudraCT websites.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Not clearly reported, but the trial was for regulatory purposes.
Allocation concealment (selection bias)	Low risk	The randomisation schedule was filed securely by interactive response technology.
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding was properly maintained throughout the study. Each participant received 2 inhalers (double-dummy).
Independent Assessment of causation (detection bias) Asthma-related events	High risk	No independent assessment of causation reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants who took ≥ 1 dose of treatment were included in the safety analysis.
Selective reporting (reporting bias)	Low risk	SAEs reported on the EU Clinical Trials Register.
Other bias	Low risk	Sponsorship was not regarded as increasing the risk of bias as the study was well designed.

Pohunek 2006

Methods	**Study Design**: a randomised, double-blind, double-dummy, active-controlled, multicentre, parallel-group study over 12 weeks from March 2002 to March 2003 at 80 centres in 8 countries: Austria (5), Belgium (11), Czech Republic (14), France (11), Hungary (12), Poland (17), Spain (8), and Switzerland (2).

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Pohunek 2006 *(Continued)*

	Run-in 2 weeks on previous dose of ICS, but LABA appears to have been withdrawn from the 40% previously taking LABA?
Participants	**Population**: 630 children (4 to 11 years) with asthma. **Baseline Characteristics**: mean age 8 years. FEV_1 92% predicted. Concomitant ICS used by all participants (mean 450 µg/day), and around 40% had previously been taking LABA. **Inclusion Criteria**: outpatients aged 4 to 11 years who had been diagnosed with asthma (as defined by the ATS) for a minimum period of 6 months, to have a pre-bronchodilator PEF ≥ 50% of predicted normal, and to have received treatment with an ICS (any brand) for ≥ 3 months before entry into the study, with the dose remaining constant (375 to 1000 µg/day) during the 30 days immediately before enrolment. Had to have a history of an average of more than 1 clinically important exercise-induced bronchoconstriction per week during the 3 months leading up to the study. **Exclusion Criteria**: used oral, parenteral, or rectal corticosteroids within 30 days of inclusion in the study; any respiratory infection affecting asthma control within the 30 days before enrolment; any significant disease or concomitant disorder; known or suspected hypersensitivity to the study medication or inhaled lactose. Use of inhaled anticholinergics, beta-blockers (including eye drops), xanthines, and other antiasthma products was not permitted during the study.
Interventions	• Budesonide/formoterol 80/4.5 µg, 2 inhalations twice daily. • Budesonide 100 µg, 2 inhalations twice daily. • Budesonide 100 µg, 2 inhalations twice daily + formoterol 4.5 µg, 2 inhalations twice daily (separate inhalers). Equivalent budesonide in each arm (400 µg metered dose). Delivery was DPI.
Outcomes	The primary efficacy variable was the change from baseline to treatment (average of the 12-week treatment period) in morning PEF. Article reports: "Serious adverse events were experienced by a total of 11 participants: 3 budesonide (fracture, laryngitis, torticollis), 5 with budesonide and formoterol in separate inhalers (appendicitis (2), vomiting, laryngitis, pneumonia) and 3 with budesonide (gastroenteritis (2) and fracture)". No deaths were reported.
Notes	Sponsored by AstraZeneca.

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) All outcomes	Low risk	Double-blind.
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed.

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Pohunek 2006 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	592 of 630 (94%) completed the study.
Selective reporting (reporting bias)	Low risk	SAEs reported by treatment group and event type in article.
Other bias	Low risk	Sponsorship was not regarded as increasing the risk of bias as the study was well designed.

Price 2002

Methods	**Study Design**: a randomised, double-blind, multicentre, parallel-group study in 152 general practices in the UK and the Republic of Ireland comprising 2 parts (4 weeks and 24 weeks). Run-in 7 to 14 days.
Participants	**Population**: 663 adolescents and adults (12 years of age and over) with mild to moderate asthma (part 1). 505 continued to part 2. **Baseline Characteristics**: mean age 38 years. Concomitant ICS used by 67% of participants. **Inclusion Criteria**: 12 years of age and older with a diagnosis of asthma confirmed in the clinical record for ≥ 3 months. Current treatment had to include an SABA alone or with an ICS (< 400 µg/day beclomethasone dipropionate or budesonide via pMDI, or < 200 µg/day fluticasone or budesonide via Turbohaler) at a constant dose for > 4 weeks. Were required to have experienced asthma symptoms (chest tightness, cough, wheeze, or shortness of breath) on a minimum of 3 days in the week before enrolment into the study. Either reversibility of PEF/FEV_1 > 12% (or > 9% of predicted normal) or a diurnal variation of > 20% on ≥ 1 day during the run-in period. **Exclusion Criteria**: more severe or recently unstable asthma, PEF < 50% predicted; currently receiving (during 4 weeks before enrolment) nebulised therapy, oral corticosteroids, leukotriene antagonist, or LABA; a clinically relevant upper respiratory tract infection in the 4 weeks leading up to enrolment, irreversible chronic airways disease.
Interventions	• Budesonide 400 µg twice daily/formoterol 9 µg twice daily. • Budesonide 400 µg twice daily + placebo. Data from part 2 used after 4 weeks' stabilisation of participants on the same treatments in part 1. Delivery was DPI.
Outcomes	In part 2, the primary outcome measure was time to the first mild asthma exacerbation. SAE data not reported in article but obtained from Jaeschke 2008.
Notes	Supported by grant from AstraZeneca.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers (Ducharme 2010b).
Allocation concealment (selection bias)	Low risk	Numbered coded solutions supplied by pharmacy (Ducharme 2010b).

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Price 2002 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind.
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	400 of 505 (79%) completed part 2.
Selective reporting (reporting bias)	Low risk	Data on SAEs from Jaeschke 2008.
Other bias	Low risk	Sponsorship was not regarded as necessarily increasing the risk of bias as the study was well designed.

Samson 2012

Methods	**Study Design**: randomised controlled study conducted in 2012 in the Philippines.
Participants	**Population**: 79 adults (18 years of age and over) diagnosed with mild to moderate persistent asthma. **Baseline Characteristics**: not reported. **Inclusion Criteria**: not reported. **Exclusion Criteria**: systemic corticosteroids, severe hepatic, renal, or cardiovascular disease, respiratory tract infection in the past 4 weeks, more than 10-pack-year smoking history, history of significant alcoholism or drug use, history of mental illness, pregnant or lactating women, use of medications including beta-blockers, and patients with acute exacerbations.
Interventions	• Budesonide/formoterol 320/9 µg. • Budesonide 400 µg. Participants were allowed to take salbutamol as required. Delivery was not reported.
Outcomes	The outcome measures included peak expiratory flow rate, nocturnal symptoms, limitations of activities, shortness of breath, and adverse events.
Notes	This publication was a conference abstract; the full publication was not identified.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to make judgement.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to make judgement.

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Samson 2012 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Insufficient information to make judgement.
Independent Assessment of causation (detection bias) Asthma-related events	Unclear risk	Insufficient information to make judgement.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to make judgement.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to make judgement.
Other bias	Unclear risk	Insufficient information to make judgement.

SD-039-0714

Methods	**Study Design:** a randomised, double-blind, multicentre, parallel-group study over 12 weeks from August 2001 to September 2002 at 122 centres in the UK (119 general practice centres and 3 hospital centres). Run-in 2 weeks on budesonide 200 µg twice daily. Efficacy and safety of budesonide/formoterol Turbuhaler (160/4.5 µg twice-daily delivered dose) compared with budesonide Turbuhaler (200 µg twice-daily metered dose) in steroid-using asthmatic adolescent participants. A double-blind, double-dummy, randomised, parallel-group, phase III, multicentre study (ATTAIN study).
Participants	**Population**: 271 steroid-using asthmatic adolescents (11 to 17 years). **Baseline Characteristics**: mean age 14 years. FEV_1 75% predicted. Concomitant ICS used by all participants. **Inclusion Criteria**: 12 to 17 years old. FEV_1 % predicted 40% to 90%, bronchodilator reversibility of ≥ 12% in FEV_1 and experiencing asthma symptoms. Receiving an ICS for perennial asthma, dose of ICS within or equal to 375 to 1000 µg daily dose (within the licenced dose for participant's age). **Exclusion Criteria**: not obvious.
Interventions	• Budesonide/formoterol 160/4.5 µg twice daily. • Budesonide 200 µg twice daily. Delivery was DPI.
Outcomes	Morning PEF as recorded daily in diary by participants. Web report indicates no deaths and 1 SAE in each group (overdose on budesonide/formoterol and bronchospasm on budesonide).
Notes	Sponsored by AstraZeneca.

Risk of bias

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

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SD-039-0714 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not reported.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind.
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	219 of 271 (81%) completed the study.
Selective reporting (reporting bias)	Low risk	SAE data in web report.
Other bias	Low risk	Sponsorship was not regarded as increasing the risk of bias as the study was well designed.

SD-039-0718

Methods	**Study Design**: a randomised, double-blind, double-dummy, active-controlled study over 12 weeks from July 2002 to October 2003 at 52 centres in the USA. Run-in 2 weeks on 100 µg budesonide twice daily.
Participants	**Population**: 411 children (6 to 15 years) with mild to moderate asthma. **Baseline Characteristics**: mean age 10 years. FEV_1 82% predicted. Concomitant ICS used by all participants (mean 235 µg/day). **Inclusion Criteria**: 6 to 15 years of age, treated long term with a low to medium dose of ICS, FEV_1 % predicted ≥ 50% on ICS therapy, older than 12 years, bronchodilator reversibility of ≥ 12% in FEV_1 and ≥ 0.20 L from the pre-salbutamol value within 15 to 30 minutes after administration of a standard dose of a fast-acting $beta_2$-agonist (salbutamol pMDI, 2 to 4 actuations (90 µg per actuation), with or without a spacer) or after administration of up to 2.5 mg nebulised salbutamol. Younger than 12 years needed to only show reversibility of ≥ 12%. Alternatively, reversibility of PEF of ≥ 15%, but not more than 50%, could be used by any patient to meet the reversibility criterion. **Exclusion Criteria**: not obvious.
Interventions	• Budesonide/formoterol 40/4.5 µg, 2 inhalations twice daily. • Budesonide 40 µg, 2 inhalations twice daily. • Formoterol 4.5 µg, 2 inhalations twice daily DPI delivery (data for this arm not included in this review). Delivery was pMDI for arms 1 and 2.
Outcomes	Primary efficacy variable: morning PEF. Web report lists no deaths and no participants with SAE in groups 1 and 2.

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SD-039-0718 *(Continued)*

Notes	Sponsored by AstraZeneca.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was stratified by age group (children younger than 8 years of age vs children 8 years and older). Participants were randomly assigned to 1 of the 3 treatment groups.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind. Treatments were given in double-dummy fashion because of the differences in devices.
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	28% dropout on budesonide/formoterol and 35% on budesonide (all randomly assigned participants in safety analysis and no events reported!).
Selective reporting (reporting bias)	Low risk	SAE data on web report.
Other bias	Low risk	Sponsorship was not regarded as increasing the risk of bias as the study was well designed.

SD-039-0719

Methods	**Study Design**: a randomised, open-label safety study over 26 weeks from July 2002 to October 2003 at 29 centres in the USA. Run-in 1 week.
Participants	**Population**: 187 children (6 to 11 years of age) with ICS-dependent asthma. **Baseline Characteristics**: mean age 9 years. FEV_1 84% predicted. Concomitant ICS used by all participants. **Inclusion Criteria**: 6 to under 12 years of age with ICS-dependent asthma. FEV_1 % predicted ≥ 50%, documented historic PEF or FEV_1 reversibility ≥ 12% from a pre-salbutamol value within 15 to 30 min after administration of a standard dose of fast-acting $beta_2$-agonist. Patients without a documented history of reversibility must have demonstrated FEV_1 reversibility as above at any time before visit 2. **Exclusion Criteria**: not obvious.
Interventions	• Budesonide/formoterol 160/4.5 µg, 2 inhalations twice daily. • Budesonide 160 µg, 2 inhalations twice daily. Delivery of budesonide/formoterol was pMDI. Delivery of budesonide was by Turbuhaler.

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SD-039-0719 *(Continued)*

Outcomes	**Outcome**: no single variable was considered to be primary. The primary objective of the study was to assess long-term safety. Web report indicates no deaths. 2 SAEs in budesonide/formoterol group (asthma and pneumonia) and 1 in budesonide group (sickle cell anaemia).
Notes	Sponsored by AstraZeneca.

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) All outcomes	High risk	Open.
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	87% completed the study.
Selective reporting (reporting bias)	Low risk	SAE reported fully.
Other bias	Low risk	Sponsorship was not regarded as increasing the risk of bias as the study was well designed.

SD-039-0725

Methods	**Study Design**: a randomised, double-blind, double-dummy, multicentre, active-controlled, parallel-group study over 12 weeks from January 2003 to August 2004 at 128 centres in the USA. Run-in 4 to 5 weeks, single-blind (participants had to be stable on budesonide/formoterol 40/4.5 µg 2 inhalations twice daily). A 12-week, randomised, double-blind, double-dummy, active-controlled study of budesonide/formoterol (Symbicort) pMDI administered once daily in children and adolescents 6 to 15 years of age with asthma.
Participants	**Population**: 522 children and adolescents (6 to 15 years) with asthma. **Baseline Characteristics**: mean age 10 years. FEV_1 78% predicted. Concomitant ICS previously used by all participants (mean 245 µg/day). **Inclusion Criteria**: 6 to 15 years of age with a documented clinical diagnosis of asthma for ≥ 6 months before screening and in stable condition. Should have received maintenance asthma treatment with ICS for ≥ 4 weeks before the screening visit. FEV_1 % predicted of between 60% and 90%, as measured approximately 24 hours after the last dose of LABA and 6 hours after the last dose of SABA. Patients

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SD-039-0725 *(Continued)*

	with an FEV_1 predicted between 90% and 95% could be included if they had an FEV_1/FVC ratio measured on screening spirometry of < 80%. Bronchodilator reversibility of ≥ 12% in FEV_1 and ≥ 0.20 L from baseline within 15 to 30 minutes after administration of a standard dose of fast-acting $beta_2$-agonist, except for participants younger than 11 years of age, who were required to show reversibility of ≥ 12% but not also a change of ≥ 0.20 L. **Exclusion Criteria**: not stated.
Interventions	• Budesonide/formoterol 80/4.5 µg, 2 inhalations once daily. • Budesonide/formoterol 40/4.5 µg, 2 inhalations twice daily. • Budesonide 80 µg, 2 inhalations once daily. Delivery was pMDI. All groups had 160 µg budesonide daily.
Outcomes	Primary variable: evening PEF (from daily diary). "There were no deaths at any time during the study." "6 subjects had an SAE during the double blind treatment period: 2 on budesonide/formoterol (40 µg twice daily; abdominal pain, asthma), 3 in budesonide/formoterol (80 once daily group; influenza, asthma 2) and one in the budesonide group (asthma)."
Notes	Sponsored by AstraZeneca.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation was stratified by age (6 to 11 years of age vs 12 to 15 years of age) at the time of screening in order to ensure an approximately uniform distribution of participants across treatment groups within each of these 2 strata.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind. To maintain blinding with the twice-daily dosing regimen, all participants randomly assigned to receive once-daily dosing were to receive the active treatment in the evening and placebo treatment with a matched device in the morning.
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	499 of 521 participants (96%) completed the study.
Selective reporting (reporting bias)	Low risk	SAEs reported by treatment group and cause.
Other bias	Low risk	Sponsorship was not regarded as increasing the risk of bias as the study was well designed.

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SD-039-0726

Methods	**Study Design**: a randomised, double-blind, double-dummy, multicentre, parallel-group, placebo- and active-controlled study over 12 weeks from April 2003 to June 2004 at 151 centres in the USA. Run-in 4- to 5-week single-blind. A 12-week, randomised, double-blind, double-dummy, placebo- and active-controlled study of budesonide/formoterol (Symbicort) pMDI administered once daily in adults with asthma.
Participants	**Population**: 752 adolescents and adults (16 to 79 years) with asthma. **Baseline Characteristics**: mean age 38 years. FEV_1 75% predicted. Concomitant ICS used by all participants. **Inclusion Criteria**: 16 years of age and older, with a documented clinical diagnosis of asthma for ≥ 6 months before screening, and in stable condition. Received maintenance asthma treatment with a low to medium dose of ICS for ≥ 4 weeks before the screening visit. FEV_1 % predicted of between 60% and 90%, measured ≥ 24 hours after the last dose of LABA and 6 hours after the last dose of SABA. **Exclusion Criteria**: not obvious.
Interventions	• Budesonide/formoterol 160/4.5 µg once daily. • Budesonide/formoterol 80/4.5 µg, 2 inhalations once daily. • Budesonide/formoterol 80/4.5 µg, 2 inhalations twice daily. • Budesonide 160 µg, 2 inhalations once daily. Placebo arm and arm 2 not used in the analysis in this review. Delivery was MDI.
Outcomes	Primary variable: evening PEF (from daily diary). SAE data obtained from web report. 5 participants suffered an SAE: 3 on budesonide/formoterol 80 twice daily (breast cancer in situ, road traffic accident, musculoskeletal chest pain), 1 on budesonide/formoterol 160 daily (prostate cancer), and 1 on budesonide (tension headache). No deaths were reported.
Notes	Sponsored by AstraZeneca.

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) All outcomes	Low risk	Double-blind.
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed.
Incomplete outcome data (attrition bias)	Low risk	707 of 751 (94%) completed the study.

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SD-039-0726 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	SAE data on web report.
Other bias	Low risk	Sponsorship was not regarded as increasing the risk of bias as the study was well designed.

Spector 2012

Methods	**Study Design:** a 12-week, randomised, double-blind, double-dummy, phase IV study comparing the efficacy and safety of budesonide/formoterol (Symbicort) pMDI 160/4.5 µg × 2 actuations twice daily with budesonide DPI 180 µg × 2 inhalations twice daily in adult and adolescent (≥ 12 years) African-American (self-reported) participants with asthma who required a medium to high dose of ICS therapy. Randomisation was stratified by asthma severity, based on daily dosage of ICS at screening (visit 1). Conducted in 46 US centres from June 2008 to September 2009. 2-week run-in on budesonide DPI 90 µg (2 puffs twice daily) and enrolled if symptomatic on 3 or more of 7 consecutive days.
Participants	**Population**: 301 adolescents and adults (12 years of age and over) with moderate to severe persistent asthma. Budesonide/formoterol 156 participants, budesonide 155 participants. **Baseline Characteristics**: mean age 39 years. FEV_1 66% predicted. Concomitant ICS used by all participants. **Inclusion Criteria**: moderate to severe persistent asthma treated long term 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 ≥ 12% and 0.20 L from the pre-salbutamol baseline value within 15 to 30 minutes after administration of a standard dose of salbutamol. **Exclusion Criteria**: requiring hospitalisation once in the preceding 6 months or emergency treatment more than once in the previous 3 months, or systemic corticosteroids in previous 30 days or omalizumab in previous 90 days.
Interventions	• Budesonide/formoterol 160/9 µg, 2 inhalations twice daily. • Budesonide 180 µg, 2 inhalations twice daily. Delivery of budesonide/formoterol was pMDI. Delivery of budesonide was DPI.
Outcomes	Primary efficacy variable was predose FEV_1. SAEs were those that were immediately life-threatening or resulted in death, significant disability, or hospitalisation. No deaths and no SAEs were reported in the article by treatment group and causation.
Notes	Sponsored by AstraZeneca.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was generated by computer-derived sequential allocation and stratification by asthma severity using balanced blocks.
Allocation concealment (selection bias)	Low risk	Randomisation was generated by computer-derived sequential allocation and stratification by asthma severity using balanced blocks.

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Spector 2012 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, double-dummy.
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed.
Incomplete outcome data (attrition bias) All outcomes	High risk	38 of 156 withdrawals on combination treatment and 53 of 155 on budesonide alone (high rate and unbalanced).
Selective reporting (reporting bias)	Low risk	SAE data fully reported.
Other bias	Low risk	Sponsorship was not regarded as increasing the risk of bias as the study was well designed.

Stirbulov 2012

Methods	**Study Design**: randomised, double-blind, multicentre, parallel-group study across 4 centres in Brazil over 12 weeks. All participants received 400 µg budesonide twice daily for 4 weeks prior to randomisation.
Participants	**Population**: 181 adults (18 years of age and over) with uncontrolled asthma. **Baseline Characteristics**: mean age not reported, mean FEV_1 % of predicted was 76%. Rescue salbutamol use and OCS use during exacerbations (courses of OCS consisting of prednisone 40 mg for 3 days, 20 mg for 3 days, and 10 mg for another 3 days) were allowed. Concominant use of other asthma treatments was not allowed. **Inclusion Criteria**: age 18 to 77 years, diagnosis of uncontrolled asthma, non-smokers. **Exclusion Criteria**: Use of OCS, LTRA, immunoglobulins, beta-blockers, digitalis, amiodarone, antifungals, antidepressants, monoamine oxidase inhibitors and tricyclics during the standardisation, atrial fibrillation, flutter, severe and complex tachyarrhythmias atrioventricular block 1, 2, and 3, diabetes mellitus, pregnancy, neuropsychiatric diseases, pulmonary malformations, tuberculosis, CF, immunosuppressive treatment, hospitalisation for asthma or respiratory infection in last 30 days, severe systemic disease.
Interventions	• Budesonide/formoterol 400/12 µg, 2 inhalations twice daily (total 800/24 µg). • Budesonide 400 µg, 2 inhalations twice daily (total 800 µg). Delivery was DPI.
Outcomes	The primary efficacy variable was increase in FEV_1 and morning PEF from baseline to end of treatment at 12 weeks.
Notes	The study was sponsored by Ache Laboratorios Farmaceuticos S.A.

Risk of bias

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

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Stirbulov 2012 *(Continued)*

Random sequence generation (selection bias)	Low risk	Randomisation was performed by permuted blocks of 4 at 1:1 ratio that was computer generated.
Allocation concealment (selection bias)	Unclear risk	Allocation method not reported.
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants were blinded.
Independent Assessment of causation (detection bias) Asthma-related events	Low risk	Investigators were blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported.
Selective reporting (reporting bias)	High risk	Safety data was not reported in the publication.
Other bias	Low risk	Sponsorship was not regarded as increasing the risk of bias as the study was well designed.

Tal 2002

Methods	**Study Design**: a randomised, double-blind, double-dummy, active-controlled, multicentre, parallel-group study over 12 weeks from November 1998 to June 1999 at 48 centres in 7 countries: Hungary (6), the Czech Republic (7), the UK (11), Spain (7), Belgium (4), Israel (4), and South Africa (4). Run-in 2 to 4 weeks on budesonide 400 µg daily (unclear if previous LABA withdrawn).
Participants	**Population**: 286 children (4 to 17 years) with asthma. **Baseline Characteristics**: mean age 11 years. FEV_1 75% predicted. Concomitant ICS used by all participants (mean 548 µg/day), previous LABA use not reported. **Inclusion Criteria**: between 4 and 17 years of age with a diagnosis of asthma (≥ 6 months), FEV_1 % predicted of 40% to 90%, bronchodilator reversibility by an increase of ≥ 15% in FEV_1 over baseline within 15 minutes of inhalation of an SABA. **Exclusion Criteria**: unstable asthma (defined as the use of oral, parenteral, or rectal corticosteroids within 30 days of study commencement), any respiratory infection affecting disease control within the previous 4 weeks, and known hypersensitivity to study medication or inhaled lactose.
Interventions	• Budesonide/formoterol 80/4.5 µg, 2 inhalations twice daily. • Budesonide 100 µg, 2 inhalations twice daily. Delivery was DPI.
Outcomes	The primary efficacy variable was the change in morning PEF from baseline to end of treatment. "A total of 7 patients in the budesonide/formoterol group had a serious adverse event requiring admission to hospital (asthma (5), larynx edema (1), pneumonia (1)." Deaths are not mentioned, nor are any events in the budesonide group. Further clarification was sought from the sponsors, who confirmed no SAEs in the budesonide group.

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Tal 2002 *(Continued)*

Notes	Sponsored by AstraZeneca.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated block randomisation list.
Allocation concealment (selection bias)	Unclear risk	Individual treatment code envelopes provided for each participant.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, double-dummy technique.
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	268 of 286 (94%) completed the study.
Selective reporting (reporting bias)	Low risk	SAEs appear to be fully reported in the article.
Other bias	Low risk	Sponsorship was not regarded as increasing the risk of bias as the study was well designed.

Weinstein 2010

Methods	**Study Design**: randomised, multicentre, double-blind, double-dummy, placebo-controlled, parallel-group study over 12 weeks at 115 sites worldwide. Run-in 2 weeks mometasone furoate 400 µg twice daily (pMDI).
Participants	**Population**: 495 adults (in the arms that were eligible for this review) (12 years of age and over) with severe asthma. **Baseline Characteristics**: mean age 48 years. FEV_1 66% predicted. Concomitant ICS used at high dose by all participants for ≥ 12 weeks (with or without LABA). **Inclusion Criteria**: asthma for ≥ 12 months (with a history of deterioration requiring oral steroids in the previous 2 to 12 months) and on a high-dose ICS regimen (with or without LABA) for ≥ 12 weeks. FEV_1 50% to 85% predicted, bronchodilator reversibility ≥ 12% in FEV_1 or 0.2 L; alternatively, PEF variability over 20%. **Exclusion Criteria**: unstable asthma between screening and baseline, smoking history more than 10 pack-years (or current smoking), past history of pregnancy or clinically significant abnormality in electrocardiogram.
Interventions	• Mometasone furoate/formoterol 400/10 µg twice daily. • Mometasone furoate 400 µg twice daily. • Mometasone furoate/formoterol 200/10 µg twice daily (not used in this review).

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Weinstein 2010 *(Continued)*

	Delivery was pMDI (the placebo and formoterol arms in this trial were not considered for this review).
Outcomes	Primary outcome mean change from baseline in FEV_1 (AUC_{0-12h}) up to week 12. SAEs were those that were immediately life-threatening or that resulted in death, significant disability, or hospitalisation. No deaths and no SAEs were reported with causation on ClinicalTrials.gov.
Notes	Sponsored by Schering-Plough.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	“Randomization was performed in blocks using random numbers generated by SAS.”
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Low risk	"Double-blind."
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	33 of 240 withdrawals on combination and 27 of 255 on mometasone furoate.
Selective reporting (reporting bias)	Low risk	Full SAE data obtained from report of NCT00381485 and from article.
Other bias	Low risk	Sponsorship was not regarded as increasing the risk of bias as the study was well designed.

Weinstein 2019

Methods	**Study Design**: randomised, multicentre, double-blind, active-controlled, parallel-group study over 26 weeks at 35 international centres.
Participants	**Population**: 11,729 adolescents and adults (12 years of age and over) with persistent asthma. **Baseline Characteristics**: mean age 45 years, concomitant ICS use by all participants. **Inclusion Criteria**: persistent asthma for ≥ 12 months, ICS use for ≥ 4 weeks prior to randomisation (ICS with or without LABA or other adjunctive asthma therapy, or using LTRA, xanthine, or SABA as monotherapy), able to discontinue current asthma medication, and history of ≥ 1 asthma exacerbation in previous 4 to 52 weeks. **Exclusion Criteria**: unstable asthma, use of high-dose ICS with or without other adjunctive therapy who have an ACQ6 total score ≥ 1.5, LTRA, xanthine or SABA monotherapy with an ACQ-6 total score < 1.5 (controlled), other significant disease (COPD, CF, other non-asthmatic lung disease), significant underlying cardiovascular condition which may contraindicate use of a beta-agonist, history of smoking greater than 10-pack years, asthma exacerbation within 4 weeks of the baseline visit, more than 4 asthma exacerbations or 2 hospitalisations within 52 weeks of the randomisation visit, known or suspect-

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Weinstein 2019 *(Continued)*

	ed hypersensitivity or intolerance to corticosteroids, beta$_2$-agonists, or any of the (inactive ingredients) excipients present in the medications used in the study, requiring chronic systemic steroids, omalizumab, or other monoclonal or polyclonal antibodies, requiring beta-blockers, history of life-threatening asthma, including an asthma episode that required intubation, associated with hypercapnia requiring non-invasive ventilatory support, lactating, pregnant, or plans to become pregnant during the course of the study.
Interventions	• Mometasone furoate/formoterol 100/5 µg or 200/5 µg, 2 inhalations twice daily (total 400/20 µg or 800/20 µg) (reported as total of both dosage groups). • Mometasone furoate 100 µg or 200 µg, 2 inhalations twice daily (total 400 µg or 800 µg) (reported as total of both dosage groups). Delivery was MDI.
Outcomes	The co-primary efficacy endpoints were time to first serious asthma outcomes (composite endpoint defined as asthma-related: hospitalisations, intubations, and deaths) in both treatment arms, and time to first severe asthma exacerbation. 5 deaths were reported in the combined mometasone/formoterol arm and 4 deaths in the mometasone-only arm. None of the deaths were asthma-related. Of the participants, 137 in the combined mometasone/formoterol arm had SAEs compared to 136 in the mometasone-only arm. 32 participants in the combined mometasone/formoterol arm had asthma-related SAEs compared to 31 participants in the mometasone-only arm.
Notes	The study was sponsored by Merck Sharp & Dohme Corp.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised, but no further information about randomisation process.
Allocation concealment (selection bias)	Unclear risk	Assumed allocation concealment, but not reported.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Participants were blinded, unclear if care providers were blinded.
Independent Assessment of causation (detection bias) Asthma-related events	Unclear risk	Outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 20% missing data.
Selective reporting (reporting bias)	Low risk	Asthma-related mortality outcome was not reported.
Other bias	Low risk	Sponsorship was not regarded as increasing the risk of bias as the study was well designed.

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Zangrilli 2011

Methods	**Study Design:** a 12-week, randomised, double-blind, active-controlled, multicentre, phase IIIB study. Carried out in 39 US centres between January 2007 and June 2008. 2-week run-in on ICS.
Participants	**Population**: 250 adults (12 years of age and over) with moderate to severe asthma based on historical daily dosing of medium- to high-dose ICS alone or in combination with LABA for 30 days or longer before enrolment. **Baseline Characteristics:** mean age 38 years. FEV_1 68% predicted. Concomitant ICS reported by 91% of participants at a mean dose of 600 µg per day, but FEV_1 rose to 72% predicted after step-down to budesonide 160 µg twice daily during run-in. **Inclusion Criteria**: male or female, Hispanic (self-reported), > 12 years of age. Moderate to severe asthma requiring treatment with an ICS. Diagnosis of asthma for ≥ 6 months. Participants had pre-bronchodilator FEV_1 of 45% to 85% of predicted normal and reversibility of 12% or greater and 0.20 L or greater. Randomly assigned participants had documented daytime or nighttime asthma symptom scores greater than 0 on 3 or more days within 7 consecutive days during a 2-week run-in period on budesonide pMDI 160 µg twice daily. **Exclusion Criteria**: patients requiring treatment with systemic corticosteroids (e.g. oral, parenteral, ocular). Patients who had required hospitalisation once or emergency treatment more than once in the preceding 6 months; used systemic corticosteroids within the previous 30 days; or had a smoking history of 10 or more pack-years.
Interventions	• Budesonide/formoterol 160/9 µg twice daily. • Budesonide 160 µg HFA twice daily. Delivery of budesonide/formoterol was pMDI. Delivery of budesonide was HFA pMDI.
Outcomes	**Primary Outcome:** mean change from baseline in morning PEF. SAEs were those that were immediately life-threatening or that resulted in death, significant disability, or hospitalisation, or that required intervention to prevent 1 of these outcomes. No deaths and no SAEs were reported in the article by treatment group and causation.
Notes	Sponsored by AstraZeneca.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization used a computer-generated allocation schedule."
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Low risk	"Double-blind (subject, caregiver, investigator, outcomes assessor)."
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed.

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Zangrilli 2011 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	18 of 127 and 21 of 123 withdrawals given combination and budesonide, respectively.
Selective reporting (reporting bias)	Low risk	Full report of SAEs in published article and at ClinicalTrials.gov.
Other bias	Low risk	Sponsorship was not regarded as increasing the risk of bias as the study was well designed.

Zetterstrom 2001

Methods	**Study Design**: a randomised, double-blind, double-dummy, active-controlled, parallel-group study over 12 weeks at 63 centres in 6 countries: Finland (7), Germany (12), Ireland (6), Norway (12), Spain (11), and Sweden (15). Run-in 2 weeks receiving usual ICS (no mention of continuing previous LABA).
Participants	**Population**: 362 adults (18 to 78 years) with asthma not controlled with ICS alone. **Baseline Characteristics**: mean age 47 years. FEV_1 74% predicted. Concomitant ICS used by all participants (mean dose 960 µg/day). **Inclusion Criteria**: 18 years of age and older, using ICS at a constant daily dose of ≥ 500 µg for ≥ 30 days before entry, FEV_1 % predicted of 50% to 90%, bronchodilator reversibility by an increase of ≥ 15% in FEV_1 over baseline after inhalation of terbutaline sulphate 1 mg (Bricanyl Turbuhaler) or salbutamol 0.4 mg. **Exclusion Criteria**: use of oral, parenteral, or rectal glucocorticosteroids within 30 days before study entry; respiratory infection; seasonal asthma; severe cardiovascular disorder; beta-blocker therapy; smoking history (10 pack-years); pregnancy or failure to use acceptable contraceptives in women of childbearing potential.
Interventions	• Budesonide/formoterol 160/4.5 µg, 2 inhalations twice daily. • Budesonide 200 µg/formoterol 4.5 µg, 2 inhalations twice daily. • Budesonide 200 µg, 2 inhalations twice daily. Delivery was DPI, equivalent to budesonide 400 µg twice-daily metered dose in all arms.
Outcomes	The primary efficacy variable was change in average morning PEF from baseline to study end. Article reports: "There were five serious adverse events in the single inhaler therapy group and one in the budesonide alone group. There was one death by suicide and four hospital admissions (due to pneumonia, liver cysts, Ischaemic stroke and intervertebral disc prolapse)". The sponsors confirmed that the death occurred in a participant who was using a combined budesonide/formoterol inhaler.
Notes	Sponsored by AstraZeneca.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerised randomisation occurred on a per-country basis.

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Zetterstrom 2001 *(Continued)*

Allocation concealment (selection bias)	Low risk	Individual treatment codes were kept in sealed envelopes until data analysis.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind; participants successively used 3 numbered inhalers (identical in appearance to the corresponding placebo) each morning and evening.
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	309 of 362 (85%) completed the study.
Selective reporting (reporting bias)	Low risk	SAE by treatment group in article.
Other bias	Low risk	Sponsorship was not regarded as increasing the risk of bias as the study was well designed.

ACQ: Asthma Control Questionnaire
AE: adverse event
ATS: American Thoracic Society
AUC: area under the curve
BAI: breath-actuated inhaler
BDP: beclomethasone
BUD: budesonide
CF: cystic fibrosis
CFC: chlorofluorocarbon
CHD: coronary heart disease
CHF: congestive heart failure
COPD: chronic obstructive pulmonary disease
DPI: dry powder inhaler
ECG: electrocardiogram
ED: emergency department
EU: European Union
FDA: US Food and Drug Administration
FEV_1: forced expiratory volume in 1 second
FVC: forced vital capacity
GINA: Global Initiative for Asthma
HFA: hydrofluoroalkane
ICS: inhaled corticosteroids
ICU: intensive care unit
LABA: long-acting $beta_2$-agonist
LTRA: leukotriene receptor agonist
MDI: metered dose inhaler
MI: myocardial infarction
OCS: oral corticosteroids
PEF: peak expiratory flow
PEFR: peak expiratory flow rate
PFM: peak flow metre
PFT: pulmonary function test
QTcB: corrected QT interval by Bazett
pMDI: pressurised metered dose inhaler
SABA: short-acting $beta_2$-agonist
SAE: serious adverse event

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SD: standard deviation
URTI: upper respiratory tract infection

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

Study	Reason for exclusion
Ankerst 2003	Short-term cross-over study
Antilla 2014	Wrong comparator
AstraZeneca 2005	Comparison with budesonide and theophylline
AstraZeneca 2005a	Ongoing study
AstraZeneca 2005b	Comparison of single-inhaler therapy with current best practice
AstraZeneca 2005c	Comparison of single-inhaler therapy with current best practice
AstraZeneca 2005d	Comparison of single-inhaler therapy with current best practice
AstraZeneca 2006	Comparison of single-inhaler therapy with ICS and terbutaline
AstraZeneca 2006a	Comparison of single-inhaler therapy with current best practice
AstraZeneca 2006b	Comparison of single-inhaler therapy with current best practice
Balanag 2006	Comparison with salbutamol in acute asthma
Barnes 2011	Wrong comparator
Barthwal 2017	Wrong study design
Bateman 2003	Budesonide and formoterol compared with higher-dose fluticasone
Bateman 2006	Acute asthma
Bateman 2018	As-needed intervention
Beasley 2016	Wrong intervention
Bodzenta-Lukaszyk 2011	8-week duration
Bouros 1999	Formoterol and beclomethasone compared with higher-dose beclomethasone
Brusselle 2011	Wrong study design
Buhl 2004	Adjustable versus fixed-dose budesonide and formoterol
Bumbacea 2010	8-week duration
Burgess 1998	Short-term cross-over study
Canonica 2004	Adjustable versus fixed-dose budesonide and formoterol
Ceylan 2004	Formoterol in comparison with montelukast in addition to low-dose ICS

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Study	Reason for exclusion
Chawes 2014	Wrong study design
ChiCTR1800019852	Wrong comparison
Dhillon 2006	Review of beclomethasone/formoterol treatment
FitzGerald 1999	No randomisation to ICS
FitzGerald 2003	Adjustable versus fixed-dose budesonide and formoterol
Haahtela 2006	Formoterol used as-needed (with or without budesonide).
Horio 2014	Wrong comparator
Ind 2004	Adjustable versus fixed-dose budesonide and formoterol
Jakopovic 2009	Uncontrolled study
Kozlik-Feldmann 1996	No randomisation to ICS
Lalloo 2003	Budesonide and formoterol compared with higher-dose ICS
Lemanske 2010	Cross-over design without same-dose ICS comparator group
Leuppi 2003	Adjustable versus fixed-dose budesonide and formoterol
Lotvall 2006	Short-term comparison of bronchodilation following fluticasone propionate/salmeterol and budesonide and formoterol
Lundborg 2006	Cost-effectiveness of single-inhaler therapy
Maspero 2010	No arm with same-dose ICS comparator
McIver 2012	Wrong study design
McIver 2012a	Wrong study design
Mitchell 2003	Comparison with higher-dose ICS
Molimard 2001	Not randomly assigned to ICS
Nayak 2010	Combined results of other studies
NCT02571777	Ongoing study and no comparator group
Novartis 2005	No random assignment to ICS
O'Byrne 2005	Budesonide and formoterol as single-inhaler therapy or fixed-dose treatment compared with higher-dose budesonide
O'Byrne 2018	As-needed intervention
Ohta 2008	8-week duration
Overbeek 2005	Duration of less than 12 weeks on each dose of budesonide

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Study	Reason for exclusion
Papi 2007	Delivery device comparison for beclomethasone/formoterol combination inhalers
Pauwels 2003	Comparison of formoterol with salbutamol as relief medication
Peters 2008a	Overview
Pleskow 2003	Not randomly assigned to ICS
Pohl 2006	Adjustable maintenance dosing study
Rabe 2006	Budesonide and formoterol single-inhaler therapy compared with higher-dose budesonide
Rosenhall 2002	Combined budesonide and formoterol inhaler compared with both medications given together in separate inhalers
Rosenhall 2003	Combined budesonide and formoterol inhaler compared with both medications given together in separate inhalers
Rosenhall 2003a	Combined budesonide and formoterol inhaler compared with both medications given together in separate inhalers
Rosenwasser 2008	Combined results of other studies
Saito 2011	Cross-over study
Scicchitano 2004	Budesonide and formoterol single-inhaler therapy compared with higher-dose budesonide
Stelmach 2007	4-week study
UMIN000010333	Study compared step-down to double-dose ICS
van der Molen 1997	No random assignment to ICS
Villa 2002	Formoterol as-needed compared with terbutaline as-needed
Von Berg 2003	No random assignment to ICS
Weinstein 2010a	Overview
White 2010	Combined results of other studies
Worth 2005	Single-inhaler therapy compared with current best practice
Zetterstrom 2001a	Single-inhaler therapy
Zetterström 2000	Single-inhaler therapy

ICS: inhaled corticosteroids

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

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NCT02554786

Trial name or title	A multi-centre randomised 52 week treatment double-blind, triple dummy parallel group study to assess the efficacy and safety of QMF149 compared to mometasone furoate in patients with asthma.
Methods	Allocation: randomised. Intervention Model: parallel assignment. Masking: double (participant, investigator). Primary Purpose: treatment.
Participants	Patients with a diagnosis of asthma for a period of ≥ 1 year prior to visit 1 (screening); aged 12 to 75 years.
Interventions	• Drug: QMF149 (indacaterol maleate/mometasone furoate) 150/160 µg once daily. • Drug: QMF149 (indacaterol maleate/mometasone furoate) 150/320 µg once daily. • Drug: mometasone furoate 400 µg once daily. • Drug: mometasone furoate 400 µg twice daily. • Drug: salmeterol/fluticasone 50/500 µg twice daily.
Outcomes	Primary Outcome Measure: • Trough FEV_1 at 26 weeks. Secondary Outcome Measures: • Trough FEV_1 at week 52. • Predose FEV_1 at week 4 and 12. • FEV_1 over 52 weeks; PEF over 26 and 52 weeks. • ACQ-7 at week 4, 12, 26, and 52. • % participants with MID of ACQ ≥ 0.5 at week 26 and 52. • Daily e-diary over 52 weeks. • Rescue medication use over 26 and 52 weeks. • Asthma exacerbation over 52 weeks. • % rescue medication-free days over 26 and 52 weeks. • Quality of life assessed by AQLQ-S 12. • Incidence of composite endpoint of serious asthma outcomes. • Adverse event, vital signs, ECG, and laboratory analysis; trough FEV_1 at week 2. • FVC over 52 weeks. • FEF over 52 weeks.
Starting date	9 September 2015
Contact information	Novartis Pharmaceuticals (1-8880669-6682; +41613241111)
Notes	Other study identifiers: CQVM149B2301; EudraCT Number 2015-002529-21.

NCT02741271

Trial name or title	Study of efficacy and long-term safety of mometasone furoate in combination with formoterol fumarate versus mometasone furoate in children (5 to 11 years of age) with persistent asthma.
Methods	Allocation: randomised.

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NCT02741271 *(Continued)*

	Intervention Model: parallel assignment. Masking: triple (participant, care provider, investigator). Masking Description: 1:1 randomisation to double-blinded. Primary Purpose: treatment.
Participants	Patients with a diagnosis of asthma of ≥ 6 months' duration prior to study start, aged 5 to 11 years.
Interventions	• Mometasone furoate 100 µg twice daily (open-label). • Mometasone furoate/formoterol 100/10 µg twice daily. • Mometasone furoate 100 µg twice daily. • Salbutamol taken as needed. • Prednisone/prednisolone.
Outcomes	Primary Outcome Measures: • Change from baseline in % predicted morning FEV_1 averaged across 60 minutes postdose; analysed across all time points (Time Frame: Baseline (Day 1) and at Weeks 1, 4, 8, and 12 of treatment (up to 12 weeks)). • Percentage of participants with adverse events (Time Frame: From time of first dose of double-blind study drug until the end of follow-up (up to 26 weeks)). • Percentage of participants discontinuing study drug due to adverse events (Time Frame: Up to 24 weeks after the first dose of double-blind study drug (up to 24 weeks)). Secondary Outcome Measures: • Change from baseline morning predose % predicted FEV_1 analysed at 4 and 2 hours, 60, 30, 15, and 5 minutes postdose on day 1 of treatment (Time Frame: Baseline (Day 1) AM predose to 5 minutes postdose (up to 4 hours postdose)). • Change from baseline morning postdose % predicted FEV_1 analysed at 4 hours postdose at Day 1 and Week 12 of treatment (Time Frame: Baseline (Day 1) and at Week 12 of treatment (up to 12 weeks)). • Average change from baseline in % predicted morning predose FEV_1 (Time Frame: Baseline and at Weeks 4, 8, and 12 of treatment (up to 12 weeks)). • Change from baseline in total daily salbutamol (SABA) use (Time Frame: Baseline and until 12 weeks of treatment (up to 12 weeks)).
Starting date	13 April 2016
Contact information	Merck Sharp & Dohme Corp.
Notes	Other study identifiers: Merck Registration Number MK-0887A-087; EudraCT Number 2009-010110-30.

ACQ: Asthma Control Questionnaire
AQLQ: Asthma Quality of Life Questionnaire
ECG: electrocardiogram
FEF: forced expiratory flow
FEV_1: forced expiratory volume in 1 second
FVC: forced vital capacity
MID: minimally important difference
PEF: peak expiratory flow
QMF: indacaterol maleate/mometasone furoate monotherapy dry powder inhaler
SABA: short-acting $beta_2$-agonist

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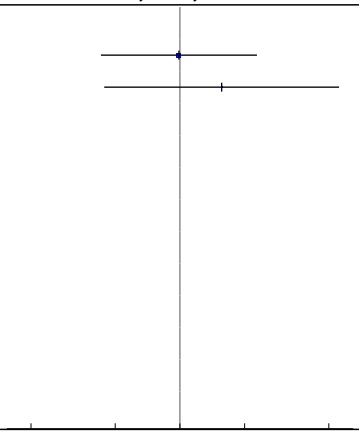
DATA AND ANALYSES

Comparison 1. Formoterol and ICS versus same-dose ICS (Peto OR, OR, risk difference)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	39	39786	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.25 [0.61, 2.56]
1.1 Adults	29	35751	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.25 [0.61, 2.56]
1.2 Children and adolescents	10	4035	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 All-cause non-fatal serious adverse events	39	39786	Odds Ratio (M-H, Fixed, 95% CI)	1.02 [0.89, 1.17]
2.1 Adults	29	35751	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.87, 1.16]
2.2 Children and adolescents	10	4035	Odds Ratio (M-H, Fixed, 95% CI)	1.33 [0.71, 2.49]
3 Asthma mortality	38	28057	Risk Difference (M-H, Fixed, 95% CI)	0.00 [-0.00, 0.00]
3.1 Adults	28	24022	Risk Difference (M-H, Fixed, 95% CI)	0.00 [-0.00, 0.00]
3.2 Children and adolescents	10	4035	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.00, 0.00]
4 Asthma-related non-fatal serious adverse events	37	39193	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.87 [0.66, 1.15]
4.1 Adults	27	35158	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.86 [0.64, 1.14]
4.2 Children and adolescents	10	4035	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.18 [0.40, 3.51]

Analysis 1.1. Comparison 1 Formoterol and ICS versus same-dose ICS (Peto OR, OR, risk difference), Outcome 1 All-cause mortality.

Study or subgroup	Formoterol and ICS n/N	Same dose ICS n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.1.1 Adults					
Brown 2012	1/377	1/364		6.71%	0.97[0.06,15.47]
Buhl 2003	1/352	0/171		2.96%	4.42[0.07,288.27]
Chuchalin 2002	0/111	0/114			Not estimable
Corren 2007	0/123	0/121			Not estimable
Corren 2013	0/110	0/113			Not estimable
D5896C00001	0/312	0/153			Not estimable
EudraCT 2010-020602-14-DE	0/192	0/184			Not estimable
Jenkins 2006	0/341	0/115			Not estimable
Kuna 2006	0/409	0/207			Not estimable
Matsunaga 2013	0/15	0/15			Not estimable
Meltzer 2012	0/182	0/188			Not estimable
Morice 2007	0/462	0/217			Not estimable



Favours formoterol & ICS — Favours same dose ICS

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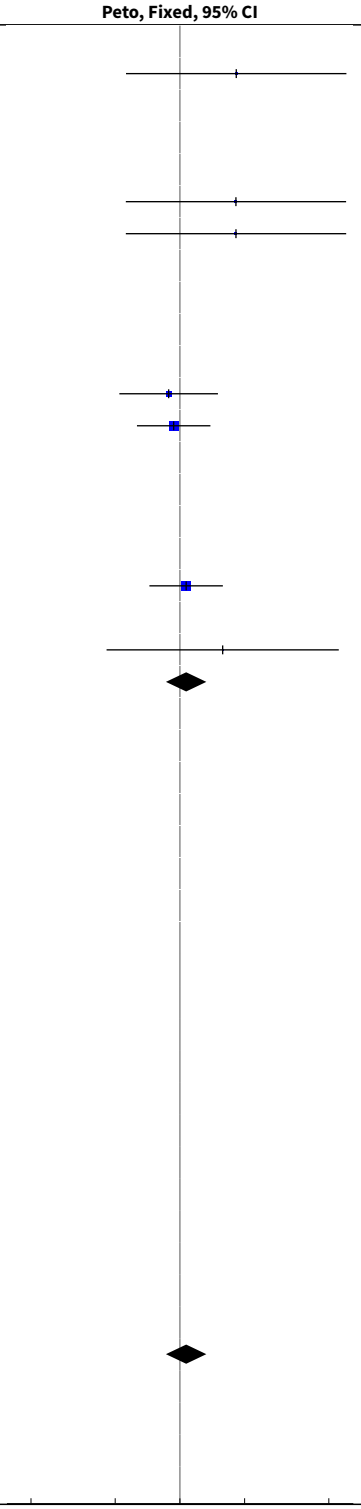
Study or subgroup	Formoterol and ICS n/N	Same dose ICS n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Murphy 2015	0/71	0/143			Not estimable
Nathan 2010	1/191	0/192		3.36%	7.43[0.15,374.34]
Nathan 2012	0/115	0/117			Not estimable
Noonan 2006	0/239	0/109			Not estimable
O'Byrne 2001	0/315	0/312			Not estimable
O'Byrne 2001	1/554	0/550		3.36%	7.34[0.15,369.72]
Pauwels 1997	1/215	0/214		3.36%	7.35[0.15,370.66]
Pauwels 1997	0/210	0/213			Not estimable
Pearlman 2013	0/119	0/119			Not estimable
Pertseva 2013	0/146	0/292			Not estimable
Peters 2008	0/443	0/133			Not estimable
Peters 2016	2/1645	3/1646		16.78%	0.67[0.12,3.87]
Peters 2016	4/4201	5/4201		30.22%	0.8[0.22,2.96]
Price 2002	0/250	0/255			Not estimable
SD-039-0726	0/301	0/145			Not estimable
Spector 2012	0/156	0/155			Not estimable
Weinstein 2010	0/255	0/240			Not estimable
Weinstein 2019	5/5868	4/5861		30.22%	1.25[0.34,4.61]
Zangrilli 2011	0/127	0/123			Not estimable
Zetterstrom 2001	1/238	0/124		3.03%	4.58[0.07,284.6]
Subtotal (95% CI)	**18645**	**17106**		**100%**	**1.25[0.61,2.56]**
Total events: 17 (Formoterol and ICS), 13 (Same dose ICS)					
Heterogeneity: Tau²=0; Chi²=4.06, df=8(P=0.85); I²=0%					
Test for overall effect: Z=0.6(P=0.55)					
1.1.2 Children and adolescents					
Morice 2008	0/415	0/207			Not estimable
NCT01475032	0/421	0/213			Not estimable
Pearlman 2017	0/183	0/90			Not estimable
Ploszczuk 2014	0/168	0/172			Not estimable
Pohunek 2006	0/417	0/213			Not estimable
SD-039-0714	0/136	0/134			Not estimable
SD-039-0718	0/128	0/145			Not estimable
SD-039-0719	0/123	0/63			Not estimable
SD-039-0725	0/352	0/169			Not estimable
Tal 2002	0/148	0/138			Not estimable
Subtotal (95% CI)	**2491**	**1544**			**Not estimable**
Total events: 0 (Formoterol and ICS), 0 (Same dose ICS)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**21136**	**18650**		**100%**	**1.25[0.61,2.56]**
Total events: 17 (Formoterol and ICS), 13 (Same dose ICS)					
Heterogeneity: Tau²=0; Chi²=4.06, df=8(P=0.85); I²=0%					
Test for overall effect: Z=0.6(P=0.55)					
Test for subgroup differences: Not applicable					



Favours formoterol & ICS — Favours same dose ICS

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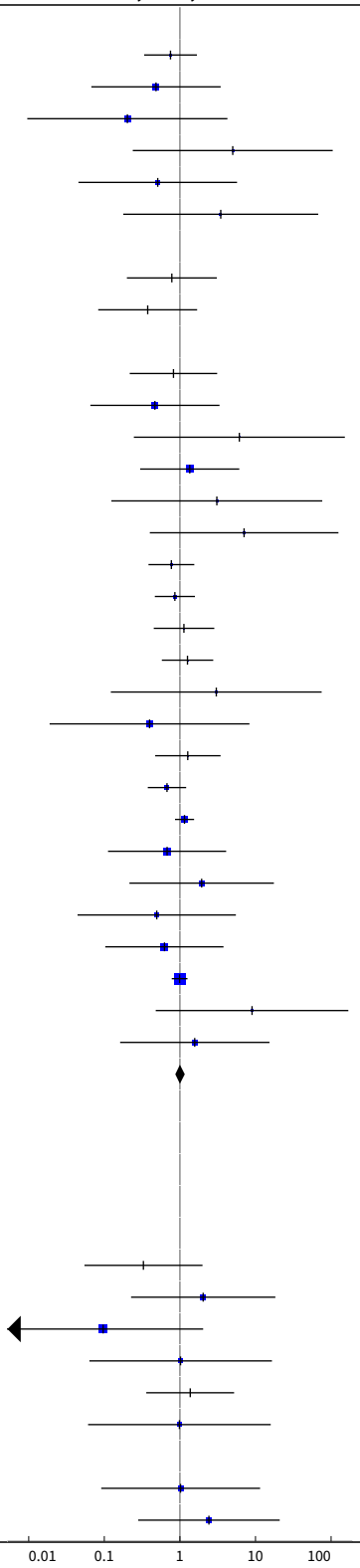
Analysis 1.2. Comparison 1 Formoterol and ICS versus same-dose ICS (Peto OR, OR, risk difference), Outcome 2 All-cause non-fatal serious adverse events.

Study or subgroup	Formoterol and ICS n/N	Same dose ICS n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
1.2.1 Adults					
Brown 2012	11/377	14/364		3.56%	0.75[0.34,1.68]
Buhl 2003	2/352	2/171		0.69%	0.48[0.07,3.46]
Chuchalin 2002	0/111	2/114		0.63%	0.2[0.01,4.25]
Corren 2007	2/123	0/121		0.13%	5[0.24,105.24]
Corren 2013	1/110	2/113		0.5%	0.51[0.05,5.7]
D5896C00001	3/312	0/153		0.17%	3.47[0.18,67.64]
EudraCT 2010-020602-14-DE	0/192	0/184			Not estimable
Jenkins 2006	7/341	3/115		1.13%	0.78[0.2,3.08]
Kuna 2006	3/409	4/207		1.36%	0.38[0.08,1.69]
Matsunaga 2013	0/15	0/15			Not estimable
Meltzer 2012	4/182	5/188		1.24%	0.82[0.22,3.11]
Morice 2007	2/462	2/217		0.7%	0.47[0.07,3.34]
Murphy 2015	1/71	0/143		0.08%	6.11[0.25,151.81]
Nathan 2010	4/191	3/192		0.75%	1.35[0.3,6.1]
Nathan 2012	1/115	0/117		0.13%	3.08[0.12,76.36]
Noonan 2006	7/239	0/109		0.17%	7.06[0.4,124.81]
O'Byrne 2001	15/315	19/312		4.68%	0.77[0.38,1.55]
O'Byrne 2001	20/554	23/550		5.73%	0.86[0.47,1.58]
Pauwels 1997	10/210	9/213		2.19%	1.13[0.45,2.85]
Pauwels 1997	15/215	12/214		2.88%	1.26[0.58,2.76]
Pearlman 2013	1/119	0/119		0.13%	3.03[0.12,75.02]
Pertseva 2013	0/146	2/292		0.43%	0.4[0.02,8.31]
Peters 2008	21/443	5/133		1.89%	1.27[0.47,3.45]
Peters 2016	19/1645	28/1646		7.12%	0.68[0.38,1.21]
Peters 2016	100/4201	87/4201		21.86%	1.15[0.86,1.54]
Price 2002	2/250	3/255		0.76%	0.68[0.11,4.09]
SD-039-0726	4/301	1/145		0.34%	1.94[0.21,17.51]
Spector 2012	1/156	2/155		0.51%	0.49[0.04,5.5]
Weinstein 2010	2/255	3/240		0.79%	0.62[0.1,3.77]
Weinstein 2019	136/5868	137/5861		34.46%	0.99[0.78,1.26]
Zangrilli 2011	4/127	0/123		0.13%	9[0.48,168.95]
Zetterstrom 2001	3/238	1/124		0.33%	1.57[0.16,15.25]
Subtotal (95% CI)	**18645**	**17106**		**95.46%**	**1[0.87,1.16]**
Total events: 401 (Formoterol and ICS), 369 (Same dose ICS)					
Heterogeneity: Tau^2=0; Chi^2=18.47, df=29(P=0.93); I^2=0%					
Test for overall effect: Z=0.05(P=0.96)					
1.2.2 Children and adolescents					
Morice 2008	2/415	3/207		1.03%	0.33[0.05,1.99]
NCT01475032	4/421	1/213		0.34%	2.03[0.23,18.31]
Pearlman 2017	0/183	2/90		0.86%	0.1[0,2.03]
Ploszczuk 2014	1/168	1/172		0.25%	1.02[0.06,16.51]
Pohunek 2006	8/417	3/213		1%	1.37[0.36,5.21]
SD-039-0714	1/136	1/134		0.26%	0.99[0.06,15.91]
SD-039-0718	0/128	0/145			Not estimable
SD-039-0719	2/123	1/63		0.33%	1.02[0.09,11.52]
SD-039-0725	5/352	1/169		0.34%	2.42[0.28,20.88]



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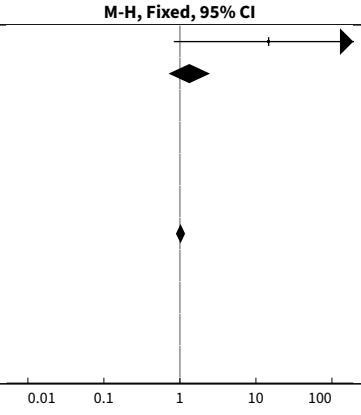
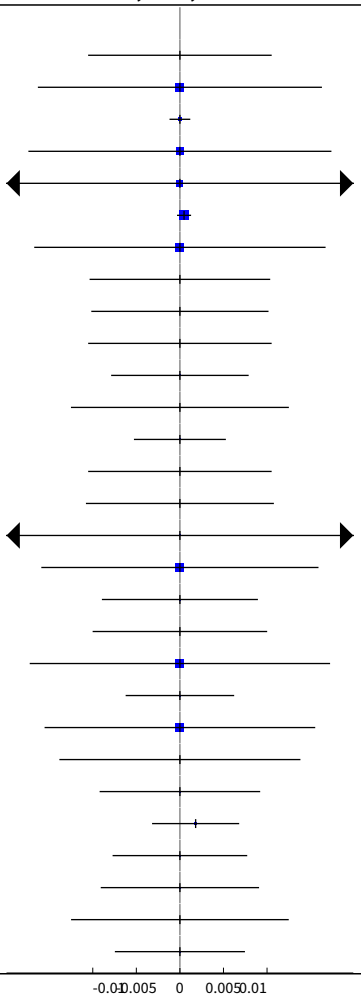
Study or subgroup	Formoterol and ICS n/N	Same dose ICS n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Tal 2002	7/148	0/138		0.13%	14.68[0.83,259.54]
Subtotal (95% CI)	**2491**	**1544**		**4.54%**	**1.33[0.71,2.49]**
Total events: 30 (Formoterol and ICS), 13 (Same dose ICS)					
Heterogeneity: Tau²=0; Chi²=8.41, df=8(P=0.39); I²=4.9%					
Test for overall effect: Z=0.88(P=0.38)					
Total (95% CI)	**21136**	**18650**		**100%**	**1.02[0.89,1.17]**
Total events: 431 (Formoterol and ICS), 382 (Same dose ICS)					
Heterogeneity: Tau²=0; Chi²=26.9, df=38(P=0.91); I²=0%					
Test for overall effect: Z=0.26(P=0.8)					
Test for subgroup differences: Chi²=0.72, df=1 (P=0.4), I²=0%					



Analysis 1.3. Comparison 1 Formoterol and ICS versus same-dose ICS (Peto OR, OR, risk difference), Outcome 3 Asthma mortality.

Study or subgroup	Formoterol and ICS n/N	Same dose ICS n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
1.3.1 Adults					
Pertseva 2013	0/146	0/292		1.44%	0[-0.01,0.01]
Pearlman 2013	0/119	0/119		0.88%	0[-0.02,0.02]
Peters 2016	0/1645	0/1646		12.2%	0[-0,0]
Corren 2013	0/110	0/113		0.83%	0[-0.02,0.02]
Murphy 2015	0/71	0/143		0.7%	0[-0.02,0.02]
Peters 2016	2/4201	0/4201		31.15%	0[-0,0]
Nathan 2012	0/115	0/117		0.86%	0[-0.02,0.02]
EudraCT 2010-020602-14-DE	0/192	0/184		1.39%	0[-0.01,0.01]
Nathan 2010	0/191	0/192		1.42%	0[-0.01,0.01]
Meltzer 2012	0/182	0/188		1.37%	0[-0.01,0.01]
Weinstein 2010	0/255	0/240		1.83%	0[-0.01,0.01]
Spector 2012	0/156	0/155		1.15%	0[-0.01,0.01]
Brown 2012	0/377	0/364		2.75%	0[-0.01,0.01]
SD-039-0726	0/301	0/145		1.45%	0[-0.01,0.01]
Peters 2008	0/443	0/133		1.52%	0[-0.01,0.01]
Matsunaga 2013	0/15	0/15		0.11%	0[-0.12,0.12]
Corren 2007	0/123	0/121		0.9%	0[-0.02,0.02]
Buhl 2003	0/352	0/171		1.71%	0[-0.01,0.01]
D5896C00001	0/312	0/153		1.52%	0[-0.01,0.01]
Chuchalin 2002	0/111	0/114		0.83%	0[-0.02,0.02]
O'Byrne 2001	0/315	0/312		2.32%	0[-0.01,0.01]
Zangrilli 2011	0/127	0/123		0.93%	0[-0.02,0.02]
Noonan 2006	0/239	0/109		1.11%	0[-0.01,0.01]
Pauwels 1997	0/210	0/213		1.57%	0[-0.01,0.01]
O'Byrne 2001	1/554	0/550		4.09%	0[-0,0.01]
Price 2002	0/250	0/255		1.87%	0[-0.01,0.01]
Pauwels 1997	0/215	0/214		1.59%	0[-0.01,0.01]
Zetterstrom 2001	0/238	0/124		1.21%	0[-0.01,0.01]
Kuna 2006	0/409	0/207		2.04%	0[-0.01,0.01]



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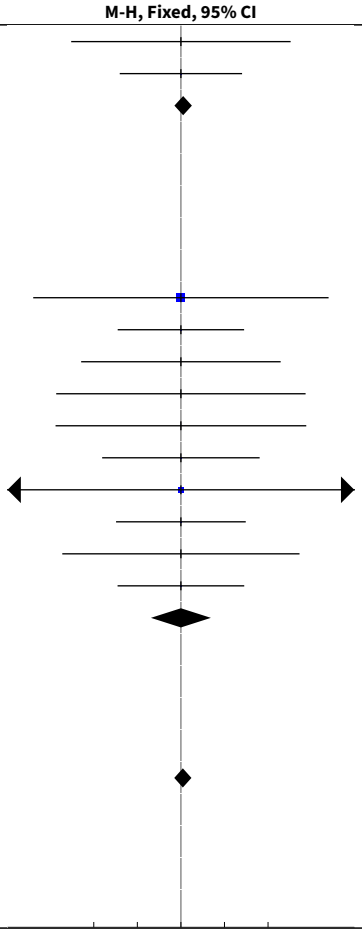
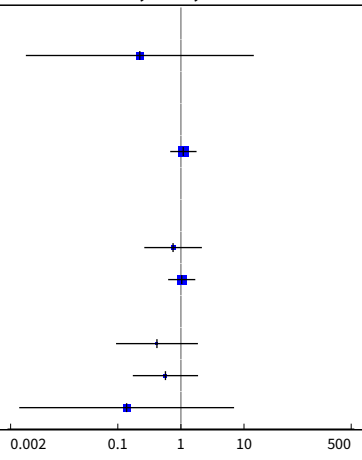
Study or subgroup	Formoterol and ICS n/N	Same dose ICS n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
Jenkins 2006	0/341	0/115		1.28%	0[-0.01,0.01]
Morice 2007	0/462	0/217		2.19%	0[-0.01,0.01]
Subtotal (95% CI)	**12777**	**11245**		**86.23%**	**0[-0,0]**
Total events: 3 (Formoterol and ICS), 0 (Same dose ICS)					
Heterogeneity: Tau²=0; Chi²=0.9, df=30(P=1); I²=0%					
Test for overall effect: Z=0.5(P=0.61)					
1.3.2 Children and adolescents					
Pearlman 2017	0/183	0/90		0.89%	0[-0.02,0.02]
NCT01475032	0/421	0/213		2.1%	0[-0.01,0.01]
Ploszczuk 2014	0/168	0/172		1.26%	0[-0.01,0.01]
SD-039-0718	0/128	0/145		1.01%	0[-0.01,0.01]
SD-039-0714	0/136	0/134		1%	0[-0.01,0.01]
SD-039-0725	0/352	0/169		1.69%	0[-0.01,0.01]
SD-039-0719	0/123	0/63		0.62%	0[-0.02,0.02]
Morice 2008	0/415	0/207		2.05%	0[-0.01,0.01]
Tal 2002	0/148	0/138		1.06%	0[-0.01,0.01]
Pohunek 2006	0/417	0/213		2.09%	0[-0.01,0.01]
Subtotal (95% CI)	**2491**	**1544**		**13.77%**	**0[-0,0]**
Total events: 0 (Formoterol and ICS), 0 (Same dose ICS)					
Heterogeneity: Tau²=0; Chi²=0, df=9(P=1); I²=0%					
Test for overall effect: Not applicable					
Total (95% CI)	**15268**	**12789**		**100%**	**0[-0,0]**
Total events: 3 (Formoterol and ICS), 0 (Same dose ICS)					
Heterogeneity: Tau²=0; Chi²=0.97, df=40(P=1); I²=0%					
Test for overall effect: Z=0.44(P=0.66)					
Test for subgroup differences: Chi²=0.02, df=1 (P=0.89), I²=0%					



Analysis 1.4. Comparison 1 Formoterol and ICS versus same-dose ICS (Peto OR, OR, risk difference), Outcome 4 Asthma-related non-fatal serious adverse events.

Study or subgroup	Formoterol and ICS n/N	Same dose ICS n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.4.1 Adults					
Pertseva 2013	0/146	1/292		0.44%	0.22[0,14.26]
Pearlman 2013	0/119	0/119			Not estimable
EudraCT 2010-020602-14-DE	0/192	0/184			Not estimable
Peters 2016	35/4201	32/4201		32.84%	1.09[0.68,1.77]
Nathan 2012	0/115	0/117			Not estimable
Murphy 2015	0/71	0/143			Not estimable
Peters 2016	6/1645	8/1646		6.89%	0.75[0.26,2.15]
Weinstein 2019	32/5868	31/5861		30.96%	1.03[0.63,1.69]
SD-039-0726	0/301	0/145			Not estimable
Pauwels 1997	2/215	5/214		3.41%	0.42[0.09,1.86]
O'Byrne 2001	4/315	7/312		5.35%	0.57[0.17,1.87]
Price 2002	0/250	1/255		0.49%	0.14[0,6.96]



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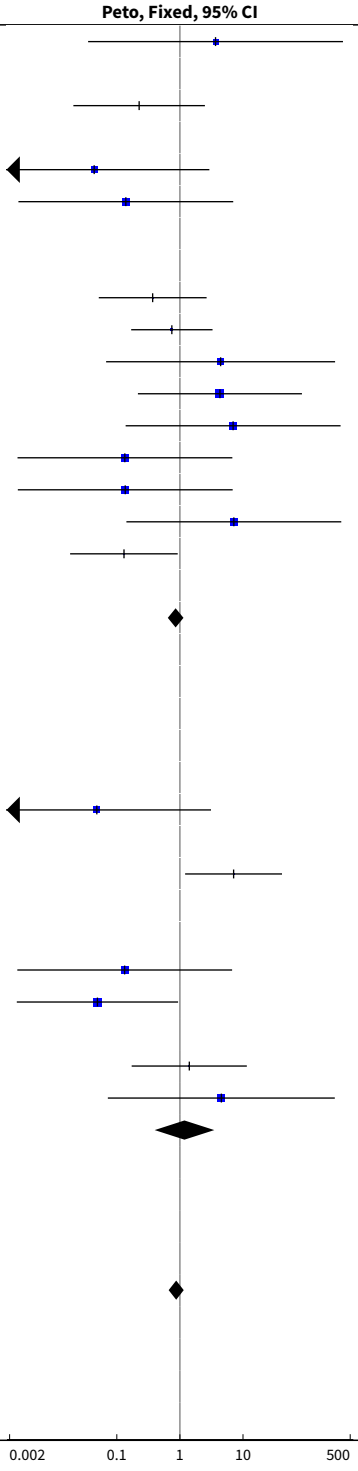
Study or subgroup	Formoterol and ICS n/N	Same dose ICS n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Peters 2008	1/443	0/133		0.35%	3.67[0.04,384.21]
Zetterstrom 2001	0/238	0/124			Not estimable
Kuna 2006	1/409	2/207		1.32%	0.23[0.02,2.49]
Jenkins 2006	0/341	0/115			Not estimable
Morice 2007	0/462	1/217		0.43%	0.04[0,2.93]
Chuchalin 2002	0/111	1/114		0.49%	0.14[0,7]
Corren 2007	0/123	0/121			Not estimable
D5896C00001	0/312	0/153			Not estimable
Pauwels 1997	1/210	3/213		1.96%	0.37[0.05,2.65]
O'Byrne 2001	3/554	4/550		3.44%	0.74[0.17,3.29]
Buhl 2003	1/352	0/171		0.43%	4.42[0.07,288.27]
Noonan 2006	2/239	0/109		0.85%	4.31[0.22,85.86]
Weinstein 2010	1/255	0/240		0.49%	6.97[0.14,351.74]
Spector 2012	0/156	1/155		0.49%	0.13[0,6.78]
Nathan 2010	0/191	1/192		0.49%	0.14[0,6.86]
Zangrilli 2011	1/127	0/123		0.49%	7.16[0.14,361.02]
Brown 2012	0/377	4/364		1.97%	0.13[0.02,0.92]
Matsunaga 2013	0/15	0/15			Not estimable
Subtotal (95% CI)	**18353**	**16805**		**93.6%**	**0.86[0.64,1.14]**
Total events: 90 (Formoterol and ICS), 102 (Same dose ICS)					
Heterogeneity: Tau²=0; Chi²=18.41, df=19(P=0.5); I²=0%					
Test for overall effect: Z=1.08(P=0.28)					
1.4.2 Children and adolescents					
Pearlman 2017	0/183	1/90		0.44%	0.05[0,3.11]
NCT01475032	0/421	0/213			Not estimable
Tal 2002	5/148	0/138		2.43%	7.1[1.21,41.53]
Pohunek 2006	0/417	0/213			Not estimable
SD-039-0718	0/128	0/145			Not estimable
SD-039-0714	0/136	1/134		0.49%	0.13[0,6.72]
Morice 2008	0/415	2/207		0.88%	0.05[0,0.94]
Ploszczuk 2014	0/168	0/172			Not estimable
SD-039-0725	3/352	1/169		1.72%	1.41[0.17,11.48]
SD-039-0719	1/123	0/63		0.44%	4.54[0.07,285.29]
Subtotal (95% CI)	**2491**	**1544**		**6.4%**	**1.18[0.4,3.51]**
Total events: 9 (Formoterol and ICS), 5 (Same dose ICS)					
Heterogeneity: Tau²=0; Chi²=12.32, df=5(P=0.03); I²=59.4%					
Test for overall effect: Z=0.3(P=0.76)					
Total (95% CI)	**20844**	**18349**		**100%**	**0.87[0.66,1.15]**
Total events: 99 (Formoterol and ICS), 107 (Same dose ICS)					
Heterogeneity: Tau²=0; Chi²=31.05, df=25(P=0.19); I²=19.47%					
Test for overall effect: Z=0.97(P=0.33)					
Test for subgroup differences: Chi²=0.32, df=1 (P=0.57), I²=0%					



Favours formoterol & ICS — Favours same dose ICS

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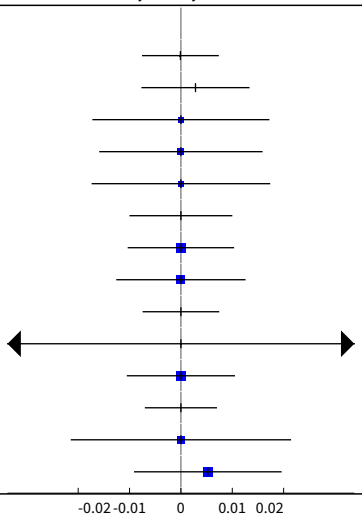
Comparison 2. Formoterol and ICS versus same-dose ICS (risk difference)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	39	39786	Risk Difference (M-H, Fixed, 95% CI)	0.00 [-0.00, 0.00]
1.1 Adults	29	35751	Risk Difference (M-H, Fixed, 95% CI)	0.00 [-0.00, 0.00]
1.2 Children and adolescents	10	4035	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.00, 0.00]
2 All-cause non-fatal serious adverse events	39	39786	Risk Difference (M-H, Fixed, 95% CI)	0.00 [-0.00, 0.00]
2.1 Adults	29	35751	Risk Difference (M-H, Fixed, 95% CI)	0.00 [-0.00, 0.00]
2.2 Children and adolescents	10	4035	Risk Difference (M-H, Fixed, 95% CI)	0.00 [-0.00, 0.01]
3 Asthma mortality	38	28057	Risk Difference (M-H, Fixed, 95% CI)	0.00 [-0.00, 0.00]
3.1 Adults	28	24022	Risk Difference (M-H, Fixed, 95% CI)	0.00 [-0.00, 0.00]
3.2 Children and adolescents	10	4035	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.00, 0.00]
4 Asthma-related non-fatal serious adverse events	37	39193	Risk Difference (M-H, Fixed, 95% CI)	-0.00 [-0.00, 0.00]
4.1 Adults	27	35158	Risk Difference (M-H, Fixed, 95% CI)	-0.00 [-0.00, 0.00]
4.2 Children and adolescents	10	4035	Risk Difference (M-H, Fixed, 95% CI)	0.00 [-0.00, 0.01]

Analysis 2.1. Comparison 2 Formoterol and ICS versus same-dose ICS (risk difference), Outcome 1 All-cause mortality.

Study or subgroup	Formoterol and ICS n/N	Same Dose ICS n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
2.1.1 Adults					
Brown 2012	1/377	1/364		1.91%	-0[-0.01,0.01]
Buhl 2003	1/352	0/171		1.19%	0[-0.01,0.01]
Chuchalin 2002	0/111	0/114		0.58%	0[-0.02,0.02]
Corren 2007	0/123	0/121		0.63%	0[-0.02,0.02]
Corren 2013	0/110	0/113		0.58%	0[-0.02,0.02]
D5896C00001	0/312	0/153		1.06%	0[-0.01,0.01]
EudraCT 2010-020602-14-DE	0/192	0/184		0.97%	0[-0.01,0.01]
Jenkins 2006	0/341	0/115		0.89%	0[-0.01,0.01]
Kuna 2006	0/409	0/207		1.42%	0[-0.01,0.01]
Matsunaga 2013	0/15	0/15		0.08%	0[-0.12,0.12]
Meltzer 2012	0/182	0/188		0.96%	0[-0.01,0.01]
Morice 2007	0/462	0/217		1.53%	0[-0.01,0.01]
Murphy 2015	0/71	0/143		0.49%	0[-0.02,0.02]
Nathan 2010	1/191	0/192		0.99%	0.01[-0.01,0.02]



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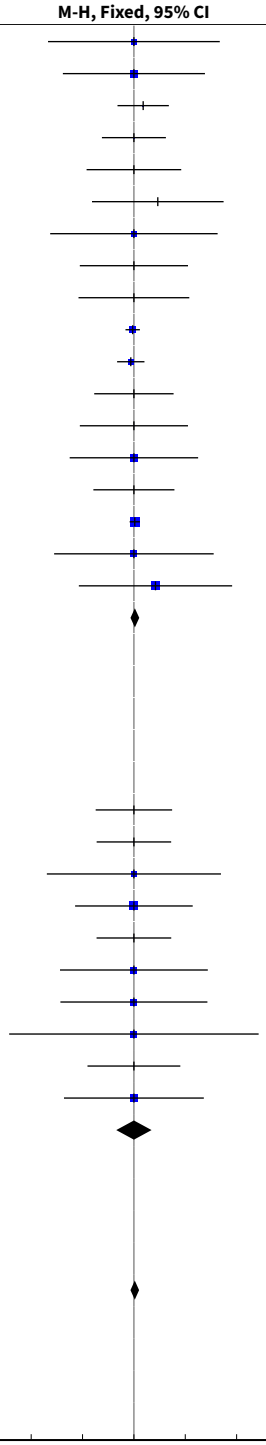
Study or subgroup	Formoterol and ICS n/N	Same Dose ICS n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
Nathan 2012	0/115	0/117		0.6%	0[-0.02,0.02]
Noonan 2006	0/239	0/109		0.77%	0[-0.01,0.01]
O'Byrne 2001	1/554	0/550		2.85%	0[-0,0.01]
O'Byrne 2001	0/315	0/312		1.62%	0[-0.01,0.01]
Pauwels 1997	0/210	0/213		1.09%	0[-0.01,0.01]
Pauwels 1997	1/215	0/214		1.11%	0[-0.01,0.02]
Pearlman 2013	0/119	0/119		0.61%	0[-0.02,0.02]
Pertseva 2013	0/146	0/292		1.01%	0[-0.01,0.01]
Peters 2008	0/443	0/133		1.06%	0[-0.01,0.01]
Peters 2016	4/4201	5/4201		21.71%	-0[-0,0]
Peters 2016	2/1645	3/1646		8.5%	-0[-0,0]
Price 2002	0/250	0/255		1.3%	0[-0.01,0.01]
SD-039-0726	0/301	0/145		1.01%	0[-0.01,0.01]
Spector 2012	0/156	0/155		0.8%	0[-0.01,0.01]
Weinstein 2010	0/255	0/240		1.28%	0[-0.01,0.01]
Weinstein 2019	5/5868	4/5861		30.31%	0[-0,0]
Zangrilli 2011	0/127	0/123		0.65%	0[-0.02,0.02]
Zetterstrom 2001	1/238	0/124		0.84%	0[-0.01,0.02]
Subtotal (95% CI)	**18645**	**17106**		**90.4%**	**0[-0,0]**
Total events: 17 (Formoterol and ICS), 13 (Same Dose ICS)					
Heterogeneity: Tau^2=0; Chi^2=2.6, df=31(P=1); I^2=0%					
Test for overall effect: Z=0.43(P=0.67)					
2.1.2 Children and adolescents					
Morice 2008	0/415	0/207		1.43%	0[-0.01,0.01]
NCT01475032	0/421	0/213		1.46%	0[-0.01,0.01]
Pearlman 2017	0/183	0/90		0.62%	0[-0.02,0.02]
Ploszczuk 2014	0/168	0/172		0.88%	0[-0.01,0.01]
Pohunek 2006	0/417	0/213		1.46%	0[-0.01,0.01]
SD-039-0714	0/136	0/134		0.7%	0[-0.01,0.01]
SD-039-0718	0/128	0/145		0.7%	0[-0.01,0.01]
SD-039-0719	0/123	0/63		0.43%	0[-0.02,0.02]
SD-039-0725	0/352	0/169		1.18%	0[-0.01,0.01]
Tal 2002	0/148	0/138		0.74%	0[-0.01,0.01]
Subtotal (95% CI)	**2491**	**1544**		**9.6%**	**0[-0,0]**
Total events: 0 (Formoterol and ICS), 0 (Same Dose ICS)					
Heterogeneity: Tau^2=0; Chi^2=0, df=9(P=1); I^2=0%					
Test for overall effect: Not applicable					
Total (95% CI)	**21136**	**18650**		**100%**	**0[-0,0]**
Total events: 17 (Formoterol and ICS), 13 (Same Dose ICS)					
Heterogeneity: Tau^2=0; Chi^2=2.58, df=41(P=1); I^2=0%					
Test for overall effect: Z=0.4(P=0.69)					
Test for subgroup differences: Chi^2=0.01, df=1 (P=0.92), I^2=0%					



Favours Formoterol & ICS

Favours same dose ICS

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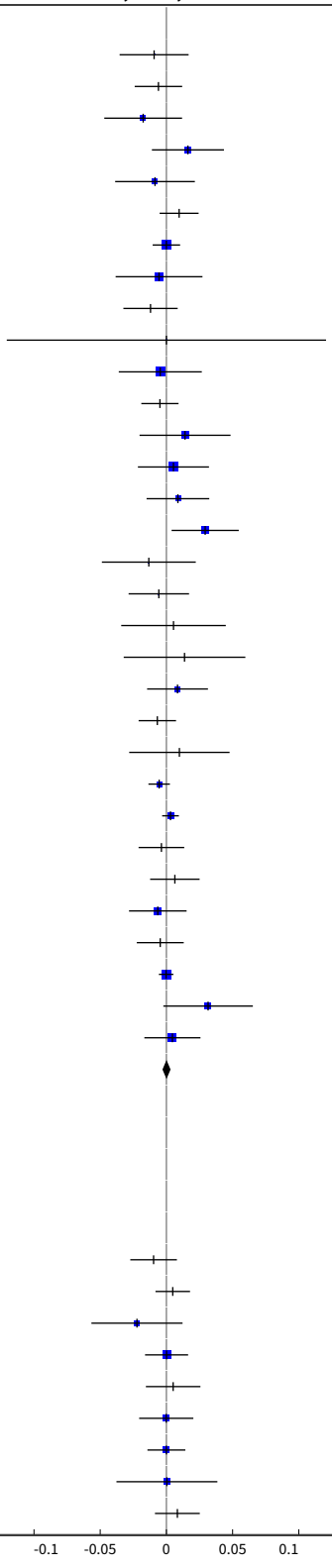
Analysis 2.2. Comparison 2 Formoterol and ICS versus same-dose ICS (risk difference), Outcome 2 All-cause non-fatal serious adverse events.

Study or subgroup	Formoterol and ICS n/N	Same Dose ICS n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
2.2.1 Adults					
Brown 2012	11/377	14/364		1.91%	-0.01[-0.04,0.02]
Buhl 2003	2/352	2/171		1.19%	-0.01[-0.02,0.01]
Chuchalin 2002	0/111	2/114		0.58%	-0.02[-0.05,0.01]
Corren 2007	2/123	0/121		0.63%	0.02[-0.01,0.04]
Corren 2013	1/110	2/113		0.58%	-0.01[-0.04,0.02]
D5896C00001	3/312	0/153		1.06%	0.01[-0.01,0.02]
EudraCT 2010-020602-14-DE	0/192	0/184		0.97%	0[-0.01,0.01]
Jenkins 2006	7/341	3/115		0.89%	-0.01[-0.04,0.03]
Kuna 2006	3/409	4/207		1.42%	-0.01[-0.03,0.01]
Matsunaga 2013	0/15	0/15		0.08%	0[-0.12,0.12]
Meltzer 2012	4/182	5/188		0.96%	-0[-0.04,0.03]
Morice 2007	2/462	2/217		1.53%	-0[-0.02,0.01]
Murphy 2015	1/71	0/143		0.49%	0.01[-0.02,0.05]
Nathan 2010	4/191	3/192		0.99%	0.01[-0.02,0.03]
Nathan 2012	1/115	0/117		0.6%	0.01[-0.01,0.03]
Noonan 2006	7/239	0/109		0.77%	0.03[0,0.05]
O'Byrne 2001	15/315	19/312		1.62%	-0.01[-0.05,0.02]
O'Byrne 2001	20/554	23/550		2.85%	-0.01[-0.03,0.02]
Pauwels 1997	10/210	9/213		1.09%	0.01[-0.03,0.04]
Pauwels 1997	15/215	12/214		1.11%	0.01[-0.03,0.06]
Pearlman 2013	1/119	0/119		0.61%	0.01[-0.01,0.03]
Pertseva 2013	0/146	2/292		1.01%	-0.01[-0.02,0.01]
Peters 2008	21/443	5/133		1.06%	0.01[-0.03,0.05]
Peters 2016	19/1645	28/1646		8.5%	-0.01[-0.01,0]
Peters 2016	100/4201	87/4201		21.71%	0[-0,0.01]
Price 2002	2/250	3/255		1.3%	-0[-0.02,0.01]
SD-039-0726	4/301	1/145		1.01%	0.01[-0.01,0.03]
Spector 2012	1/156	2/155		0.8%	-0.01[-0.03,0.02]
Weinstein 2010	2/255	3/240		1.28%	-0[-0.02,0.01]
Weinstein 2019	136/5868	137/5861		30.31%	-0[-0.01,0.01]
Zangrilli 2011	4/127	0/123		0.65%	0.03[-0,0.07]
Zetterstrom 2001	3/238	1/124		0.84%	0[-0.02,0.03]
Subtotal (95% CI)	**18645**	**17106**		**90.4%**	**0[-0,0]**
Total events: 401 (Formoterol and ICS), 369 (Same Dose ICS)					
Heterogeneity: Tau^2=0; Chi^2=24.33, df=31(P=0.8); I^2=0%					
Test for overall effect: Z=0.05(P=0.96)					
2.2.2 Children and adolescents					
Morice 2008	2/415	3/207		1.43%	-0.01[-0.03,0.01]
NCT01475032	4/421	1/213		1.46%	0[-0.01,0.02]
Pearlman 2017	0/183	2/90		0.62%	-0.02[-0.06,0.01]
Ploszczuk 2014	1/168	1/172		0.88%	0[-0.02,0.02]
Pohunek 2006	8/417	3/213		1.46%	0.01[-0.02,0.03]
SD-039-0714	1/136	1/134		0.7%	-0[-0.02,0.02]
SD-039-0718	0/128	0/145		0.7%	0[-0.01,0.01]
SD-039-0719	2/123	1/63		0.43%	0[-0.04,0.04]
SD-039-0725	5/352	1/169		1.18%	0.01[-0.01,0.03]



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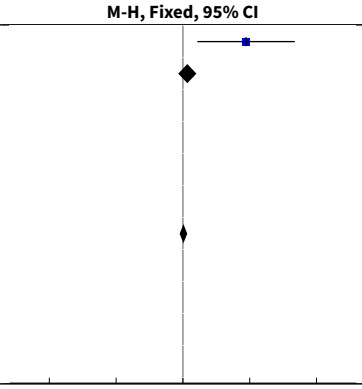
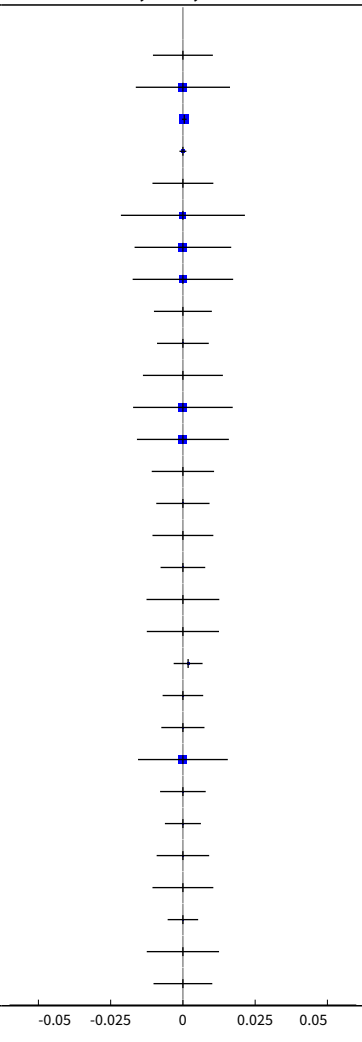
Study or subgroup	Formoterol and ICS n/N	Same Dose ICS n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
Tal 2002	7/148	0/138		0.74%	0.05[0.01,0.08]
Subtotal (95% CI)	**2491**	**1544**		**9.6%**	**0[-0,0.01]**
Total events: 30 (Formoterol and ICS), 13 (Same Dose ICS)					
Heterogeneity: Tau²=0; Chi²=10.68, df=9(P=0.3); I²=15.73%					
Test for overall effect: Z=0.95(P=0.34)					
Total (95% CI)	**21136**	**18650**		**100%**	**0[-0,0]**
Total events: 431 (Formoterol and ICS), 382 (Same Dose ICS)					
Heterogeneity: Tau²=0; Chi²=35.15, df=41(P=0.73); I²=0%					
Test for overall effect: Z=0.27(P=0.79)					
Test for subgroup differences: Chi²=0.71, df=1 (P=0.4), I²=0%					



Analysis 2.3. Comparison 2 Formoterol and ICS versus same-dose ICS (risk difference), Outcome 3 Asthma mortality.

Study or subgroup	Formoterol and ICS n/N	Same Dose ICS n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
2.3.1 Adults					
EudraCT 2010-020602-14-DE	0/192	0/184		1.39%	0[-0.01,0.01]
Pearlman 2013	0/119	0/119		0.88%	0[-0.02,0.02]
Peters 2016	2/4201	0/4201		31.15%	0[-0,0]
Peters 2016	0/1645	0/1646		12.2%	0[-0,0]
Pertseva 2013	0/146	0/292		1.44%	0[-0.01,0.01]
Murphy 2015	0/71	0/143		0.7%	0[-0.02,0.02]
Nathan 2012	0/115	0/117		0.86%	0[-0.02,0.02]
Corren 2013	0/110	0/113		0.83%	0[-0.02,0.02]
D5896C00001	0/312	0/153		1.52%	0[-0.01,0.01]
Buhl 2003	0/352	0/171		1.71%	0[-0.01,0.01]
Noonan 2006	0/239	0/109		1.11%	0[-0.01,0.01]
Chuchalin 2002	0/111	0/114		0.83%	0[-0.02,0.02]
Corren 2007	0/123	0/121		0.9%	0[-0.02,0.02]
Peters 2008	0/443	0/133		1.52%	0[-0.01,0.01]
Pauwels 1997	0/210	0/213		1.57%	0[-0.01,0.01]
SD-039-0726	0/301	0/145		1.45%	0[-0.01,0.01]
Price 2002	0/250	0/255		1.87%	0[-0.01,0.01]
Jenkins 2006	0/341	0/115		1.28%	0[-0.01,0.01]
Zetterstrom 2001	0/238	0/124		1.21%	0[-0.01,0.01]
O'Byrne 2001	1/554	0/550		4.09%	0[-0,0.01]
Morice 2007	0/462	0/217		2.19%	0[-0.01,0.01]
Kuna 2006	0/409	0/207		2.04%	0[-0.01,0.01]
Zangrilli 2011	0/127	0/123		0.93%	0[-0.02,0.02]
Weinstein 2010	0/255	0/240		1.83%	0[-0.01,0.01]
O'Byrne 2001	0/315	0/312		2.32%	0[-0.01,0.01]
Pauwels 1997	0/215	0/214		1.59%	0[-0.01,0.01]
Meltzer 2012	0/182	0/188		1.37%	0[-0.01,0.01]
Brown 2012	0/377	0/364		2.75%	0[-0.01,0.01]
Spector 2012	0/156	0/155		1.15%	0[-0.01,0.01]
Nathan 2010	0/191	0/192		1.42%	0[-0.01,0.01]



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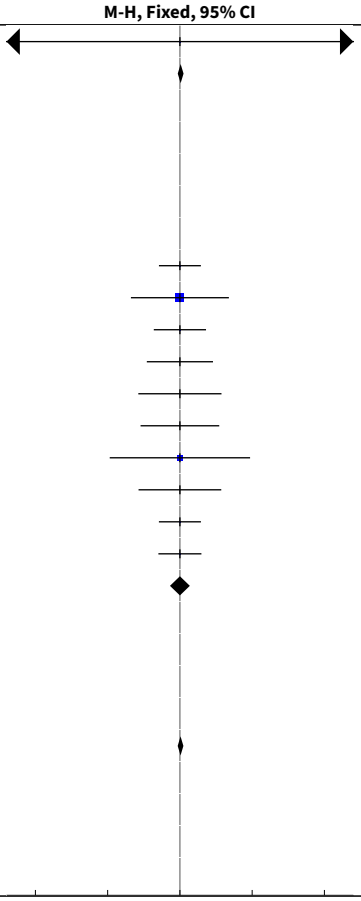
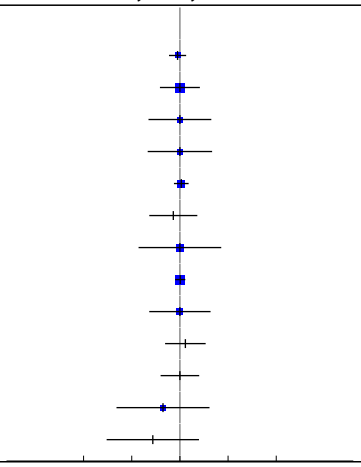
Study or subgroup	Formoterol and ICS n/N	Same Dose ICS n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
Matsunaga 2013	0/15	0/15		0.11%	0[-0.12,0.12]
Subtotal (95% CI)	**12777**	**11245**		**86.23%**	**0[-0,0]**
Total events: 3 (Formoterol and ICS), 0 (Same Dose ICS)					
Heterogeneity: Tau²=0; Chi²=0.9, df=30(P=1); I²=0%					
Test for overall effect: Z=0.5(P=0.61)					
2.3.2 Children and adolescents					
NCT01475032	0/421	0/213		2.1%	0[-0.01,0.01]
Pearlman 2017	0/183	0/90		0.89%	0[-0.02,0.02]
SD-039-0725	0/352	0/169		1.69%	0[-0.01,0.01]
Ploszczuk 2014	0/168	0/172		1.26%	0[-0.01,0.01]
SD-039-0714	0/136	0/134		1%	0[-0.01,0.01]
Tal 2002	0/148	0/138		1.06%	0[-0.01,0.01]
SD-039-0719	0/123	0/63		0.62%	0[-0.02,0.02]
SD-039-0718	0/128	0/145		1.01%	0[-0.01,0.01]
Pohunek 2006	0/417	0/213		2.09%	0[-0.01,0.01]
Morice 2008	0/415	0/207		2.05%	0[-0.01,0.01]
Subtotal (95% CI)	**2491**	**1544**		**13.77%**	**0[-0,0]**
Total events: 0 (Formoterol and ICS), 0 (Same Dose ICS)					
Heterogeneity: Tau²=0; Chi²=0, df=9(P=1); I²=0%					
Test for overall effect: Not applicable					
Total (95% CI)	**15268**	**12789**		**100%**	**0[-0,0]**
Total events: 3 (Formoterol and ICS), 0 (Same Dose ICS)					
Heterogeneity: Tau²=0; Chi²=0.97, df=40(P=1); I²=0%					
Test for overall effect: Z=0.44(P=0.66)					
Test for subgroup differences: Chi²=0.02, df=1 (P=0.89), I²=0%					



Favours Formoterol & ICS — Favours same dose ICS

Analysis 2.4. Comparison 2 Formoterol and ICS versus same-dose ICS (risk difference), Outcome 4 Asthma-related non-fatal serious adverse events.

Study or subgroup	Formoterol and ICS n/N	Same Dose ICS n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
2.4.1 Adults					
Peters 2016	6/1645	8/1646		8.64%	-0[-0.01,0]
EudraCT 2010-020602-14-DE	0/192	0/184		0.99%	0[-0.01,0.01]
Pearlman 2013	0/119	0/119		0.62%	0[-0.02,0.02]
Nathan 2012	0/115	0/117		0.61%	0[-0.02,0.02]
Peters 2016	35/4201	32/4201		22.05%	0[-0,0]
Pertseva 2013	0/146	1/292		1.02%	-0[-0.02,0.01]
Murphy 2015	0/71	0/143		0.5%	0[-0.02,0.02]
Weinstein 2019	32/5868	31/5861		30.78%	0[-0,0]
Corren 2007	0/123	0/121		0.64%	0[-0.02,0.02]
Buhl 2003	1/352	0/171		1.21%	0[-0.01,0.01]
D5896C00001	0/312	0/153		1.08%	0[-0.01,0.01]
Chuchalin 2002	0/111	1/114		0.59%	-0.01[-0.03,0.02]
Pauwels 1997	2/215	5/214		1.13%	-0.01[-0.04,0.01]



Favours Formoterol & ICS — Favours same dose ICS

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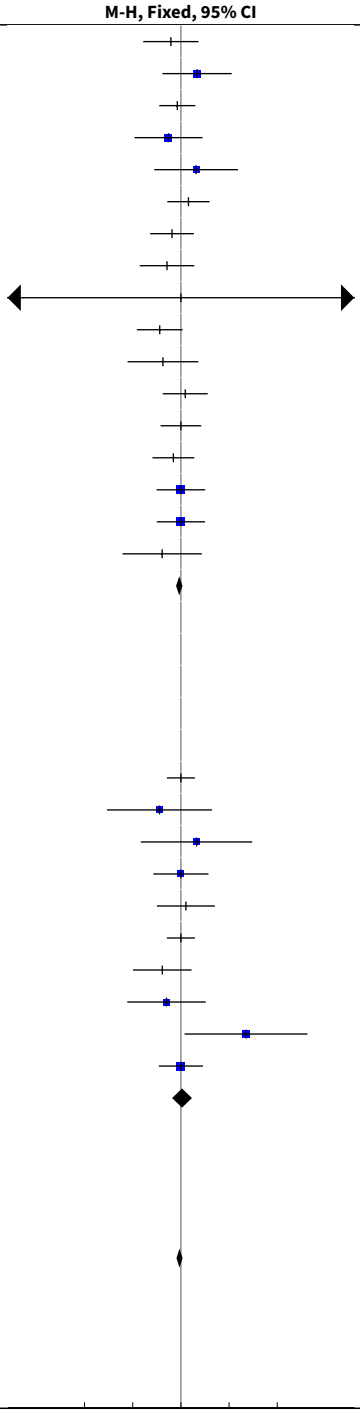
Study or subgroup	Formoterol and ICS n/N	Same Dose ICS n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
Nathan 2010	0/191	1/192		1.01%	-0.01[-0.02,0.01]
Noonan 2006	2/239	0/109		0.79%	0.01[-0.01,0.03]
O'Byrne 2001	3/554	4/550		2.9%	-0[-0.01,0.01]
Spector 2012	0/156	1/155		0.82%	-0.01[-0.02,0.01]
Zangrilli 2011	1/127	0/123		0.66%	0.01[-0.01,0.03]
Weinstein 2010	1/255	0/240		1.3%	0[-0.01,0.01]
Morice 2007	0/462	1/217		1.55%	-0[-0.02,0.01]
Kuna 2006	1/409	2/207		1.44%	-0.01[-0.02,0.01]
Matsunaga 2013	0/15	0/15		0.08%	0[-0.12,0.12]
Brown 2012	0/377	4/364		1.94%	-0.01[-0.02,0]
Pauwels 1997	1/210	3/213		1.11%	-0.01[-0.03,0.01]
Peters 2008	1/443	0/133		1.07%	0[-0.01,0.01]
SD-039-0726	0/301	0/145		1.03%	0[-0.01,0.01]
Price 2002	0/250	1/255		1.33%	-0[-0.01,0.01]
Jenkins 2006	0/341	0/115		0.9%	0[-0.01,0.01]
Zetterstrom 2001	0/238	0/124		0.86%	0[-0.01,0.01]
O'Byrne 2001	4/315	7/312		1.65%	-0.01[-0.03,0.01]
Subtotal (95% CI)	**18353**	**16805**		**90.25%**	**-0[-0,0]**
Total events: 90 (Formoterol and ICS), 102 (Same Dose ICS)					
Heterogeneity: Tau²=0; Chi²=12.86, df=29(P=1); I²=0%					
Test for overall effect: Z=1.02(P=0.31)					
2.4.2 Children and adolescents					
NCT01475032	0/421	0/213		1.48%	0[-0.01,0.01]
Pearlman 2017	0/183	1/90		0.63%	-0.01[-0.04,0.02]
SD-039-0719	1/123	0/63		0.44%	0.01[-0.02,0.04]
SD-039-0718	0/128	0/145		0.71%	0[-0.01,0.01]
SD-039-0725	3/352	1/169		1.2%	0[-0.01,0.02]
Pohunek 2006	0/417	0/213		1.48%	0[-0.01,0.01]
Morice 2008	0/415	2/207		1.45%	-0.01[-0.02,0.01]
SD-039-0714	0/136	1/134		0.71%	-0.01[-0.03,0.01]
Tal 2002	5/148	0/138		0.75%	0.03[0,0.07]
Ploszczuk 2014	0/168	0/172		0.89%	0[-0.01,0.01]
Subtotal (95% CI)	**2491**	**1544**		**9.75%**	**0[-0,0.01]**
Total events: 9 (Formoterol and ICS), 5 (Same Dose ICS)					
Heterogeneity: Tau²=0; Chi²=7.62, df=9(P=0.57); I²=0%					
Test for overall effect: Z=0.22(P=0.82)					
Total (95% CI)	**20844**	**18349**		**100%**	**-0[-0,0]**
Total events: 99 (Formoterol and ICS), 107 (Same Dose ICS)					
Heterogeneity: Tau²=0; Chi²=20.23, df=39(P=0.99); I²=0%					
Test for overall effect: Z=0.89(P=0.37)					
Test for subgroup differences: Chi²=0.27, df=1 (P=0.6), I²=0%					



Favours Formoterol & ICS — Favours same dose ICS

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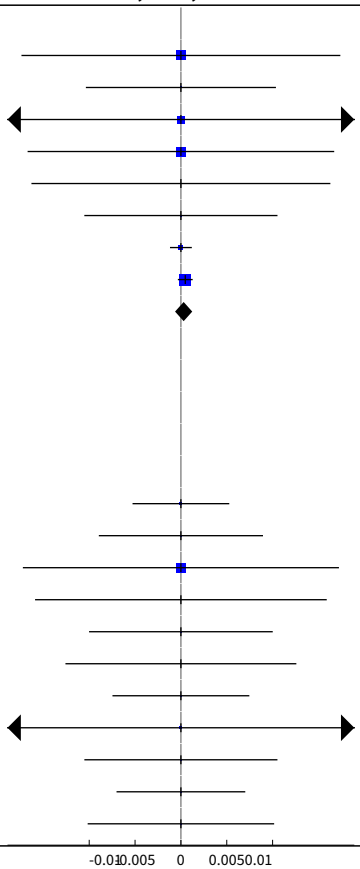
Comparison 3. Sensitivity analysis for adults: formoterol and ICS versus same-dose ICS (risk difference, Peto OR)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Asthma mortality	28	24022	Risk Difference (M-H, Fixed, 95% CI)	0.00 [-0.00, 0.00]
1.1 Independent outcome assessment	7	13414	Risk Difference (M-H, Fixed, 95% CI)	0.00 [-0.00, 0.00]
1.2 No reported independent outcome assessment	21	10608	Risk Difference (M-H, Fixed, 95% CI)	0.00 [-0.00, 0.00]
2 Asthma-related non-fatal serious adverse events	27	35158	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.86 [0.64, 1.14]
2.1 Independent outcome assessment	6	13191	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.01 [0.65, 1.56]
2.2 No reported independent outcome assessment	21	21967	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.76 [0.52, 1.10]

Analysis 3.1. Comparison 3 Sensitivity analysis for adults: formoterol and ICS versus same-dose ICS (risk difference, Peto OR), Outcome 1 Asthma mortality.

Study or subgroup	Formoterol and ICS n/N	Same dose ICS n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
3.1.1 Independent outcome assessment					
Corren 2013	0/110	0/113		0.96%	0[-0.02,0.02]
EudraCT 2010-020602-14-DE	0/192	0/184		1.62%	0[-0.01,0.01]
Murphy 2015	0/71	0/143		0.82%	0[-0.02,0.02]
Nathan 2012	0/115	0/117		1%	0[-0.02,0.02]
Pearlman 2013	0/119	0/119		1.02%	0[-0.02,0.02]
Pertseva 2013	0/146	0/292		1.67%	0[-0.01,0.01]
Peters 2016	0/1645	0/1646		14.15%	0[-0,0]
Peters 2016	2/4201	0/4201		36.12%	0[-0,0]
Subtotal (95% CI)	**6599**	**6815**		**57.36%**	**0[-0,0]**
Total events: 2 (Formoterol and ICS), 0 (Same dose ICS)					
Heterogeneity: Tau²=0; Chi²=0.44, df=7(P=1); I²=0%					
Test for overall effect: Z=0.63(P=0.53)					
3.1.2 No reported independent outcome assessment					
Brown 2012	0/377	0/364		3.18%	0[-0.01,0.01]
Buhl 2003	0/352	0/171		1.98%	0[-0.01,0.01]
Chuchalin 2002	0/111	0/114		0.97%	0[-0.02,0.02]
Corren 2007	0/123	0/121		1.05%	0[-0.02,0.02]
D5896C00001	0/312	0/153		1.77%	0[-0.01,0.01]
Jenkins 2006	0/341	0/115		1.48%	0[-0.01,0.01]
Kuna 2006	0/409	0/207		2.36%	0[-0.01,0.01]
Matsunaga 2013	0/15	0/15		0.13%	0[-0.12,0.12]
Meltzer 2012	0/182	0/188		1.59%	0[-0.01,0.01]
Morice 2007	0/462	0/217		2.54%	0[-0.01,0.01]
Nathan 2010	0/191	0/192		1.65%	0[-0.01,0.01]



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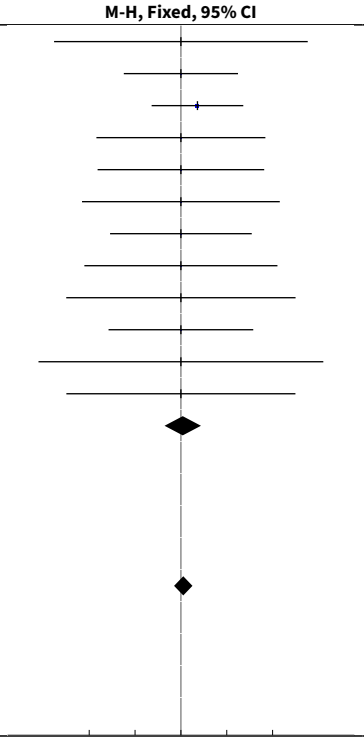
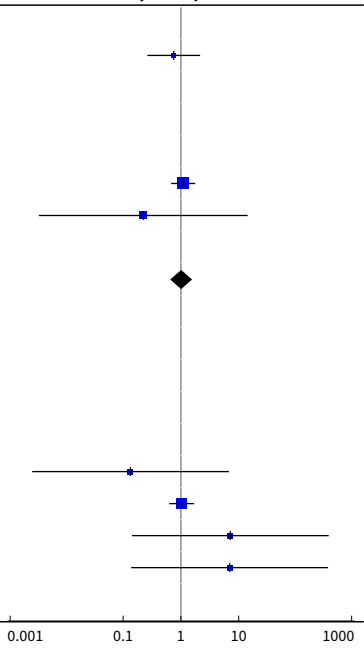
Study or subgroup	Formoterol and ICS n/N	Same dose ICS n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
Noonan 2006	0/239	0/109		1.29%	0[-0.01,0.01]
O'Byrne 2001	0/315	0/312		2.7%	0[-0.01,0.01]
O'Byrne 2001	1/554	0/550		4.75%	0[-0,0.01]
Pauwels 1997	0/210	0/213		1.82%	0[-0.01,0.01]
Pauwels 1997	0/215	0/214		1.84%	0[-0.01,0.01]
Peters 2008	0/443	0/133		1.76%	0[-0.01,0.01]
Price 2002	0/250	0/255		2.17%	0[-0.01,0.01]
SD-039-0726	0/301	0/145		1.68%	0[-0.01,0.01]
Spector 2012	0/156	0/155		1.34%	0[-0.01,0.01]
Weinstein 2010	0/255	0/240		2.13%	0[-0.01,0.01]
Zangrilli 2011	0/127	0/123		1.07%	0[-0.02,0.02]
Zetterstrom 2001	0/238	0/124		1.4%	0[-0.01,0.01]
Subtotal (95% CI)	**6178**	**4430**		**42.64%**	**0[-0,0]**
Total events: 1 (Formoterol and ICS), 0 (Same dose ICS)					
Heterogeneity: Tau^2=0; Chi^2=0.43, df=22(P=1); I^2=0%					
Test for overall effect: Z=0.2(P=0.84)					
Total (95% CI)	**12777**	**11245**		**100%**	**0[-0,0]**
Total events: 3 (Formoterol and ICS), 0 (Same dose ICS)					
Heterogeneity: Tau^2=0; Chi^2=0.9, df=30(P=1); I^2=0%					
Test for overall effect: Z=0.5(P=0.61)					
Test for subgroup differences: Chi^2=0.01, df=1 (P=0.93), I^2=0%					



Analysis 3.2. Comparison 3 Sensitivity analysis for adults: formoterol and ICS versus same-dose ICS (risk difference, Peto OR), Outcome 2 Asthma-related non-fatal serious adverse events.

Study or subgroup	Formoterol and ICS n/N	Same dose ICS n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
3.2.1 Independent outcome assessment					
Peters 2016	6/1645	8/1646		7.36%	0.75[0.26,2.15]
EudraCT 2010-020602-14-DE	0/192	0/184			Not estimable
Pearlman 2013	0/119	0/119			Not estimable
Nathan 2012	0/115	0/117			Not estimable
Peters 2016	35/4201	32/4201		35.09%	1.09[0.68,1.77]
Pertseva 2013	0/146	1/292		0.47%	0.22[0,14.26]
Murphy 2015	0/71	0/143			Not estimable
Subtotal (95% CI)	**6489**	**6702**		**42.92%**	**1.01[0.65,1.56]**
Total events: 41 (Formoterol and ICS), 41 (Same dose ICS)					
Heterogeneity: Tau^2=0; Chi^2=0.92, df=2(P=0.63); I^2=0%					
Test for overall effect: Z=0.04(P=0.97)					
3.2.2 No reported independent outcome assessment					
Spector 2012	0/156	1/155		0.53%	0.13[0,6.78]
Weinstein 2019	32/5868	31/5861		33.08%	1.03[0.63,1.69]
Zangrilli 2011	1/127	0/123		0.53%	7.16[0.14,361.02]
Weinstein 2010	1/255	0/240		0.53%	6.97[0.14,351.74]
SD-039-0726	0/301	0/145			Not estimable



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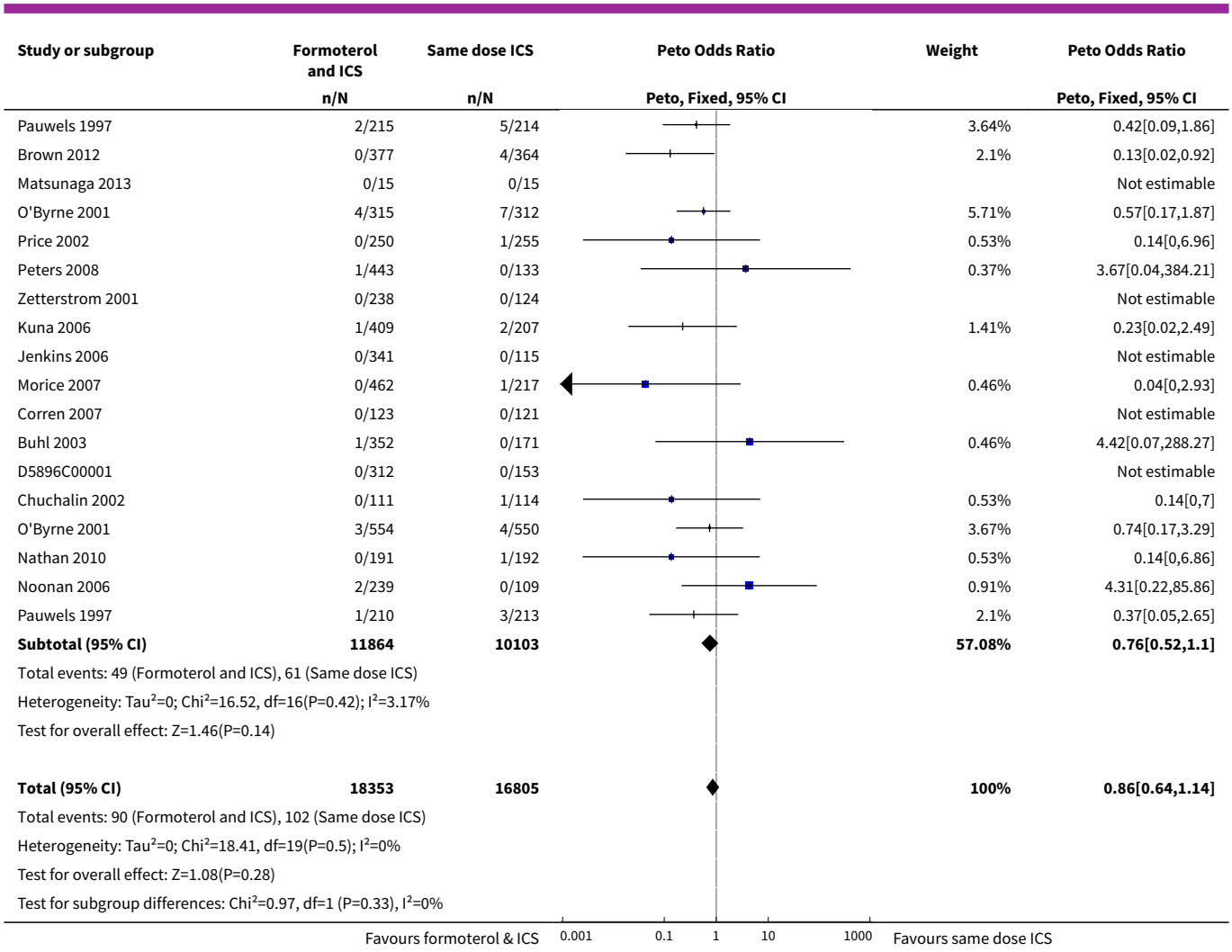

Comparison 4. Formoterol and ICS versus same-dose ICS (fixed-effect versus random-effects)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	39	39786	Odds Ratio (M-H, Fixed, 95% CI)	1.17 [0.60, 2.29]
1.1 Adults	29	35751	Odds Ratio (M-H, Fixed, 95% CI)	1.17 [0.60, 2.29]
1.2 Children and adolescents	10	4035	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 All-cause non-fatal serious adverse events	39	39786	Odds Ratio (M-H, Fixed, 95% CI)	1.02 [0.89, 1.17]
2.1 Adults	29	35751	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.87, 1.16]
2.2 Children and adolescents	10	4035	Odds Ratio (M-H, Fixed, 95% CI)	1.33 [0.71, 2.49]
3 Asthma mortality	38	28057	Risk Difference (M-H, Fixed, 95% CI)	0.00 [-0.00, 0.00]

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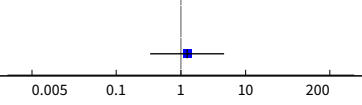
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
3.1 Adults	28	24022	Risk Difference (M-H, Fixed, 95% CI)	0.00 [-0.00, 0.00]
3.2 Children and adolescents	10	4035	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.00, 0.00]
4 Asthma-related non-fatal serious adverse events	37	39193	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.87 [0.66, 1.15]
4.1 Adults	27	35158	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.86 [0.64, 1.14]
4.2 Children and adolescents	10	4035	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.18 [0.40, 3.51]

Analysis 4.1. Comparison 4 Formoterol and ICS versus same-dose ICS (fixed-effect versus random-effects), Outcome 1 All-cause mortality.

Study or subgroup	Formoterol and ICS n/N	Same dose ICS n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
4.1.1 Adults					
Brown 2012	1/377	1/364		6.42%	0.97[0.06,15.49]
Buhl 2003	1/352	0/171		4.23%	1.46[0.06,36.12]
Chuchalin 2002	0/111	0/114			Not estimable
Corren 2007	0/123	0/121			Not estimable
Corren 2013	0/110	0/113			Not estimable
D5896C00001	0/312	0/153			Not estimable
EudraCT 2010-020602-14-DE	0/192	0/184			Not estimable
Jenkins 2006	0/341	0/115			Not estimable
Kuna 2006	0/409	0/207			Not estimable
Matsunaga 2013	0/15	0/15			Not estimable
Meltzer 2012	0/182	0/188			Not estimable
Morice 2007	0/462	0/217			Not estimable
Murphy 2015	0/71	0/143			Not estimable
Nathan 2010	1/191	0/192		3.13%	3.03[0.12,74.88]
Nathan 2012	0/115	0/117			Not estimable
Noonan 2006	0/239	0/109			Not estimable
O'Byrne 2001	0/315	0/312			Not estimable
O'Byrne 2001	1/554	0/550		3.16%	2.98[0.12,73.4]
Pauwels 1997	0/210	0/213			Not estimable
Pauwels 1997	1/215	0/214		3.15%	3[0.12,74.06]
Pearlman 2013	0/119	0/119			Not estimable
Pertseva 2013	0/146	0/292			Not estimable
Peters 2008	0/443	0/133			Not estimable
Peters 2016	2/1645	3/1646		18.94%	0.67[0.11,3.99]
Peters 2016	4/4201	5/4201		31.58%	0.8[0.21,2.98]
Price 2002	0/250	0/255			Not estimable
SD-039-0726	0/301	0/145			Not estimable
Spector 2012	0/156	0/155			Not estimable
Weinstein 2010	0/255	0/240			Not estimable
Weinstein 2019	5/5868	4/5861		25.28%	1.25[0.34,4.65]



Favours formoterol & ICS — Favours same dose ICS

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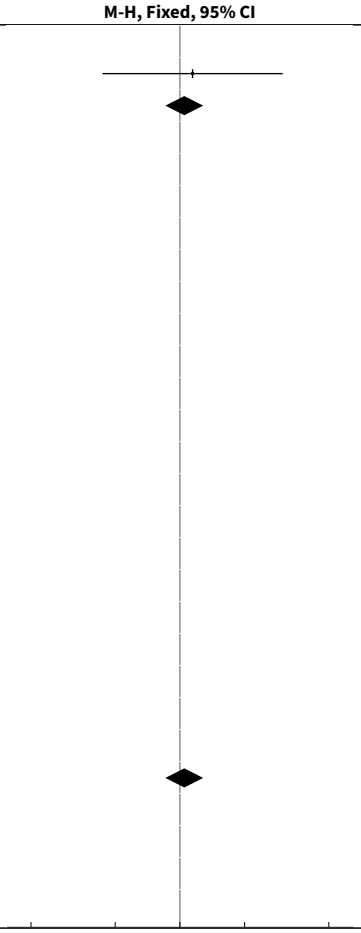
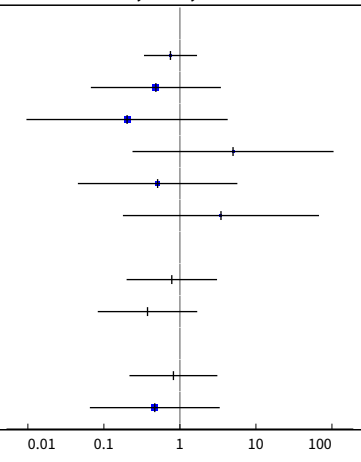
Study or subgroup	Formoterol and ICS n/N	Same dose ICS n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Zangrilli 2011	0/127	0/123			Not estimable
Zetterstrom 2001	1/238	0/124		4.12%	1.57[0.06,38.89]
Subtotal (95% CI)	**18645**	**17106**		**100%**	**1.17[0.6,2.29]**
Total events: 17 (Formoterol and ICS), 13 (Same dose ICS)					
Heterogeneity: Tau²=0; Chi²=1.78, df=8(P=0.99); I²=0%					
Test for overall effect: Z=0.45(P=0.65)					
4.1.2 Children and adolescents					
Morice 2008	0/415	0/207			Not estimable
NCT01475032	0/421	0/213			Not estimable
Pearlman 2017	0/183	0/90			Not estimable
Ploszczuk 2014	0/168	0/172			Not estimable
Pohunek 2006	0/417	0/213			Not estimable
SD-039-0714	0/136	0/134			Not estimable
SD-039-0718	0/128	0/145			Not estimable
SD-039-0719	0/123	0/63			Not estimable
SD-039-0725	0/352	0/169			Not estimable
Tal 2002	0/148	0/138			Not estimable
Subtotal (95% CI)	**2491**	**1544**			**Not estimable**
Total events: 0 (Formoterol and ICS), 0 (Same dose ICS)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**21136**	**18650**		**100%**	**1.17[0.6,2.29]**
Total events: 17 (Formoterol and ICS), 13 (Same dose ICS)					
Heterogeneity: Tau²=0; Chi²=1.78, df=8(P=0.99); I²=0%					
Test for overall effect: Z=0.45(P=0.65)					
Test for subgroup differences: Not applicable					



Analysis 4.2. Comparison 4 Formoterol and ICS versus same-dose ICS (fixed-effect versus random-effects), Outcome 2 All-cause non-fatal serious adverse events.

Study or subgroup	Formoterol and ICS n/N	Same dose ICS n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
4.2.1 Adults					
Brown 2012	11/377	14/364		3.56%	0.75[0.34,1.68]
Buhl 2003	2/352	2/171		0.69%	0.48[0.07,3.46]
Chuchalin 2002	0/111	2/114		0.63%	0.2[0.01,4.25]
Corren 2007	2/123	0/121		0.13%	5[0.24,105.24]
Corren 2013	1/110	2/113		0.5%	0.51[0.05,5.7]
D5896C00001	3/312	0/153		0.17%	3.47[0.18,67.64]
EudraCT 2010-020602-14-DE	0/192	0/184			Not estimable
Jenkins 2006	7/341	3/115		1.13%	0.78[0.2,3.08]
Kuna 2006	3/409	4/207		1.36%	0.38[0.08,1.69]
Matsunaga 2013	0/15	0/15			Not estimable
Meltzer 2012	4/182	5/188		1.24%	0.82[0.22,3.11]
Morice 2007	2/462	2/217		0.7%	0.47[0.07,3.34]



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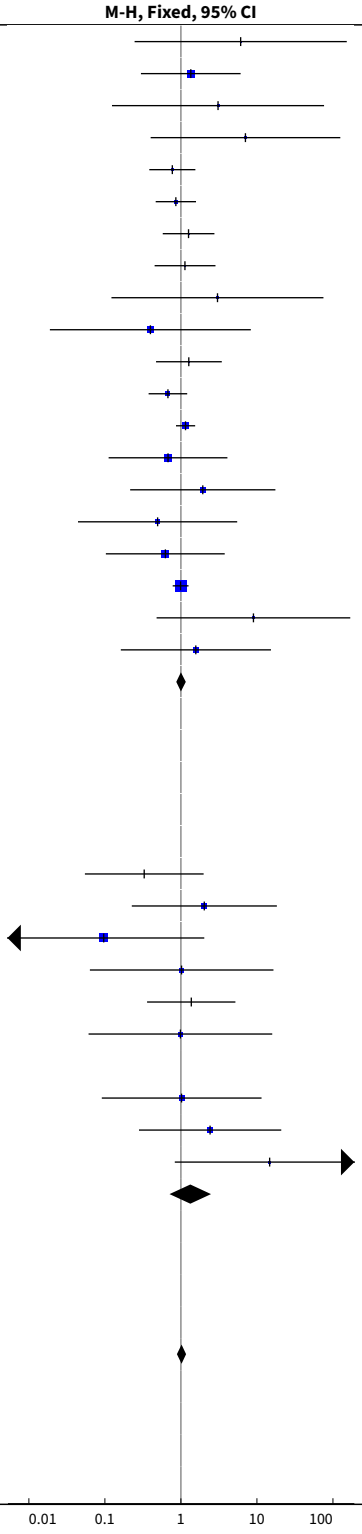
Study or subgroup	Formoterol and ICS n/N	Same dose ICS n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Murphy 2015	1/71	0/143		0.08%	6.11[0.25,151.81]
Nathan 2010	4/191	3/192		0.75%	1.35[0.3,6.1]
Nathan 2012	1/115	0/117		0.13%	3.08[0.12,76.36]
Noonan 2006	7/239	0/109		0.17%	7.06[0.4,124.81]
O'Byrne 2001	15/315	19/312		4.68%	0.77[0.38,1.55]
O'Byrne 2001	20/554	23/550		5.73%	0.86[0.47,1.58]
Pauwels 1997	15/215	12/214		2.88%	1.26[0.58,2.76]
Pauwels 1997	10/210	9/213		2.19%	1.13[0.45,2.85]
Pearlman 2013	1/119	0/119		0.13%	3.03[0.12,75.02]
Pertseva 2013	0/146	2/292		0.43%	0.4[0.02,8.31]
Peters 2008	21/443	5/133		1.89%	1.27[0.47,3.45]
Peters 2016	19/1645	28/1646		7.12%	0.68[0.38,1.21]
Peters 2016	100/4201	87/4201		21.86%	1.15[0.86,1.54]
Price 2002	2/250	3/255		0.76%	0.68[0.11,4.09]
SD-039-0726	4/301	1/145		0.34%	1.94[0.21,17.51]
Spector 2012	1/156	2/155		0.51%	0.49[0.04,5.5]
Weinstein 2010	2/255	3/240		0.79%	0.62[0.1,3.77]
Weinstein 2019	136/5868	137/5861		34.46%	0.99[0.78,1.26]
Zangrilli 2011	4/127	0/123		0.13%	9[0.48,168.95]
Zetterstrom 2001	3/238	1/124		0.33%	1.57[0.16,15.25]
Subtotal (95% CI)	**18645**	**17106**		**95.46%**	**1[0.87,1.16]**
Total events: 401 (Formoterol and ICS), 369 (Same dose ICS)					
Heterogeneity: Tau²=0; Chi²=18.47, df=29(P=0.93); I²=0%					
Test for overall effect: Z=0.05(P=0.96)					
4.2.2 Children and adolescents					
Morice 2008	2/415	3/207		1.03%	0.33[0.05,1.99]
NCT01475032	4/421	1/213		0.34%	2.03[0.23,18.31]
Pearlman 2017	0/183	2/90		0.86%	0.1[0,2.03]
Ploszczuk 2014	1/168	1/172		0.25%	1.02[0.06,16.51]
Pohunek 2006	8/417	3/213		1%	1.37[0.36,5.21]
SD-039-0714	1/136	1/134		0.26%	0.99[0.06,15.91]
SD-039-0718	0/128	0/145			Not estimable
SD-039-0719	2/123	1/63		0.33%	1.02[0.09,11.52]
SD-039-0725	5/352	1/169		0.34%	2.42[0.28,20.88]
Tal 2002	7/148	0/138		0.13%	14.68[0.83,259.54]
Subtotal (95% CI)	**2491**	**1544**		**4.54%**	**1.33[0.71,2.49]**
Total events: 30 (Formoterol and ICS), 13 (Same dose ICS)					
Heterogeneity: Tau²=0; Chi²=8.41, df=8(P=0.39); I²=4.9%					
Test for overall effect: Z=0.88(P=0.38)					
Total (95% CI)	**21136**	**18650**		**100%**	**1.02[0.89,1.17]**
Total events: 431 (Formoterol and ICS), 382 (Same dose ICS)					
Heterogeneity: Tau²=0; Chi²=26.9, df=38(P=0.91); I²=0%					
Test for overall effect: Z=0.26(P=0.8)					
Test for subgroup differences: Chi²=0.72, df=1 (P=0.4), I²=0%					



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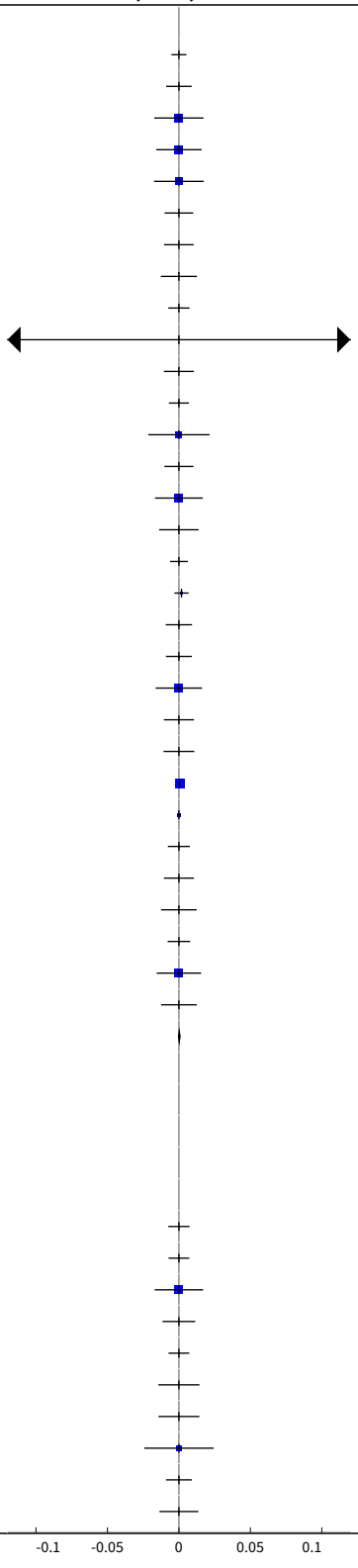
Analysis 4.3. Comparison 4 Formoterol and ICS versus same-dose ICS (fixed-effect versus random-effects), Outcome 3 Asthma mortality.

Study or subgroup	Formoterol and ICS n/N	Same dose ICS n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
4.3.1 Adults					
Brown 2012	0/377	0/364		2.75%	0[-0.01,0.01]
Buhl 2003	0/352	0/171		1.71%	0[-0.01,0.01]
Chuchalin 2002	0/111	0/114		0.83%	0[-0.02,0.02]
Corren 2007	0/123	0/121		0.9%	0[-0.02,0.02]
Corren 2013	0/110	0/113		0.83%	0[-0.02,0.02]
D5896C00001	0/312	0/153		1.52%	0[-0.01,0.01]
EudraCT 2010-020602-14-DE	0/192	0/184		1.39%	0[-0.01,0.01]
Jenkins 2006	0/341	0/115		1.28%	0[-0.01,0.01]
Kuna 2006	0/409	0/207		2.04%	0[-0.01,0.01]
Matsunaga 2013	0/15	0/15		0.11%	0[-0.12,0.12]
Meltzer 2012	0/182	0/188		1.37%	0[-0.01,0.01]
Morice 2007	0/462	0/217		2.19%	0[-0.01,0.01]
Murphy 2015	0/71	0/143		0.7%	0[-0.02,0.02]
Nathan 2010	0/191	0/192		1.42%	0[-0.01,0.01]
Nathan 2012	0/115	0/117		0.86%	0[-0.02,0.02]
Noonan 2006	0/239	0/109		1.11%	0[-0.01,0.01]
O'Byrne 2001	0/315	0/312		2.32%	0[-0.01,0.01]
O'Byrne 2001	1/554	0/550		4.09%	0[-0,0.01]
Pauwels 1997	0/210	0/213		1.57%	0[-0.01,0.01]
Pauwels 1997	0/215	0/214		1.59%	0[-0.01,0.01]
Pearlman 2013	0/119	0/119		0.88%	0[-0.02,0.02]
Pertseva 2013	0/146	0/292		1.44%	0[-0.01,0.01]
Peters 2008	0/443	0/133		1.52%	0[-0.01,0.01]
Peters 2016	2/4201	0/4201		31.15%	0[-0,0]
Peters 2016	0/1645	0/1646		12.2%	0[-0,0]
Price 2002	0/250	0/255		1.87%	0[-0.01,0.01]
SD-039-0726	0/301	0/145		1.45%	0[-0.01,0.01]
Spector 2012	0/156	0/155		1.15%	0[-0.01,0.01]
Weinstein 2010	0/255	0/240		1.83%	0[-0.01,0.01]
Zangrilli 2011	0/127	0/123		0.93%	0[-0.02,0.02]
Zetterstrom 2001	0/238	0/124		1.21%	0[-0.01,0.01]
Subtotal (95% CI)	**12777**	**11245**		**86.23%**	**0[-0,0]**
Total events: 3 (Formoterol and ICS), 0 (Same dose ICS)					
Heterogeneity: Tau²=0; Chi²=0.9, df=30(P=1); I²=0%					
Test for overall effect: Z=0.5(P=0.61)					
4.3.2 Children and adolescents					
Morice 2008	0/415	0/207		2.05%	0[-0.01,0.01]
NCT01475032	0/421	0/213		2.1%	0[-0.01,0.01]
Pearlman 2017	0/183	0/90		0.89%	0[-0.02,0.02]
Ploszczuk 2014	0/168	0/172		1.26%	0[-0.01,0.01]
Pohunek 2006	0/417	0/213		2.09%	0[-0.01,0.01]
SD-039-0714	0/136	0/134		1%	0[-0.01,0.01]
SD-039-0718	0/128	0/145		1.01%	0[-0.01,0.01]
SD-039-0719	0/123	0/63		0.62%	0[-0.02,0.02]
SD-039-0725	0/352	0/169		1.69%	0[-0.01,0.01]
Tal 2002	0/148	0/138		1.06%	0[-0.01,0.01]



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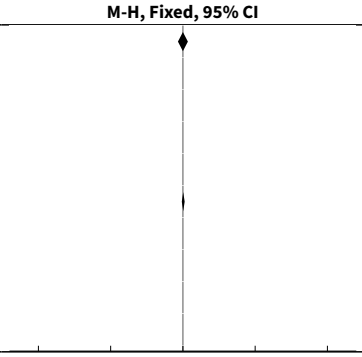
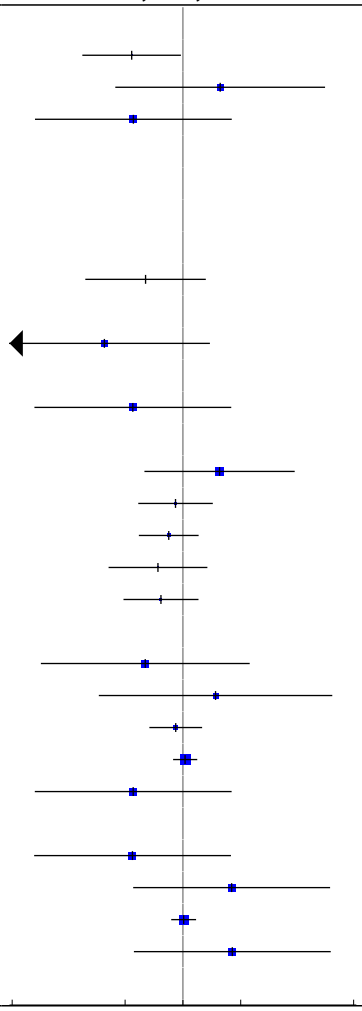
Study or subgroup	Formoterol and ICS n/N	Same dose ICS n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
Subtotal (95% CI)	**2491**	**1544**		**13.77%**	**0[-0,0]**
Total events: 0 (Formoterol and ICS), 0 (Same dose ICS)					
Heterogeneity: Tau^2=0; Chi^2=0, df=9(P=1); I^2=0%					
Test for overall effect: Not applicable					
Total (95% CI)	**15268**	**12789**		**100%**	**0[-0,0]**
Total events: 3 (Formoterol and ICS), 0 (Same dose ICS)					
Heterogeneity: Tau^2=0; Chi^2=0.97, df=40(P=1); I^2=0%					
Test for overall effect: Z=0.44(P=0.66)					
Test for subgroup differences: Chi^2=0.02, df=1 (P=0.89), I^2=0%					



Favours formoterol & ICS — Favours same dose ICS

Analysis 4.4. Comparison 4 Formoterol and ICS versus same-dose ICS (fixed-effect versus random-effects), Outcome 4 Asthma-related non-fatal serious adverse events.

Study or subgroup	Formoterol and ICS n/N	Same dose ICS n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
4.4.1 Adults					
Brown 2012	0/377	4/364		1.97%	0.13[0.02,0.92]
Buhl 2003	1/352	0/171		0.43%	4.42[0.07,288.27]
Chuchalin 2002	0/111	1/114		0.49%	0.14[0,7]
Corren 2007	0/123	0/121			Not estimable
D5896C00001	0/312	0/153			Not estimable
EudraCT 2010-020602-14-DE	0/192	0/184			Not estimable
Jenkins 2006	0/341	0/115			Not estimable
Kuna 2006	1/409	2/207		1.32%	0.23[0.02,2.49]
Matsunaga 2013	0/15	0/15			Not estimable
Morice 2007	0/462	1/217		0.43%	0.04[0,2.93]
Murphy 2015	0/71	0/143			Not estimable
Nathan 2010	0/191	1/192		0.49%	0.14[0,6.86]
Nathan 2012	0/115	0/117			Not estimable
Noonan 2006	2/239	0/109		0.85%	4.31[0.22,85.86]
O'Byrne 2001	3/554	4/550		3.44%	0.74[0.17,3.29]
O'Byrne 2001	4/315	7/312		5.35%	0.57[0.17,1.87]
Pauwels 1997	1/210	3/213		1.96%	0.37[0.05,2.65]
Pauwels 1997	2/215	5/214		3.41%	0.42[0.09,1.86]
Pearlman 2013	0/119	0/119			Not estimable
Pertseva 2013	0/146	1/292		0.44%	0.22[0,14.26]
Peters 2008	1/443	0/133		0.35%	3.67[0.04,384.21]
Peters 2016	6/1645	8/1646		6.89%	0.75[0.26,2.15]
Peters 2016	35/4201	32/4201		32.84%	1.09[0.68,1.77]
Price 2002	0/250	1/255		0.49%	0.14[0,6.96]
SD-039-0726	0/301	0/145			Not estimable
Spector 2012	0/156	1/155		0.49%	0.13[0,6.78]
Weinstein 2010	1/255	0/240		0.49%	6.97[0.14,351.74]
Weinstein 2019	32/5868	31/5861		30.96%	1.03[0.63,1.69]
Zangrilli 2011	1/127	0/123		0.49%	7.16[0.14,361.02]
Zetterstrom 2001	0/238	0/124			Not estimable



Favours formoterol & ICS — Favours same dose ICS

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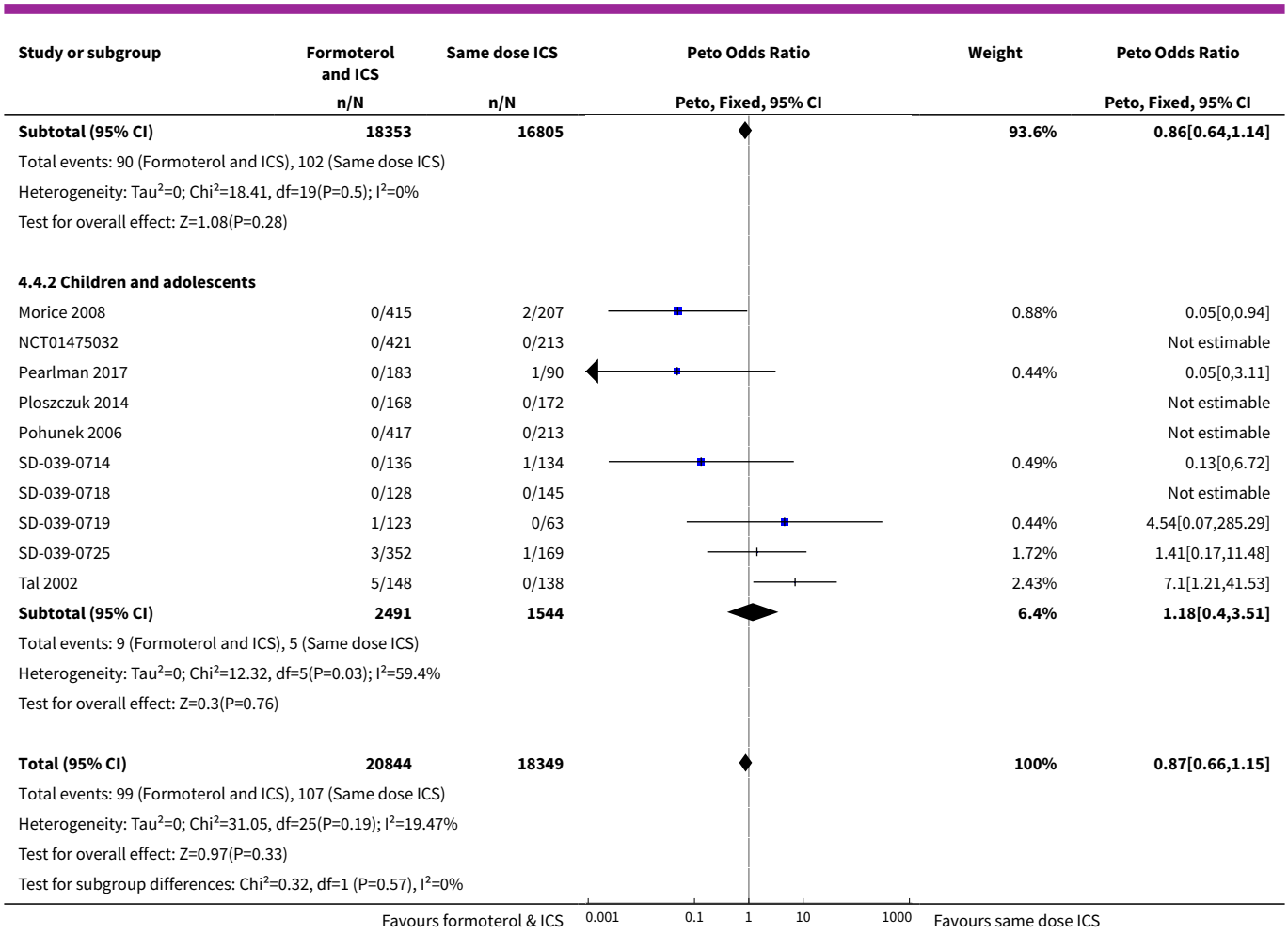

Comparison 5. Subgroup analysis for different LABA + ICS combinations

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause serious adverse events	28	35246	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.01 [0.87, 1.16]
1.1 High-dose budesonide in adults	10	12618	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.07 [0.85, 1.36]
1.2 Moderate-dose budesonide in adults	11	8144	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.94 [0.69, 1.28]
1.3 Beclomethasone	1	376	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 Mometasone	4	12977	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.99 [0.78, 1.24]
1.5 Fluticasone	4	1131	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.92 [0.20, 4.16]

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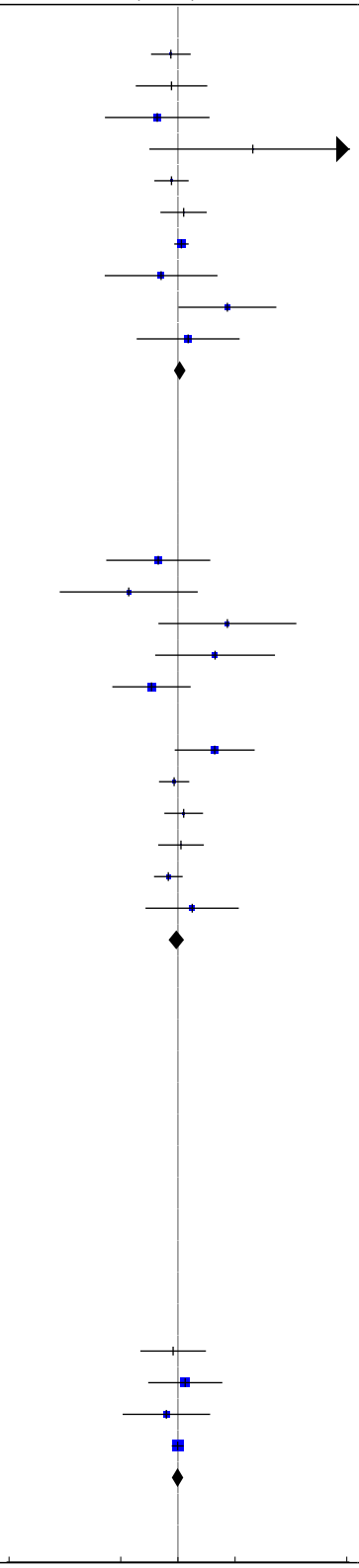
Analysis 5.1. Comparison 5 Subgroup analysis for different LABA + ICS combinations, Outcome 1 All-cause serious adverse events.

Study or subgroup	Experimental n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
5.1.1 High-dose budesonide in adults					
Brown 2012	11/377	14/364		3.31%	0.75[0.34,1.67]
Jenkins 2006	7/341	3/115		1.01%	0.77[0.18,3.26]
Morice 2007	2/462	2/217		0.47%	0.43[0.05,3.57]
Murphy 2015	1/71	0/143		0.12%	20.37[0.32,1308.56]
O'Byrne 2001	15/315	19/312		4.41%	0.77[0.39,1.54]
Peters 2008	21/443	5/133		2.42%	1.26[0.49,3.19]
Peters 2016	100/4201	87/4201		25.01%	1.15[0.86,1.54]
Spector 2012	1/156	2/155		0.41%	0.51[0.05,4.92]
Zangrilli 2011	4/127	0/123		0.54%	7.33[1.02,52.7]
Zetterstrom 2001	3/238	1/124		0.49%	1.51[0.19,12.04]
Subtotal (95% CI)	**6731**	**5887**		**38.19%**	**1.07[0.85,1.36]**
Total events: 165 (Experimental), 133 (Control)					
Heterogeneity: Tau^2=0; Chi^2=8.98, df=9(P=0.44); I^2=0%					
Test for overall effect: Z=0.6(P=0.55)					
5.1.2 Moderate-dose budesonide in adults					
Buhl 2003	2/352	2/171		0.48%	0.45[0.06,3.68]
Chuchalin 2002	0/111	2/114		0.27%	0.14[0.01,2.22]
Corren 2007	2/123	0/121		0.27%	7.33[0.46,117.87]
D5896C00001	3/312	0/153		0.36%	4.47[0.4,49.92]
Kuna 2006	3/409	4/207		0.85%	0.34[0.07,1.67]
Matsunaga 2013	0/15	0/15			Not estimable
Noonan 2006	7/239	0/109		0.81%	4.4[0.88,22.04]
O'Byrne 2001	20/554	23/550		5.66%	0.86[0.47,1.58]
Pauwels 1997	15/215	12/214		3.47%	1.26[0.58,2.75]
Pauwels 1997	10/210	9/213		2.49%	1.13[0.45,2.84]
Peters 2016	19/1645	28/1646		6.34%	0.68[0.38,1.21]
SD-039-0726	4/301	1/145		0.59%	1.78[0.27,11.65]
Subtotal (95% CI)	**4486**	**3658**		**21.59%**	**0.94[0.69,1.28]**
Total events: 85 (Experimental), 81 (Control)					
Heterogeneity: Tau^2=0; Chi^2=13.55, df=10(P=0.19); I^2=26.19%					
Test for overall effect: Z=0.41(P=0.68)					
5.1.3 Beclomethasone					
EudraCT 2010-020602-14-DE	0/192	0/184			Not estimable
Subtotal (95% CI)	**192**	**184**			**Not estimable**
Total events: 0 (Experimental), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
5.1.4 Mometasone					
Meltzer 2012	4/182	5/188		1.2%	0.82[0.22,3.09]
Nathan 2010	4/191	3/192		0.94%	1.34[0.3,5.98]
Weinstein 2010	2/255	3/240		0.68%	0.63[0.11,3.66]
Weinstein 2019	136/5868	137/5861		36.48%	0.99[0.78,1.26]
Subtotal (95% CI)	**6496**	**6481**		**39.3%**	**0.99[0.78,1.24]**
Total events: 146 (Experimental), 148 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.49, df=3(P=0.92); I^2=0%					



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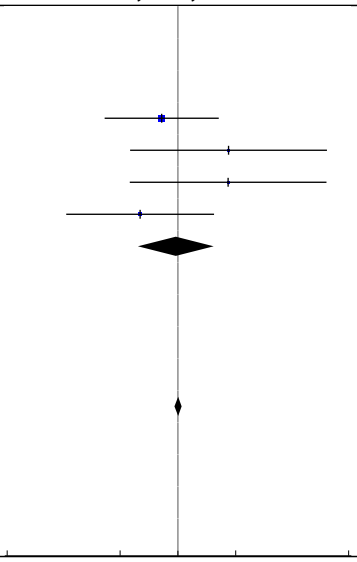
Study or subgroup	Experimental n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Test for overall effect: Z=0.13(P=0.9)					
5.1.5 Fluticasone					
Corren 2013	1/110	2/113		0.41%	0.52[0.05,5.09]
Nathan 2012	1/115	0/117		0.14%	7.52[0.15,378.97]
Pearlman 2013	1/119	0/119		0.14%	7.39[0.15,372.38]
Pertseva 2013	0/146	2/292		0.24%	0.22[0.01,4.22]
Subtotal (95% CI)	**490**	**641**		**0.92%**	**0.92[0.2,4.16]**
Total events: 3 (Experimental), 4 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.32, df=3(P=0.35); I^2=9.57%					
Test for overall effect: Z=0.11(P=0.91)					
Total (95% CI)	**18395**	**16851**		**100%**	**1.01[0.87,1.16]**
Total events: 399 (Experimental), 366 (Control)					
Heterogeneity: Tau^2=0; Chi^2=26.88, df=28(P=0.52); I^2=0%					
Test for overall effect: Z=0.09(P=0.93)					
Test for subgroup differences: Chi^2=0.55, df=1 (P=0.91), I^2=0%					



Favours LABA+ICS 0.001 0.1 1 10 1000 Favours ICS[control]

ADDITIONAL TABLES

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Table 1. Adults daily metred dose and delivery of beclomethasone, budesonide, fluticasone, or mometasone with formoterol

Study ID	Age (years)	N on formoterol	N on ICS alone	Daily metered dose (µg), (steroid)	Daily metered dose formoterol (µg)	Once daily	Twice daily	Combined inhalers	Separate inhalers	DPI	pMDI	Duration (weeks)
Brown 2012	12+	377	364	800 (BUD)	24		✓	✓			✓	52
Buhl 2003	18+	352	171	400 (BUD)	12	✓	✓	✓		✓		12
Chuchalin 2002	18+	111	114	400 (BUD)	24		✓		✓	✓		12
Corren 2007	12+	123	121	400 (BUD)	24		✓	✓		✓		12
Corren 2013	12+	110	113	500 (FP)	20		✓		✓		✓	12
D5896C00001	12+	312	153	400 (BUD)	12/24	✓	✓	✓			✓	12
EudraCT 2010-020602-14-DE	18+	192	184	800 (BEC)	24			✓			✓	12
Jenkins 2006	12+	341	115	1600 (BUD)	48		✓	✓	✓	✓		24
Kuna 2006	18+	409	207	200 (BUD)	12	✓	✓	✓		✓		12
Matsunaga 2013	20+	15	15	400 (BUD)	12		✓	✓			✓	24
Meltzer 2012	12+	182	188	200 (MOM)	20		✓	✓				26
Morice 2007	12+	462	217	800 (BUD)	24		✓	✓		✓	✓	12
Murphy 2015	12+	71	143	800 (BUD)	24		✓	✓			✓	12
Nathan 2010	12+	12191	192	400 (MOM)	20		✓	✓			✓	26
Nathan 2012	12+	115	117	200 (FP)	20		✓	✓			✓	12
Noonan 2006	12+	239	109	400 (BUD)	24		✓	✓	✓	✓	✓	12
O'Byrne 2001	18+	554	550	400 (BUD)	12		✓		✓	✓		52

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Table 1. Adults daily metred dose and delivery of beclomethasone, budesonide, fluticasone, or mometasone with formoterol *(Continued)*

O'Byrne 2001	18+	315	312	800 (BUD)	12	✓		✓	✓		52
Pauwels 1997	18+	210	213	200 (BUD)	24	✓		✓	✓		52
Pauwels 1997	18+	215	214	800 (BUD)	24	✓		✓	✓		52
Pearlman 2013	12+	119	119	200 (FP)	20	✓	✓			✓	12
Pertseva 2013	12+	146	292	500 (FP)	20	✓	✓				12
Peters 2008	12+	443	133	1600 (BUD)	48	✓	✓			✓	52
Peters 2016	12+	4201	4201	800 (BUD)	24	✓	✓			✓	26
Peters 2016	12+	1645	1646	400 (BUD)	24	✓	✓			✓	26
Price 2002	12+	250	255	800 (BUD)	24	✓		✓	✓		24
SD-039-0726	16+	301	145	200 (BUD)	12/24✓	✓	✓			✓	12
Spector 2012	12+	156	155	800 (BUD)	24	✓	✓		✓	✓	12
Weinstein 2010	12+	255	240	800 (MOM)	20	✓	✓			✓	12
Weinstein 2019	12+	5868	5861	400 or 800 (MOM)	20	✓	✓			✓	26
Zangrilli 2011	12+	127	123	800 (BUD)	24	✓	✓			✓	12
Zetterstrom 2001	18+	238	124	800 (BUD)	24	✓	✓	✓	✓		12

Abbreviations: BEC: beclomethasone; BUD: budesonide; DPI: dry powder inhaler; FP: fluticasone propionate; ICS: inhaled corticosteroids; MOM: mometasone; pMDI: pressurised metered dose inhaler.

Table 2. Children daily metred dose and delivery of beclomethasone, budesonide, fluticasone, or mometasone with formoterol

Study ID	Age (years)	N on formoterol	N on ICS alone	Daily metered dose (µg), (steroid)	Daily metered dose formoterol (µg)	Once daily	Twice daily	Combined inhalers	Separate inhalers	DPI	pMDI	Duration (weeks)

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Table 2. Children daily metred dose and delivery of beclomethasone, budesonide, fluticasone, or mometasone with formoterol *(Continued)*

Morice 2008	6 to 11	415	207	200 (BUD)	24		✓	✓		✓	✓	12
NCT01475032	5 to 12	421	213	200 (BEC)	24		✓	✓			✓	12
Pearlman 2017	6 to 12	183	90	400 (BUD)	12/24		✓	✓			✓	12
Ploszczuk 2014	2 to 11	169	172	200 (FP)	20		✓	✓		✓		12
Pohunek 2006	4 to 11	417	213	400 (BUD)	24		✓	✓	✓	✓		12
SD-039-0714	11 to 17	136	134	400 (BUD)	12		✓	✓		✓		12
SD-039-0718	6 to 15	128	145	200 (BUD)	24		✓	✓			✓	12
SD-039-0719	6 to 11	123	63	400 (BUD)	24		✓	✓		✓	✓	26
SD-039-0725	6 to 15	352	169	200 (BUD)	12/24	✓	✓	✓			✓	12
Tal 2002	4 to 17	148	138	400 (BUD)	24		✓	✓		✓		12

Abbreviations: BEC: beclomethasone; BUD: budesonide; DPI: dry powder inhaler; FP: fluticasone propionate; ICS: inhaled corticosteroids; MOM: mometasone; pMDI: pressurised metered dose inhaler.

Table 3. Summary of pooled odds ratios

Peto OR meta-analysis: regular formoterol in addition to regular ICS versus ICS alone							
	N events F/ICS	**Total N F/ICS**	**N events ICS**	**Total N ICS**	**Peto OR**	**CI start**	**CI end**
All-cause mortality							
Adults	17	18,645	13	17,106	Peto OR 1.25	0.61	2.56
Children and adolescents	0	2491	0	1544	-	-	-
All-cause non-fatal serious adverse events							
Adults	401	18,645	369	17,106	OR 1.00	0.87	1.16
Children and adolescents	30	2491	13	1544	OR 1.33	0.71	2.49

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Table 3. Summary of pooled odds ratios *(Continued)*

Asthma-related mortality							
Adults	3	12,777	0	11,245	-	-	-
Children and adolescents	0	2491	0	1544	-	-	-
Asthma-related serious adverse events							
Adults	90	18,353	102	16,805	Peto OR 0.86	0.64	1.14
Children and adolescents	9	2491	5	1544	Peto OR 1.18	0.40	3.51

Abbreviations: CI: confidence interval; ICS: inhaled corticosteroids; F: formoterol; N: number of participants; OR: odds ratio.

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Table 4. Mortality by cause of death

Study ID	Age (years)	Treatment given	Cause of death (N)
Buhl 2003	18+	Formoterol and budesonide	Cardiac arrest (1)
O'Byrne 2001	18+	Formoterol and budesonide (separate inhalers)	Status asthmaticus, followed by septic shock (1)
Pauwels 1997	18+	Formoterol and budesonide (separate inhalers)	Suicide (1)
Zetterstrom 2001	18+	Formoterol and budesonide	Suicide (1)
Brown 2012	12+	Formoterol and budesonide	Cerebrovascular accident (1)
Brown 2012	12+	Budesonide	Homicide (1)
Nathan 2010	12+	Formoterol and mometasone	Uterine leiomyosarcoma (1)
Jenkins 2006	12+	Formoterol and budesonide	Pulmonary embolus (but the death occurred after the control budesonide arm was discontinued so was not included in the meta-analysis) (1)
Peters 2016	12+	Formoterol and budesonide (low dose)	Road traffic accident (1), suicide (1)
Peters 2016	12+	Formoterol and budesonide (high dose)	Acute myocardial infarction (1), electric shock (1), asthma-related death (2)
Peters 2016	12+	Budesonide (low dose)	Pancytopenia (1), cerebrovascular event (1), pneumonitis (1)
Peters 2016	12+	Budesonide (high dose)	Coronary artery insufficiency (1), myocardial ischaemia (1), death of unknown cause* (1), road traffic accident (1), cerebrovascular event (1)
Weinstein 2019	12+	Mometasone and formoterol	Suicide (1), cardiomyopathy (1), coronary artery thrombosis (1), chronic obstructive pulmonary disease (1), ischaemic stroke (1)
Weinstein 2019	12+	Mometasone	Suicide (1), pulmonary embolism (1), gastrointestinal necrosis (1), pneumonia (1)

*The participant died at home suddenly, with no history of exacerbation or other adverse or serious adverse event, and without consulting a health practitioner.
Abbreviations: N: number of participants.

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Table 5. Summary of pooled risk differences

Risk difference meta-analysis: regular formoterol in addition to regular ICS versus ICS alone							
	N events F/ICS	**Total N F/ICS**	**N events ICS**	**Total N ICS**	**Risk difference**	**CI start**	**CI end**
All-cause mortality							
Adults	17	18,645	13	17,106	0.0002	−0.0007	0.0010
Children and adolescents	0	2491	0	1544	0.0000	−0.0034	0.0034
All-cause non-fatal serious adverse events							
Adults	401	18,645	369	17,106	0.0001	−0.0030	0.0031
Children and adolescents	30	2491	13	1544	0.0033	−0.0035	0.0101
Asthma-related mortality							
Adults	3	12,777	0	11,245	0.0003	−0.0007	0.0013
Children and adolescents	0	2491	0	1544	0.0000	−0.0034	0.0034
Asthma-related serious adverse events							
Adults	90	18,353	102	16,805	−0.0009	−0.0025	0.0008
Children and adolescents	9	2491	5	1544	0.0006	−0.0046	0.0057

Abbreviations: CI: confidence interval; F: formoterol; ICS: inhaled corticosteroid; N: number of participants.

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Table 6. Sensitivity analysis for asthma-related non-fatal serious adverse events

	Full data set	Independent outcome assessment	Excluding separate inhalers
Peto OR (adults)	(Peto OR 0.86, 95% CI 0.64 to 1.14; participants = 35,158; studies = 30)	(Peto OR 1.01, 95% CI 0.65 to 1.56; participants = 13,191; studies = 7)	(Peto OR 0.94, 95% CI 0.69 to 1.28; participants = 30,679; studies = 30)
Peto OR (children)	(Peto OR 1.18, 95% CI 0.40 to 3.51; participants = 4035; studies = 10)	Insufficient data	(Peto OR 1.18, 95% CI 0.40 to 3.51; participants = 4035; studies = 10)

Abbreviations: CI: confidence interval; OR: odds ratio.

APPENDICES

Appendix 1. 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) defines 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;
- is a congenital anomaly/birth defect.

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

Appendix 2. Search methods up to August 2012

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

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

Searches were conducted up to August 2012 with no restriction on language of publication.

Appendix 3. Sources and search methods for the Cochrane Trials Register

Electronic searches: core databases

Database	Dates searched	Frequency of search
CENTRAL (via the Cochrane Register of Studies (CRS))	From inception	Monthly
MEDLINE (Ovid SP)	1946 onwards	Weekly
Embase (Ovid SP)	1974 onwards	Weekly
PsycINFO (Ovid SP)	1967 onwards	Monthly

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(Continued)

CINAHL (EBSCO)	1937 onwards	Monthly
AMED (EBSCO)	From inception	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 Cochrane Airways Trials Register

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/

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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. Search strategies from 2012 to 2019

Database: Cochrane Airways Trials Register

Platform: Cochrane Register of Studies

Dates covered: August 2012 to February 2019

#1 AST:MISC1

#2 MeSH DESCRIPTOR Asthma Explode All

#3 asthma*:ti,ab

#4 #1 or #2 or #3

#5 MeSH DESCRIPTOR Adrenergic beta-2 Receptor Agonists

#6 (long-acting or "long acting") NEAR ((beta* NEAR3 (agonist* OR adrenergic*)) OR bronchodilat*)

#7 LABA:TI,AB

#8 MESH DESCRIPTOR Salmeterol Xinafoate

#9 salmeterol:ti,ab,kw

#10 MESH DESCRIPTOR Formoterol Fumarate

#11 formoterol:ti,ab,kw

#12 eformoterol:ti,ab,kw

#13 (Advair OR Symbicort OR Serevent OR Foradil OR Oxis):ti,ab,kw

#14 #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13

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#15 #4 AND #14

#16 MESH DESCRIPTOR Drug-Related Side Effects and Adverse Reactions EXPLODE ALL

#17 MESH DESCRIPTOR Drug Monitoring

#18 MESH DESCRIPTOR Adverse Drug Reaction Reporting Systems

#19 MESH DESCRIPTOR Product Surveillance, Postmarketing EXPLODE ALL

#20 MESH DESCRIPTOR Mortality EXPLODE ALL

#21 serious or safety or surveillance or mortality or death or intubat* or adverse or toxic* or complication* or tolerability or harm*

#22 #16 OR #17 OR #18 OR #19 OR #20 OR #21

#23 #15 AND #22

Database: ClinicalTrials.gov

Dates covered: August 2012 to February 2019

Condition: asthma
Intervention: salmeterol OR formoterol
Outcome measures: serious OR safety OR surveillance OR mortality OR death OR harm OR toxicity OR tolerability OR adverse OR complication OR intubate
Study type: Interventional

Database: WHO ICTRP

Dates covered: August 2012 to February 2019

Condition: asthma
Intervention: salmeterol OR formoterol

Appendix 5. Trade-off between mortality risks and quality of life

We were not able to identify studies to address the trade-offs between mortality risks and quality of life of combined formoterol and ICS compared with ICS alone. However, a recently published Cochrane Review comparing combined salmeterol and ICS with ICS alone reported that a death over six months salmeterol in combination with ICS would need from two thousand to ten thousand people to benefit from the treatment. For further explanation please refer to Cates 2018.

WHAT'S NEW

Date	Event	Description
20 November 2019	Amended	Funding statement and disclaimer added to acknowledgements.

HISTORY

Protocol first published: Issue 1, 2008
Review first published: Issue 2, 2009

Date	Event	Description
28 October 2019	Amended	Clarified that 3 deaths were due to asthma in the plain language summary following feedback from the Cochrane translation team.
13 November 2017	New search has been performed	Literature search run.

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Date	Event	Description
13 November 2017	New citation required and conclusions have changed	The 2019 update of this review includes 12 new trials recruiting 26,540 adults, and three new trials recruiting 1429 children and adolescents taking regular formoterol in combination with budesonide, mometasone, beclomethasone, or fluticasone (Corren 2013; EudraCT 2010-020602-14-DE; Matsunaga 2013; Murphy 2015; Nathan 2012; NCT01475032; Paggiaro 2016; Pearlman 2013; Pearlman 2017; Pertseva 2013; Peters 2016; Ploszczuk 2014; Samson 2012; Stirbulov 2012; Weinstein 2019). Two large studies that were previously identified as ongoing trials are included in this update (Peters 2016; Weinstein 2019). There was one new abstract, Samson 2012, and two full-text articles (Paggiaro 2016; Stirbulov 2012), which provided no outcome data. A new author, SJ, was added, and one author, R Jaeschke, stepped down.
29 October 2012	New citation required and conclusions have changed	With the addition of data from six new trials in adults, we found a significant reduction of asthma-related serious adverse events in adults on regular formoterol with inhaled corticosteroids, however this did not translate into a similar reduction in all-cause serious adverse events.
22 October 2012	New search has been performed	The 2012 update of this review includes six new trials, which recruited 2550 adults and adolescents given regular formoterol in combination with budesonide or mometasone (Brown 2012; Meltzer 2012; Nathan 2010; Spector 2012; Weinstein 2010; Zangrilli 2011). There were no new studies in children, but two large ongoing studies have been identified in adults and adolescents, each intending to recruit 11,000 participants. They are expected to report in 2017 (NCT01444430; NCT01471340).

CONTRIBUTIONS OF AUTHORS

SJ: trial selection, data extraction, and co-writing of the 2019 update.

CJC: conception of the idea and co-writing of protocol with MJC. Trial selection, data extraction, and co-writing of the original review and the 2012 and 2019 updates.

RJ: trial selection, data extraction, and co-writing of the original review.

MF and SS: data extraction and co-writing of the 2012 update.

Contributions of editorial team

Rebecca Fortescue (Co-ordinating Editor): edited the review; advised on methodology, interpretation, and content; approved the final review prior to publication.

Toby Lasserson (Editor): edited the review; advised on methodology, interpretation, and content; approved the final review prior to publication.

Emma Dennett (Managing Editor): co-ordinated the editorial process; advised on interpretation and content; edited the review.

Emma Jackson (Assistant Managing Editor): conducted peer review; edited the Plain language summary and Reference sections of the protocol and the review.

Elizabeth Stovold (Information Specialist): designed the search strategy; ran the searches; edited the Search methods section.

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DECLARATIONS OF INTEREST

SJ: none known.

SS: none known.

MF: received payment from AstraZeneca for a lecture. None of the sponsors or funding institutions had any role in gathering, analysing, or interpreting the data, and they have no right to approve or disapprove any submitted paper.

CJC: is a Co-ordinating Editor for the Cochrane Airways Group.

SOURCES OF SUPPORT

Internal sources

- NHS R&D, UK.

External sources

- National Institute for Health Research, UK.

  Cochrane Programme Grant 16/114/21: NHS priorities in the management of chronic respiratory disease
- European Union (FP7) Health, Other.

  ASTROLAB project (EC HEALTH-F5-2011-282593)

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We used Peto odds ratio for primary meta-analysis of odds ratios, as otherwise the results are largely dependent on the zero correction adopted. Single-inhaler therapy and adjustable maintenance dosing were not included in the review, nor was comparison with higher-dose inhaled corticosteroids (ICS). This was done because we decided to restrict our attention to the question of regular use of formoterol, in addition to the same ICS regimen, in both active and control arms. Subgroup analysis was not attempted on the basis of asthma severity, but was carried out on different ICS molecules and high and moderate budesonide doses for this update. Sensitivity analysis for asthma serious adverse events was also carried out restricting the analysis to combined inhalers following peer review suggestion that adding formoterol in a separate inhaler could result in discontinuation of ICS.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Inhalation; Adrenal Cortex Hormones [*adverse effects] [therapeutic use]; Adrenergic beta-2 Receptor Agonists [administration & dosage] [*adverse effects]; Anti-Asthmatic Agents [administration & dosage] [*adverse effects] [therapeutic use]; Asthma [*drug therapy]; Drug Therapy, Combination; Formoterol Fumarate [*adverse effects] [therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Humans

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