Stopping long-acting beta$_2$-agonists (LABA) for adults with asthma well controlled by LABA and inhaled corticosteroids (Review)

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[Intervention Review]

Stopping long-acting beta$_2$-agonists (LABA) for adults with asthma well controlled by LABA and inhaled corticosteroids

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Editorial group: Cochrane Airways Group.
Publication status and date: New, published in Issue 6, 2015.
Review content assessed as up-to-date: 9 April 2015.

Citation: Ahmad S, Kew KM, Normansell R. Stopping long-acting beta$_2$-agonists (LABA) for adults with asthma well controlled by LABA and inhaled corticosteroids. *Cochrane Database of Systematic Reviews* 2015, Issue 6. Art. No.: CD011306. DOI: 10.1002/14651858.CD011306.pub2.

ABSTRACT

Background

Poorly controlled asthma often leads to preventable exacerbations that require additional medications, as well as unscheduled hospital and clinic visits.

Long-acting beta$_2$-agonists (LABA) are commonly given to adults with asthma whose symptoms are not well controlled by inhaled corticosteroids (ICS). US and UK regulators have issued warnings for LABA in asthma, and now recommend they be used "for the shortest duration of time required to achieve control of asthma symptoms and discontinued, if possible, once asthma control is achieved".

Objectives

To compare cessation of long-acting beta$_2$-agonists (LABA) versus continued use of LABA/inhaled corticosteroids (LABA/ICS) for adults whose asthma is well controlled, and to determine whether stopping LABA:

1. results in loss of asthma control or deterioration in quality of life;

2. increases the likelihood of asthma attacks or 'exacerbations'; or

3. increases or decreases the likelihood of serious adverse events of any cause.

Search methods

We searched the Cochrane Airways Group Specialised Register (CAGR), www.ClinicalTrials.gov, www.who.int/ictrp/en/, reference lists of primary studies and existing reviews and manufacturers' trial registries (GlaxoSmithKline (GSK) and AstraZeneca). We searched all databases from their inception to April 2015, and we imposed no restriction on language of publication.

Selection criteria

We looked for parallel randomised controlled trials (RCTs) of at least eight weeks' duration, in which adults whose asthma was well controlled by any dose of ICS+LABA combination therapy were randomly assigned to (1) step-down therapy to ICS alone versus (2) continuation of ICS and LABA.

Data collection and analysis

Two review authors independently screened all records identified by the search strategy. We used an Excel extraction tool to manage searches, document reasons for inclusion and exclusion and extract descriptive and numerical data from trials meeting inclusion criteria.

Prespecified primary outcomes were (1) exacerbations requiring oral steroids, (2) asthma control and (3) all-cause serious adverse events.

Main results

Six randomised, double-blind studies between 12 and 24 weeks' long met the inclusion criteria. Five studies contributed data to the meta-analysis, assigning 2781 people with stable asthma to the comparison of interest. The definition of stable asthma and inclusion criteria varied across studies, and Global Initiative for Asthma (GINA) criteria were not used. Risk of bias across studies was generally low, and most evidence was rated as moderate quality.

Stopping LABA might increase the number of people having exacerbations and requiring oral corticosteroids (odds ratio (OR) 1.74, 95% confidence interval (CI) 0.83 to 3.65; participants = 1257; studies = 4), although the confidence intervals did not exclude the possibility that stopping LABA was beneficial; over 17 weeks, 19 people per 1000 who continued their LABA had an exacerbation, compared with 32 per 1000 when LABA were stopped (13 more per 1000, 95% CI 3 fewer to 46 more).

People who stopped LABA had worse scores on the Asthma Control Questionnaire (mean difference (MD) 0.24, 95% CI 0.13 to 0.35; participants = 645; studies = 3) and on measures of asthma-related quality of life (standardised mean difference (SMD) 0.36, 95% CI 0.15 to 0.57; participants = 359; studies = 2) than those who continued LABA, but the effects were not clinically relevant.

Too few events occurred for investigators to tell whether stopping LABA has a greater effect on serious adverse events compared with continuing LABA+ICS (OR 0.82, 95% CI 0.28 to 2.42; participants = 1342; studies = 5), and no study reported exacerbations requiring an emergency department visit or hospitalisation as a separate outcome. Stopping LABA may result in fewer adverse events of any kind compared with continuing, although the effect was not statistically significant (OR 0.83, 95% CI 0.66 to 1.05; participants = 1339; studies = 5), and stopping LABA made people more likely to withdraw from participation in research studies (OR 1.95, 95% CI 1.47 to 2.58; participants = 1352; studies = 5).

Authors' conclusions

This review suggests that stopping LABA in adults who have stable asthma while they are taking a combination of LABA and ICS inhalers may increase the likelihood of asthma exacerbations that require treatment with oral corticosteroids, but this is not certain. Stopping LABA may slightly reduce asthma control and quality of life, but evidence was insufficient to show whether this had an effect on important outcomes such as serious adverse events and exacerbations requiring hospital admission, and longer trials are warranted. Trialists should include patient-important outcomes such as asthma control and quality of life and should use validated measurement tools. Definitions of exacerbations should be provided.

PLAIN LANGUAGE SUMMARY

What is the evidence for stopping long-acting beta$_2$-agonists for adults with stable asthma using combination therapy?

Stopping long-acting beta$_2$-agonists (LABA) for adults whose asthma is stable with LABA and inhaled corticosteroid (ICS) treatment may increase the number of asthma attacks that require treatment with extra corticosteroids, but this remains uncertain. Stopping LABA may also slightly reduce quality of life and asthma control. We could not tell whether stopping LABA changed serious side effects or the likelihood of having to go to the hospital for an asthma attack.

Why is the question important?

Poorly controlled asthma often leads to attacks that require additional medications, hospital stays or treatment in the emergency department. Long-acting beta$_2$-agonists (LABA) are inhaled drugs that can be added to inhaled corticosteroids (ICS) to improve symptoms and reduce asthma attacks for adults whose asthma is not well controlled by ICS alone. However, some drug authorities have issued warnings for LABA in asthma because of safety concerns and now recommend that they be used for the shortest duration possible, then stopped once control of asthma symptoms is achieved. We believed it was important to assess evidence provided by high-quality studies.

How did we answer the question?

We looked for studies at least 8 weeks' long that compared a group of people with stable asthma who stopped taking LABA versus a group who continued taking ICS+LABA together. We were mainly interested in determining whether stopping LABA had an effect on asthma attacks, asthma control or side effects.

What did we find out?

We included in the data analyses five studies of people with stable asthma. We rated the overall quality of evidence as moderate for most outcomes, meaning that additional studies are likely to change our confidence in what we found. It looked as though people who stopped LABA might be more likely to have asthma attacks needing treatment with oral steroids, but this is uncertain. Over 17 weeks, 19 of 1000 people continuing their LABA had an attack, compared with 32 of 1000 who stopped taking LABA. This means that 13 more people in 1000 would have an attack if they stopped their LABA, but the uncertainty meant that between 3 fewer and 46 more could be affected.

Asthma control and asthma-related quality of life were a bit worse among people who stopped taking LABA, and we could not tell whether stopping LABA increased serious side effects or admission to the hospital.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Stopp ing LABA compared with continuing use of LABA+ICS for adults with well-controlled asthma

Patient or population: adults with asthma well controlled on LABA and ICS
Settings: outpatient
Intervention: LABA stopped
Comparison: LABA continued
Both groups were taking the same dose of ICS
Time point: calculated as the weighted mean duration of studies contributing to each analysis

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	LABA continued	LABA stopped				
Exacerbation: systemic corticosteroids 17 weeks	19 per 1000	32 per 1000 (16 to 65)	**OR 1.74** (0.83 to 3.65)	1257 (4 RCTs)	⊕⊕⊕◯ Moderate[a]	
Asthma control: ACQ 17 weeks	Mean ACQ score in the control group was 0.68[b]	Mean score of people who stopped LABA was **0.24 points worse** (0.13 higher to 0.35 higher)	-	645 (3 RCTs)	⊕⊕⊕◯ Moderate[c]	MCID = 0.5, so difference is not clinically significant
Serious adverse events 17 weeks	13 per 1000	11 per 1000 (4 to 31)	**OR 0.82** (0.28 to 2.42)	1342 (5 RCTs)	⊕⊕⊕◯ Moderate	
Asthma-related quality of life 12 weeks	Mean asthma-related quality of life in the control group was 1.18	Mean score of people who stopped LABA was **0.36 standard deviations worse** (0.15 worse to 0.57 worse)	-	359 (2 RCTs)	⊕⊕⊕◯ Moderate[c,]	

Exacerbation: hospital 17 weeks	0 per 1000	0 per 1000 (0 to 0)	Not estimable	1342 (5 RCTs)	⊕⊕◯◯ Low	No one in either group was hospitalised for an asthma exacerbation
Adverse events (all) 17 weeks	521 per 1000	474 per 1000 (417 to 533)	**OR 0.83** (0.66 to 1.05)	1339 (5 RCTs)	⊕⊕⊕◯ Moderate	
Withdrawal (all) 17 weeks	159 per 1000	269 per 1000 (217 to 327)	**OR 1.95** (1.47 to 2.58)	1352 (5 RCTs)	⊕⊕⊕◯ Moderate	

*The basis for the **assumed risk** (e.g.median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR**: Odds ratio; **LABA**: Long-acting beta$_2$-agonists; **ICS**: Inhaled corticosteroids; **ACQ**: Asthma Control Questionnaire; **AQLQ**: Asthma Quality of Life Questionnaire.

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

[a] Confidence intervals include both significant harm and possible benefit of stopping LABA.
[b] Confidence intervals include significant benefit and harm of either treatment strategy, and 16 events were reported across all studies.
[c] Quality of life and asthma control are important patient-centred outcomes and were not reported by at least 3 studies (-1 publication bias).
[d] Difficult to judge imprecision because the data were analysed with SMD (Reddel used the Marks AQLQ, and Berger used the Juniper, which are coded in opposite directions on different scales). The Juniper has an MCID of 0.5, and the MD between groups in this study was 0.37 (no downgrade).
[e] No events were observed, so it was impossible to discern a difference between groups. This may be due to the length of the trials and the severity of illness of the population (-2 imprecision).
[f] Confidence intervals include significant benefit of stopping LABA and do not exclude benefit of continuing LABA.
[g] We planned to look at total withdrawal as it is not affected by the possible bias of assigning reasons for dropouts, but for this reason we were unable to make assumptions about why participants were more likely to withdraw from the trial if they stopped their LABA.
[h] Weighted mean of control group scores in Godard 2008 and Koenig 2008 (Berger 2010 not included in calculation, as researchers reported data as change from baseline).
[i] Control group endpoint score on the Marks AQLQ in Reddel 2010. Berger 2010, the only other study in the analysis, reported change from baseline on the Juniper scale.

BACKGROUND

Description of the condition

Asthma is a long-term condition that affects the airways and is associated with varying degrees of cough, wheeze, shortness of breath and chest tightness. Despite advances in management, asthma continues to pose a significant economic burden, costing the National Health Service a billion pounds each year and causing more than a million lost working days (BTS 2011). Costs to the health service include direct drug and treatment costs, but a significant burden comes from poorly controlled asthma leading to preventable exacerbations that require hospital stay or treatment in the emergency department (BTS 2011).

Asthma prevalence is thought to have stabilised after increases between 1960 and 2000. Changes varied geographically and have been linked to various factors, including air pollution, tobacco legislation, diet and prevalence of other atopic diseases (Anderson 2005). Current estimates of UK asthma prevalence are around 8% for adults and 9% for children, translating to 5.4 million people currently receiving treatment (Asthma UK). It is estimated that the worldwide prevalence of asthma is 250 million, with most of the burden of disease reported in low- and middle-income countries (Global Asthma Report 2014).

The approach to asthma management is stepwise, to gain symptom control and reduce future risks of exacerbation with minimum effective doses of medication. Therapy at step 1 consists of an as-required short-acting beta$_2$-agonist (SABA) for symptom control (GINA 2014). Although some people with asthma can manage their symptoms with as-required medications (e.g. salbutamol), around two-thirds require regular treatment with inhaled corticosteroids alone or in combination with other longer-acting bronchodilator medications (Hoare 2003). Several national guidelines are available for the treatment of patients with asthma in community and emergency settings, and these recommend broadly similar treatment steps aimed at achieving and maintaining daily symptom control while preventing exacerbations (BTS/SIGN 2012; GINA 2014; NAEPP 2007).

Description of the intervention

Inhaled corticosteroids (ICS) are the primary recommended prevention therapy for people with persistent asthma who do not gain sufficient control by using as-needed reliever medications (step 2) (BTS/SIGN 2012; GINA 2014). Regular use of ICS has been shown to improve lung function while reducing the need for reliever medications (Adams 2008; Adams 2009).

National treatment guidelines recommend long-acting beta$_2$-agonists (LABA) as the preferred add-on therapy to ICS when a person does not achieve asthma control with ICS and short-acting reliever medication (BTS/SIGN 2012; GINA 2014). Combination therapy with LABA+ICS can be given at low dose at step 3, and at medium or high dose at step 4. Evidence from randomised trials has shown that adding LABA to ICS improves lung function and symptoms, and reduces the frequency of exacerbations, in adults whose asthma is not well controlled by ICS alone (Ducharme 2008), and that this approach is preferable to increasing ICS dose (Ducharme 2010).

However, despite demonstrated benefits of LABA add-on therapy in adults, large studies and meta-analyses have shown a link between beta$_2$-agonist use and increased asthma morbidity and mortality (Cates 2014; Nelson 2006; Salpeter 2006), leading in 2005 to a US Food and Drug Administration (FDA) black box warning - the most severe warning applied to prescription medication to highlight increased risk of serious adverse events (Aaronson 2006). FDA analyses of clinical trials showed "increased risk of severe worsening of asthma symptoms, leading to hospitalisation in both children and adults and death in some patients with asthma" (FDA 2010). As a result, the FDA has mandated that drug companies must conduct clinical trials to assess the safety of LABA used in asthma, with trials expected to yield results by 2017. It has not been established whether either of the two most widely used LABA - salmeterol or formoterol - is safer than the other in adult asthma (Cates 2014).

Although investigators have shown that the detrimental effects of regular LABA are reduced when used in combination with ICS (Cates 2014; Ernst 2006), particularly when the two drugs are delivered in a combination inhaler (FDA 2010), a Cochrane review was not able to conclude whether risk of adverse events remains higher with the combination than with ICS alone (Ducharme 2008). In line with the stepwise approach to asthma treatment (BTS/SIGN 2012; GINA 2014), manufacturers' labels are required to state that LABA should be used only "for the shortest duration of time required to achieve control of asthma symptoms and discontinued, if possible, once asthma control is achieved".

How the intervention might work

Inhaled corticosteroids reduce mucus buildup and exacerbations by reducing inflammation in the airways (Barnes 1993), and can be taken once (fluticasone furoate) or twice daily (e.g. beclomethasone, budesonide, fluticasone propionate). LABA can also be taken once (vilanterol) or twice daily (formoterol, salmeterol), and act as a bronchodilator by relaxing bronchial wall smooth muscle (Nelson 1995).

Much debate has surrounded possible causal links between LABA and increased mortality and morbidity (Cates 2012; Tattersfield 2006). Theories of LABA-related death and adverse events include direct toxicity of the drugs themselves (in particular, their cardiac effects (e.g. Brown 1983)), reduced response over time causing gradual worsening of disease (Lipworth 1997) and delay in receiving medical help caused by masking of underlying inflammation (the delay hypothesis (e.g. Bijl-Hofland 2001)). It has been sug-

gested that the delay hypothesis is linked to a reduction in compliance with appropriate ICS treatment (Johnston 2009), although this is largely a historical issue that has arisen since the introduction of combination inhalers. Confounding by severity, in the sense that people with more severe disease are likely to be taking LABA, has now been dismissed, as it cannot explain the overall increase in mortality reported in the 1960s and 1970s, and in the light of evidence from large case-control studies (e.g. Crane 1989).

A UK confidential inquiry into asthma mortality in 2012-2013 identified 195 deaths attributable to asthma (National Review of Asthma Deaths (NRAD) 2014). Of these, a significant proportion of patients showed poor compliance with medication regimens (48%) or were overusing short-acting beta$_2$-agonists (39%) - potential confounding factors that could influence outcomes in this review.

Why it is important to do this review

Despite established evidence of safety issues associated with use of LABA in uncontrolled asthma, only limited data are available to support or guide discontinuation once asthma control is achieved. It is unclear whether potential risks of stopping LABA for patients who have achieved asthma control (i.e. increased likelihood of exacerbations and reduced quality of life) outweigh potential risks of continuing LABA therapy.

The risk-benefit ratio may be different in children and adolescents, as "the risks of hospitalisation and poor outcomes are of particular concern for children" (FDA 2010), and particular issues with compliance may be seen among the younger population. For this reason, all child and adolescent studies will be synthesised in a separate review.

OBJECTIVES

To compare cessation of long-acting beta$_2$-agonists (LABA) versus continued use of LABA/inhaled corticosteroids (LABA/ICS) for adults whose asthma is well controlled, and to determine whether stopping LABA:

1. results in loss of asthma control or deterioration in quality of life;

2. increases the likelihood of asthma attacks or 'exacerbations'; or

3. increases or decreases the likelihood of serious adverse events of any cause.

METHODS

Criteria for considering studies for this review

Types of studies

We included parallel randomised controlled trials (RCTs) of at least 8 weeks' duration. We included studies reported as full-text articles, those published as abstracts only and unpublished data. We did not include cross-over trials, as they are not suitable for assessing long-term outcomes.

Types of participants

We included studies of adults age 18 or older whose asthma is currently well controlled with any dose of maintenance long-acting beta$_2$-agonists (LABA) and inhaled corticosteroids (ICS). Participants' asthma control was classified according to prespecified criteria (e.g. a score lower than 1.5 on the Asthma Control Questionnaire (ACQ)), or the criteria for control described in GINA 2014 guidelines (i.e. daytime symptoms and need for rescue inhaler twice or less often per week, with no nocturnal symptoms or limitations in daily activities).

If researchers included both adults and children and did not provide data for adults alone, we included studies if mean age was over 18 in both groups of participants. When studies were found that included only a subset of relevant participants, we included them only if study authors were able to provide disaggregated data for participants who fit the inclusion criteria. We excluded studies that included participants with other chronic respiratory co-morbidities (e.g. chronic obstructive pulmonary disease).

Types of interventions

We included studies in which adults whose asthma was well controlled by any dose of ICS+LABA combination therapy were randomly assigned to:

1. step-down therapy to ICS alone (continued at the same dose received before randomisation); or
2. continued use of ICS and LABA (any preparation at the same dose received before randomisation).

We included any LABA (formoterol, salmeterol, vilanterol) and any dose of ICS (budesonide, mometasone, fluticasone propionate, fluticasone furoate) used to treat asthma delivered in a combination inhaler or in separate inhalers. We allowed studies in which researchers gave a different ICS to participants in the intervention group, provided it was given at the same beclomethasone dipropionate (BDP) equivalent dose as the ICS received before LABA was stopped, as this may reflect what happens in practice (e.g. replacing salmeterol/fluticasone with beclomethasone).

One possible treatment strategy for asthma at step 4 is to reduce the dose of LABA and ICS concurrently, once asthma control has been achieved (rather than stopping LABA); however, we did not include in the review studies addressing the effects of this intervention, as this is a separate clinical question.

We included trials that allowed short-acting reliever medications, provided they were not given as part of the randomly assigned treatment.

Types of outcome measures

Primary outcomes

1. Exacerbation requiring systemic corticosteroids.
2. Asthma control* (measured on a validated scale, e.g. Asthma Control Questionnaire (ACQ)).
3. Serious adverse events (all cause).

Primary outcomes were chosen to represent an important measure of resource use, a patient-important outcome and safety.

Secondary outcomes

1. Quality of life* (measured on a validated scale, e.g. Asthma Quality of Life Questionnaire).
2. Exacerbations requiring hospitalisation or emergency department visit (participants with at least one).
3. Adverse events (all cause).
4. Withdrawals.

Reporting in the trial one or more of the outcomes listed here was not an inclusion criterion for the review.

*If more than one scale measuring the same construct is reported within a study, or if different scales are used across studies, we will analyse results using standardised mean differences.

Search methods for identification of studies

Electronic searches

We identified trials from the Cochrane Airways Group Specialised Register (CAGR), which is maintained by the Trials Search Co-ordinator for the Group. The Register contains trial reports identified through systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), the Allied and Complementary Medicine Database (AMED) and PsycINFO, and by handsearching of respiratory journals and meeting abstracts (see Appendix 1 for further details). We searched all records in the CAGR using the search strategy presented in Appendix 2.

We also conducted a search of ClinicalTrials.gov (www.ClinicalTrials.gov) and the World Health Organization (WHO) trials portal (www.who.int/ictrp/en/). We searched all databases from their inception up to April 2015, and we imposed no restriction on language of publication.

Searching other resources

We checked reference lists of all primary studies and review articles to look for additional references. We searched relevant manufacturers' websites (GlaxoSmithKline (GSK) and AstraZeneca) for trial information, and we contacted field experts to request information about unpublished or ongoing studies.

On 3 March 2015, we searched for errata or retractions from included studies published in full text on PubMed (www.ncbi.nlm.nih.gov/pubmed).

Data collection and analysis

Selection of studies

Two review authors (KK and SA) independently screened titles and abstracts for inclusion of all potential studies identified as a result of the search, and coded them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We retrieved the full-text study reports or publications, and two review authors (KK and SA) independently screened the full-text articles to identify studies for inclusion. We identified and recorded reasons for exclusion of ineligible studies, resolving disagreements through discussion or, if required, by consultation with a third person. We identified and excluded duplicates and collated multiple reports of the same study, so that each study, rather than each report, is the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram and a Characteristics of excluded studies table.

Data extraction and management

We used a Microsoft Excel data collection form, which has been piloted on at least one study in the review, to document study characteristics and outcome data. Both review authors (KK and SA) extracted the following study characteristics from included studies.

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

One review author (KK) independently extracted outcome data from included studies. We noted in the Characteristics of included studies table if outcome data were not reported in a useable way. We resolved disagreements by reaching consensus or by involving a third person. One review author (KK) transferred data into the Review Manager (Review Manager (RevMan)) file. We double-

checked that data were entered correctly by comparing data presented in the systematic review versus those provided in the study reports. A second review author (SA) spot-checked study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Two review authors (KK and SA) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved disagreements by discussion or through involvement of a third person. We assessed risk of bias according to the following domains.

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other bias.

We graded 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 'Risk of bias' judgements across different studies for each of the domains listed. We considered blinding separately for different key outcomes when necessary (e.g. for unblinded outcome assessment, risk of bias will be greater for quality of life ratings than for number of exacerbations). When information on risk of bias was related to unpublished data or correspondence with a study author, we noted this in the 'Risk of bias' table.

When uncertainties were due to insufficient reporting, we contacted the study author or the sponsor for additional information. When considering treatment effects, we took into account risk of bias for studies that contributed to this outcome.

Assesment of bias in conducting the systematic review

We conducted the review according to the published protocol and reported deviations from it in the Differences between protocol and review section.

Measures of treatment effect

We analysed dichotomous data as odds ratios, and continuous data as mean differences or standardised mean differences. We entered data presented as a scale with a consistent direction of effect. We narratively described skewed data reported as medians and interquartile ranges.

We undertook meta-analyses only when this was meaningful (i.e. when treatments, participants and the underlying clinical question were similar enough for pooling to make sense).

When multiple trial arms were reported in a single trial, we included only the relevant arms. When two comparisons (e.g. drug A vs placebo and drug B vs placebo) were combined in the same meta-analysis, we halved the control group to avoid double-counting.

When changes from baseline and endpoint scores were available for continuous data, we used changes from baseline unless most studies reported endpoint scores. When a study reported outcomes at multiple time points, we used the end-of-study measurement.

When both an analysis using only participants who completed the trial and an analysis imputing data for participants who were randomly assigned but did not provide endpoint data (e.g. last observation carried forward) were available, we used the latter.

Unit of analysis issues

For dichotomous outcomes, we used participants rather than events as the unit of analysis (i.e. number of adults admitted to the hospital rather than number of admissions per adult). However, if exacerbations were reported as rate ratios, we analysed them on this basis.

Dealing with missing data

We contacted investigators or study sponsors to verify key study characteristics and to obtain missing numerical outcome data when possible (e.g. when a study was identified as an abstract only). When this was not possible, and missing data were thought to introduce serious bias, we explored the impact of including such studies in the overall assessment of results by performing a sensitivity analysis**.**

Assessment of heterogeneity

We used the I^2 statistic to measure heterogeneity among the trials in each analysis. If we identified substantial heterogeneity, we reported this and explored possible causes by performing prespecified subgroup analyses.

Assessment of reporting biases

As we did not have more than 10 trials for pooling, we did not create and examine a funnel plot to explore possible small study and publication biases. We considered the impact of unpublished trials in the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) ratings for each outcome (GRADEpro; Higgins 2011).

Data synthesis

We used a random-effects model for all analyses, as we expected variation in effects due to differences in study populations and methods. We performed sensitivity analyses using a fixed-effect model.

'Summary of findings' table

We created a 'Summary of findings' table to present data for the seven prespecified outcomes. We presented the pooled analysis in each case, and noted in the comments column significant differences between subgroups. We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it related to studies that contributed data to the meta-analyses for prespecified outcomes. We used methods and recommendations as described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) by using GRADEpro software. We justified all decisions to downgrade or upgrade the quality of studies by using footnotes, and we made comments when necessary to aid the reader's understanding of the review.

Subgroup analysis and investigation of heterogeneity

We planned the following subgroup analyses for primary outcomes, using the formal test for subgroup differences provided in Review Manager (version 5.3) (Review Manager (RevMan)).

1. Mean steroid dose (according to GINA 2014, defined as low, medium and high cutoffs).
2. Type of inhaler used in the comparison group (LABA/ICS combination inhaler vs separate inhalers).
3. Type of LABA being stopped (formoterol, salmeterol).

Mean steroid dose of the population in each study may reflect differences in disease severity and may have effects on outcomes after LABA therapy is stopped. We used the boundaries for low, medium and high as described in GINA 2014 for ex-actuator doses.

Participants using combination inhalers may be less likely to experience potential adverse effects of LABA treatment, as this removes the risk associated with taking the LABA inhaler without ICS. Combination inhalers may also be associated with generally better compliance with treatment.

Differences in stopping different types of LABA may be due to variations in pharmacological properties and duration of action.

Sensitivity analysis

We planned to carry out sensitivity analyses for the primary analyses, excluding the following.

1. Studies at high risk of bias for blinding.
2. Unpublished data (i.e. no peer-reviewed full paper available).

RESULTS

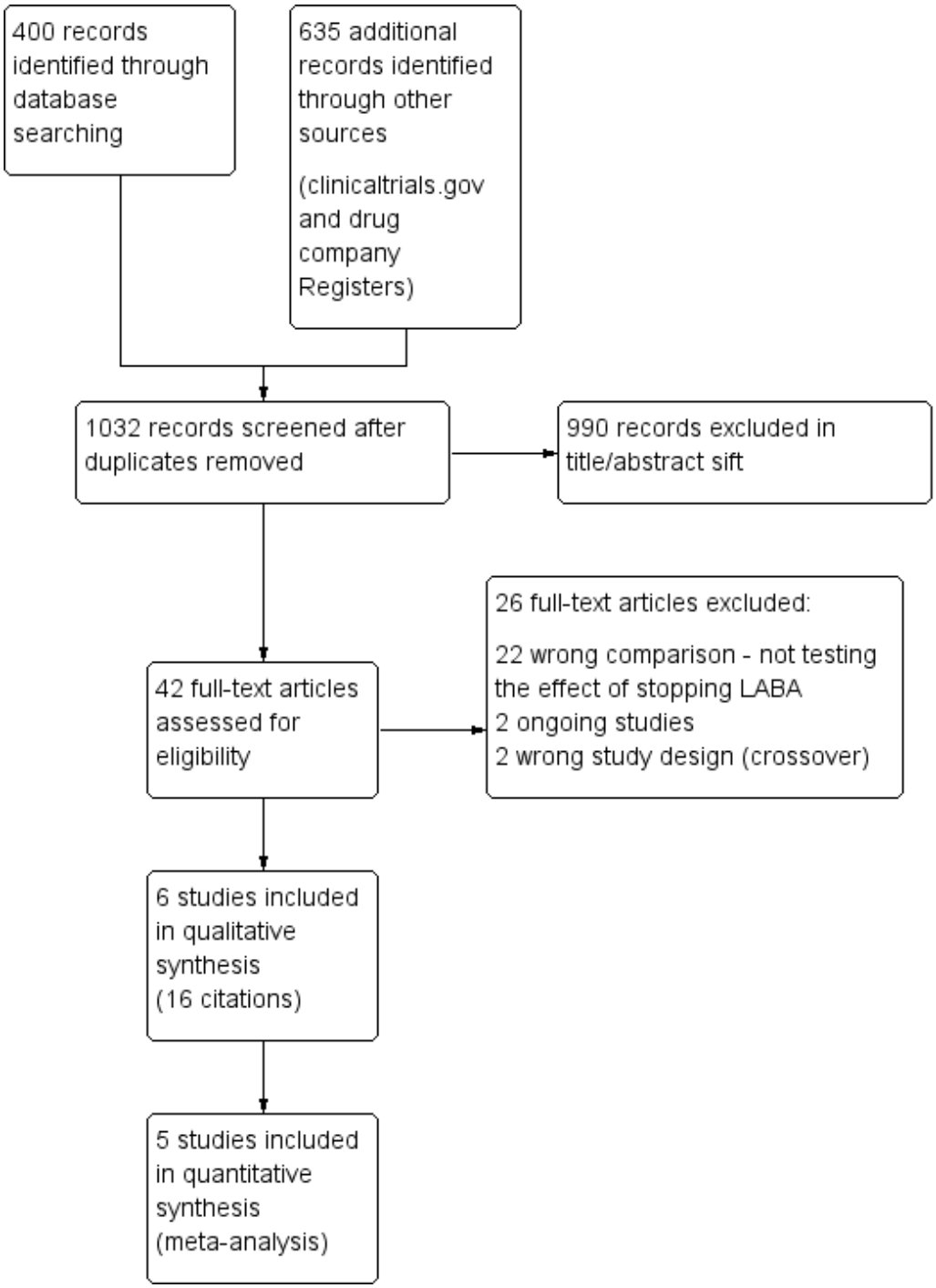
Description of studies

We included in the Characteristics of included studies section detailed descriptions of studies fulfilling the criteria specified in the protocol. We compiled excluded studies for which full texts were viewed, along with reasons for exclusion, in the Characteristics of excluded studies section.

Results of the search

Database searching retrieved 400 references, and our additional searches of industry databases and relevant reference lists yielded 635 records. We removed three duplicates, leaving 1032 unique references. Of these, we excluded 990 after sifting titles and abstracts and assessed full texts of the remaining 42 studies. Twenty-six of these did not meet the inclusion criteria (Figure 1).

Figure 1. Study flow diagram.



Included studies

Six studies (16 citations) met the inclusion criteria, but one reported no outcomes that could be included in our meta-analysis (Slankard 2011). Descriptions from here on will relate to the five studies that contributed data to the meta-analysis. Those five studies randomly assigned 2781 people with a diagnosis of asthma to the comparisons of interest in this review. GSK SAS40037 contributed the largest sample size to the analyses, with 824 people randomly assigned across four intervention groups. Reddel 2010 included the smallest number of people, with 82 participants randomly assigned to the two arms relevant to this review.

Design and duration

All five studies in the quantitative analysis were multi-centre, randomised, parallel-group controlled trials, taking place at between three and 124 centres. One study, Slankard 2011, was included only in the qualitative analysis and was not a multi-centre trial. All studies were double-blind. Berger 2010 and Reddel 2010 had a duration of 12 weeks. The duration of treatment in GSK SAS40037, Koenig 2008 and Slankard 2011 was 16 weeks, and Godard 2008 lasted for 24 weeks but reported its primary outcome at 12 weeks. All studies had a run-in period, which varied between studies from two weeks to eight weeks, when participants received usual ICS+LABA therapy with rescue SABA.

Participant inclusion and exclusion criteria

We provided detailed explanations of inclusion and exclusion criteria in Characteristics of included studies. All trials included outpatients at least 15 years of age; mean participant age was above 18 years, leading us to treat them as adult studies. All participants had a diagnosis of stable or well-controlled asthma characterised at study entry, but criteria varied. For inclusion based on stable asthma, Berger 2010 based definitions of mild to moderate asthma on ICS use, Godard 2008 assessed whether current asthma therapy controlled asthma, GSK SAS40037 required a forced expiratory volume of 1 second (FEV_1) of 40% to 85% of their predicted normal value, Koenig 2008 required an FEV_1 between 40% and 80% of their predicted value and Reddel 2010 required that participants had not had an exacerbation in the preceding four weeks. None of the trials used the Global Initiative for Asthma (GINA) definition for mild to moderate asthma or the Asthma Control Questionnaire (ACQ) as part of the inclusion criteria. All trials recruited participants taking regular ICS and LABA therapy with an as-needed SABA rescue inhaler. Three studies excluded participants with a smoking history $\geq$ 10 pack-years (Godard 2008; Reddel 2010; Slankard 2011). Four studies excluded people who had recently taken systemic corticosteroids (Berger 2010, Godard 2008 and Koenig 2008 within one month, Reddel 2010 within three months).

Baseline characteristics of participants

We extracted baseline characteristics of participants from each trial and presented them in the Characteristics of included studies section, along witha summary in Table 1.

Participants' ages across trials had a similar mean value in each trial, ranging from 40 to 49 years. All trials recruited more women than men (between 34.8% male in Slankard 2011 and 49% male in Reddel 2010). Trials that provided demographic information described a predominantly Caucasian sample population (ranging from 82.6% to 88% white). Participants' mean percentage predicted FEV_1 was reported in three trials, ranging between 83% and 91% at randomisation (Berger 2010; Godard 2008; Reddel 2010).

Characteristics of the interventions

In all studies, a combination ICS+LABA inhaler was administered before step-down to LABA, and in four of five studies included in the analysis, the LABA was salmeterol: salmeterol/fluticasone 50/250 mcg twice daily in Godard 2008 and Reddel 2010, and salmeterol/fluticasone 50/100 mcg twice daily in GSK SAS40037 and Koenig 2008. In Berger 2010, the combination therapy was formoterol/budesonide 9/160 mcg twice daily (Table 1). No studies used a different ICS in the comparison group than in the intervention group. All studies used albuterol as the reliever medication in acute exacerbations.

The design of Reddel 2010 meant that only data reported at week 12 were relevant to this review, as ICS were downtitrated between week 12 and the 52 week endpoint.

Outcomes and analysis structure

Asthma exacerbations were not uniformly defined, but we were able to confirm data for the primary outcome with the author team of another review, who had obtained unpublished information directly from the study sponsors (Brozek 2012). We incorporated additional unpublished data from this review for some studies in the ACQ and quality of life analyses with permission from the review authors. We removed these unpublished data in a planned sensitivity analysis.

Several measures of asthma control were used in these studies, and not all were validated. We analysed the ACQ and narratively summarised data from other non-validated measures, including percentage of symptom- and rescue-free days and the number of people meeting GINA definitions for totally controlled and well-controlled asthma.

We subgrouped results according to the ICS+LABA combination used in the comparison group (i.e. fluticasone/salmeterol or budesonide/formoterol), but it was not possible to perform planned subgroup analyses for ICS dose or inhaler type because the studies were similar in these respects.

Excluded studies

We excluded 26 records after viewing full texts, in most cases because the study was not designed to test the effects of stopping LABA versus continuing it. We excluded two studies because they used a cross-over design, which was prespecified as exclusionary in our protocol, and two studies likely to meet the inclusion criteria have not yet been completed (NCT01437995; NCT02094937). We outlined details of reasons for exclusion of studies in the Characteristics of excluded studies section.

Risk of bias in included studies

We outlined details of risk of bias for each included study and reasoning behind ratings in Characteristics of included studies, and a summary of risk of bias judgements by study and domain (selection bias, performance bias, detection bias, attrition bias, reporting bias, other bias) can be found in Figure 2. Most ratings in most domains for included studies were low risk, with the exception of attrition bias and other bias.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Allocation

All of the included studies were described as randomised, but very little published information was available on the methods used in any of the included studies. One study described random sequence generation in sufficient detail to warrant a low risk rating (Reddel 2010), and the other studies were given low risk ratings on the basis of prior contact with study sponsors. Slankard 2011 was published as an abstract and provided inadequate information regarding the randomisation procedure, so bias was rated as unclear.

Blinding

Across studies, we found no evidence of risk of bias related to blinding of participants or observers. All studies were described as double-blind, and study authors described measures such as matched inhalers to hide group allocation from participants and personnel; we therefore assumed that those measuring outcomes were also blinded.

Incomplete outcome data

Risk of bias due to high or unbalanced dropout was mixed across studies. We rated one study (GSK SAS40037) as high risk because, although all randomly assigned participants were included in the analysis, dropout was high in both groups and was higher in the group for which LABA was stopped, which may have led to underestimation of the effects. We rated two studies as unclear because, although the dropout rate was low overall, it was somewhat unbalanced and was much higher in the ICS group (14%) than in the LABA+ICS group (4%) (Reddel 2010), or the number of withdrawals was not reported (Koenig 2008); we rated two studies as low risk.

Selective reporting

All named outcomes were reported in the published reports or were made available by study authors or sponsors via a previous review team (Brozek 2012), and we rated all included studies as low risk. We rated Slankard 2011 as high risk because the data could not be included in the meta-analysis, and several outcomes were not reported at all. Only a conference abstract was available; therefore this was used for qualitative analysis only.

Other potential sources of bias

During the course of the Koenig 2008 study, recruitment of participants was placed on hold pending analysis of data from the Salmeterol Multicenter Asthma Resarch Trial (SMART) and was subsequently terminated, with approximately 161 participants per treatment group (target was 206 per group). It is unclear whether potential sources of bias threatened the validity of the findings, or the size and direction of the treatment effect. We identified no other sources of bias in the remaining studies.

Effects of interventions

See: **Summary of findings for the main comparison** Stopping LABA compared with continuing use of LABA+ICS for adults with well-controlled asthma

Primary outcomes

Exacerbation requiring systemic corticosteroids

Nineteen people per 1000 who continued their LABA had an exacerbation, compared with 32 per 1000 for whom LABA was stopped (13 more per 1000, 95% CI 3 fewer to 46 more). Confidence intervals did not exclude the possibility that stopping LABA was better (OR 1.74, 95% CI 0.83 to 3.65; participants = 1257; studies = 4; I^2 = 0%; moderate quality; Analysis 1.1), so we downgraded the quality of the evidence for imprecision. A sensitivity analysis using only the published data yielded a slightly larger point estimate with similar imprecision (OR 1.89, 95% CI 0.85 to 4.22).

Asthma control

People who stopped their LABA had worse scores on the Asthma Control Questionnaire (ACQ) than those who continued (MD 0.24, 95% CI 0.13 to 0.35; participants = 645; studies = 3; I^2 = 0%; Analysis 1.2), but the effect was around half the size of the established minimal clinically important difference (MCID) for this scale, which is 0.5 units (Juniper 1999). We rated the evidence as of moderate quality, having downgraded this for possible publication bias because three studies did not report what we considered to be a very important outcome. Data for two of the studies were not available in published reports but were included with permission from Brozek 2012, who acquired additional data from the study sponsors for inclusion in their systematic review. Without this unpublished data, the effect favoured continuing LABA to a lesser extent and was very imprecise (MD 0.12, 95% CI -0.24 to 0.48).

We chose not to meta-analyse several other measures related to 'control' that were reported in these studies; some were inconsistently reported, and others were not measured on validated scales. Four studies reporting diary card data showed loss of control measured as symptom-free days, and three saw a reduction in rescue-free days and night-time awakenings. These outcomes were considered to provide low-quality evidence because variation in the

magnitude and direction of effects was evident across studies, and because metrics of asthma control were considered indirect or incomplete.

Godard 2008 used GINA-defined criteria for 'well-controlled' and 'totally controlled' asthma, and found that 47% of those for whom LABA were stopped were considered 'totally controlled' and 77% 'well controlled' after 24 weeks, compared with 73% and 85% of those who continued combination therapy.

Reddel 2010 measured a 'Total Asthma Score' based on a composite score of asthma symptoms, rescue use and peak flow over the preceding four weeks (Reddel 2010 supplement) and found no differences between groups (4.74 (SD 2.21) in those who stopped LABA, 4.54 (SD 2.21) in those who continued LABA).

Serious adverse events (all cause)

All studies reported serious adverse events but only 16 events were observed, so it was not clear if stopping LABA was safer than continuing LABA (OR 0.82, 95% CI 0.28 to 2.42; participants = 1342; studies = 5; I^2 = 0%; Analysis 1.3). We downgraded the evidence for imprecision and rated it as moderate quality because confidence intervals included significant benefit and harm for both treatment strategies. None of the data were unpublished, so there was no need to perform a sensitivity analysis.

Secondary outcomes

Asthma-related quality of life

Quality of life declined in those who stopped taking their LABA compared with those who continued, but this was measured on two different scales with different properties, so it is unclear whether the difference was clinically significant (SMD 0.36, 95% CI 0.15 to 0.57; participants = 359; studies = 2; I^2 = 0%). Data for Berger 2010 were not reported sufficiently in the published reports for inclusion in the meta-analysis, but complete data were included with permission from Brozek 2012, who acquired additional data from the study sponsors. Berger 2010 also reported a responder analysis for the Asthma Quality of Life Questionnaire (AQLQ) (6.6% vs 14%) that was not statistically significant but supported the findings of the main AQLQ analysis. Evidence was rated of moderate quality because the outcome was available in only two of the included studies, so we deemed that publication bias was possible.

Exacerbations requiring hospitalisation or emergency department visit

None of the included studies reported this outcome separately, so no data were available for analysis. We downgraded the evidence twice for imprecision and rated the quality as low, but the lack of events might have reflected the length of studies conducted or the severity of participants recruited.

Adverse events (all cause)

Fewer people who stopped their LABA had adverse events, although the upper confidence interval did not exclude the possibility that stopping LABA was harmful (OR 0.83, 95% CI 0.66 to 1.05; participants = 1339; studies = 5; I^2 = 4%; Analysis 1.6). We downgraded the evidence for this imprecision and rated the quality as moderate.

Withdrawals

More people who stopped taking their LABA dropped out before completion of the studies (OR 1.95, 95% CI 1.47 to 2.58; participants = 1352; studies = 5; I^2 = 6%; Analysis 1.7). We planned to look at total withdrawals, as they are not affected by the possible bias of assigning reasons for dropouts, but for this reason, we were unable to make assumptions about why participants were more likely to withdraw from the trial if they stopped their LABA than if they continued LABA. We downgraded the evidence for indirectness for this reason and rated the quality as moderate.

Subgroup analyses

Mean ICS dose

All studies reporting exacerbations requiring systemic steroids used ICS doses classified as low in GINA 2014, so it was not possible to perform the subgroup analysis.

Inhaler type

All studies reporting exacerbations requiring oral steroids used combination inhalers, so it was not possible to perform the subgroup analysis.

Type of LABA

We subgrouped included studies by the LABA that was delivered in the comparison group. Three studies reporting exacerbations requiring systemic steroids used salmeterol and one used formoterol, and the test for subgroup differences was not significant (I^2 = 0%; Analysis 2.1). Confidence intervals for each subgroup effect were very wide because of the small quantity of available data, so it is difficult to know whether a difference was present that was not detected. For asthma control measured on the ACQ, the effect favouring continuing LABA was larger in the study using formoterol than in the two using salmeterol, but the test for subgroup differences was not significant (I^2 = 28%, P = 0.24; Analysis 2.2), and this determination was based on a very small number of

studies. For serious adverse events, the effect was more in favour of stopping LABA in the formoterol study than in the four that used salmeterol, but confidence intervals were very wide and overlapping; the test for subgroup differences was not significant (I^2 = 0%; Analysis 2.3).

Sensitivity analysis

Studies at high risk of bias for blinding

We rated no studies as having high risk of bias for either of the blinding domains, so a sensitivity analysis on this basis was not necessary.

Unpublished data

We removed from the primary outcomes in sensitivity analyses additional unpublished data included with permission from the authors of Brozek 2012. . We reported these results under each of the primary outcomes.

DISCUSSION

Summary of main results

Six randomised, double-blind studies between 12 and 24 weeks long met the inclusion criteria. The five studies contributing data assigned 2781 people with stable asthma to the comparison of interest (stepping down from LABA+ICS to ICS alone) or to the control group (continuation of LABA+ICS), although the definition of stable asthma and the inclusion criteria varied across studies.

In the primary analysis, evidence from four studies indicated that stopping LABA might increase the number of people having exacerbations requiring systemic corticosteroids, but the effect was not statistically significant, as the confidence intervals did not exclude the possibility that stopping LABA was beneficial; over 17 weeks, 19 people per 1000 who continued their LABA had an exacerbation, compared with 32 per 1000 for whom LABA was stopped (13 more per 1000, 95% CI 3 fewer to 46 more).

Moderate-quality evidence suggests that stopping LABA was associated with loss of asthma control as measured by the ACQ and with worse asthma-related quality of life than for those who continued LABA, but the effects were not clinically significant. Other unvalidated measures of control, such as symptom-free days and use of reliever medication, were presented in a narrative synthesis and showed variable results. No included study reported exacerbations requiring an emergency department visit or hospitalisation as a separate outcome.

Serious adverse events were too rare in these studies to show whether stopping LABA was better or worse than continuing LABA; this may be a reflection of the severity of illness among participants and of study duration. Stopping LABA may result in fewer adverse events of any kind compared with continuing LABA, but this effect was not statistically significant, and stopping LABA made people more likely to withdraw from research studies.

Overall completeness and applicability of evidence

We were unable to perform the subgroup analyses that we had set out in the protocol. As all of the studies reporting exacerbations requiring systemic steroids used ICS doses classified as low in GINA 2014, and as all used combination inhalers, it was not possible to perform subgroup analyses for mean ICS dose or for inhaler type.

Although all included studies had stable asthma as part of their inclusion criteria, no standardised internationally recognised severity parameter grading system such as GINA 2014 (or other severity scoring systems) was used. This would have reduced potential clinical heterogeneity between studies and would have increased applicability for a clinical audience. Treatment protocols for the intervention varied between studies in terms of medication, dosage and frequency, and inconsistencies in how LABA was stepped down were observed.

Some outcomes with great clinical importance, such as quality of life, were sparsely reported, with only two studies providing data on these. In addition, we could not comment on long-term effects of stopping LABA, as all included studies were of relatively short duration - between 12 and 24 weeks - possibly not sufficient for long-term effects to become apparent. Serious adverse events were reported at the end of each study period, and if further events occurred beyond this time, they could not be recorded, which may impact the completeness of evidence. A recent overview of LABA safety in asthma highlighted three ongoing long-term trials that will be best placed to assess the safety implications of prolonged combination therapy (Cates 2014).

Baseline demographics indicated a Caucasian bias among participants. A more diverse study population would increase generalisability of the results.

Quality of the evidence

Review authors assessed the quality of the outcome data by using GRADEpro software and recommendations provided by The Cochrane Collaboration; we summarised results of this analysis in Summary of findings for the main comparison. We assessed all outcomes except exacerbations requiring hospital admission or an emergency department visit as of moderate quality, but we downgraded evidence quality for a variety of reasons. Heterogeneity

across individual outcomes was not statistically significant, as reflected by low I^2 values.

We downgraded both asthma control and asthma-related quality of life on the basis that although they are important patient-centred outcomes, they were not reported by investigators in at least three of the studies.

We downgraded the evidence for exacerbations requiring systemic corticosteroids and for exacerbations requiring hospital or emergency department treatment because of imprecision. In the case of exacerbations requiring systemic corticosteroids, confidence intervals show both significant harm and possible benefit of stopping LABA. For exacerbations requiring hospital or emergency department treatment, no events were observed. This may reflect both duration of the trials and asthma severity in the studied populations. Similarly, evidence for both serious adverse events and all adverse events was downgraded because of imprecision.

Indirectness is more challenging to assess. The recruited population of participants with stable asthma may not have been the most appropriate group on whom to assess outcomes such as exacerbations requiring systemic corticosteroids and hospital admission, given the short duration of the studies, leading to few events and imprecision. However, all outcomes are directly clinically relevant and are not surrogate markers.

To resolve uncertainties related to risk of bias and missing data, we made an effort to contact all study authors. We received an acknowledgement of contact from Reddel 2010, Koenig 2008 and Slankard 2011. Reddel 2010 provided additional data, and we received no response from GSK SAS40037.

Potential biases in the review process

Standard Cochrane methods were used to create this review process. Two independent review authors extracted study characteristics and numerical data and resolved discrepancies through discussion and, if necessary, consultation with a third independent review author. Two independent review authors also made risk of bias decisions. Review authors reported no conflicts of interest. Two independent review authors performed extensive literature searches and subsequent screening of published data and conference abstracts. Studies were not limited by language of publication. Given that a thorough search strategy was used, it is unlikely that any available published studies were missed by the study selection process. Review authors also attempted to contact all study authors to obtain additional information about outcomes and to clarify study methods to ensure accurate risk of bias decisions. We received detailed replies and additional data from one study author; others did not receive the request or were unable to provide the information requested.

Agreements and disagreements with other studies or reviews

We identified an existing systematic review conducted by Brozek 2012 to assess evidence supporting discontinuation of LABA therapy in adults and older children with stable asthma controlled by a combination of ICS and LABA. We included supplemental data from this review in this Cochrane review with their permission. Their inclusion criteria differed from ours, as they included children (lower limit age cutoff was four years) and restricted LABA type to salmeterol or formoterol. Their search strategy yielded the same five studies identified by our independent search strategy (Berger 2010; Godard 2008; GSK SAS40037; Koenig 2008; Reddel 2010). We identified these and an additional study (Slankard 2011), although this latter study could not be included in our quantitative analysis, as we had insufficient information beyond the abstract. The conclusion from Brozek 2012 was that no statistically significant results were reported for any outcomes that would demonstrate benefit derived from LABA step-down compared with continued use of LABA and ICS.

Brozek 2012 assessed additional outcomes, such as morning peak flow and prebronchodilator peak flow rates, and included unpublished quality of life data. Disagreements regarding evidence quality ratings were noted between this review and Brozek 2012, with the latter downgrading most outcomes for indirectness because review authors noted that studies did not always make clear whether participants were well controlled on long-term combination therapy, or whether they had been given combination therapy during a run-in as part of the study. They also noted the issue regarding the short duration of studies with particular relevance to the outcomes for which events were rare (e.g. hospital admissions, serious adverse events).

AUTHORS' CONCLUSIONS

Implications for practice

This review suggests that stopping LABA in adults who have stable asthma while taking a combination of LABA and ICS inhalers may increase the likelihood of asthma exacerbations requiring treatment with systemic corticosteroids, but this was not certain. Stopping LABA may slightly reduce asthma control and quality of life, but evidence was insufficient to permit judgement on the possibility of an effect on other important outcomes such as serious adverse events and exacerbations requiring hospital admission.

Implications for research

Given the clinical importance of this question and its relevance to international guidelines, it is perhaps surprising that only six studies met our inclusion criteria, leading to limited conclusions. Given the relative infrequency of exacerbations, especially severe exacerbations, longer trials are warranted. Trialists should include

patient-important outcomes such as asthma control and quality of life and should use validated measurement tools. Definitions of exacerbations should be provided, Our inability to perform subgroup analysis according to baseline ICS dose suggests that further trials examining the effects of stepping down for those requiring higher doses of ICS are warranted.

ACKNOWLEDGEMENTS

We acknowledge Chris Cates for commenting critically on the protocol and the review.

We are extremely grateful to the team who prepared the Brozek 2012 review - Jan Brozek, Monica Kraft, Jerry Krishnan, Michelle Cloutier, Stephen Lazarus, James Li, Nancy Santesso, Robert Strunk, and Thomas Casale - for allowing us to use in our meta-analyses the unpublished data that they had retrieved from study sponsors..

CRG Funding Acknowledgement: The National Institute for Health Research (NIHR) is the largest single funder of the Cochrane Airways Group.

Disclaimer: The views and opinions expressed herein are those of the review authors and do not necessarily reflect those of the NIHR, the National Health Service or the Department of Health.

The Background and Methods sections of this review are based on a standard template used by the Cochrane Airways Group.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Berger 2010

Methods	**Design**: randomised, double-blind, parallel-group, double-dummy, placebo- and active-controlled multi-centre trial Enrolment commenced in April 2003, and the study was completed in June 2004. The trial included 116 centres in the USA. Duration of treatment was 12 weeks
Participants	**Population**: 752 eligible participants with stable asthma after a run-in period were randomly assigned in a 1:1:1:1:1 ratio at each site to receive the following: The comparison of budesonide/formoterol 80/4.5 mcg × 2 inhalations twice daily and budesonide 160 mcg × 2 inhalations once daily was relevant to this review, but participants were also randomly assigned to budesonide/formoterol 160/4.5 mcg × 2 inhalations once daily, budesonide/formoterol 80/4.5 mcg × 2 inhalations once daily and placebo pMDI × 2 inhalations twice daily **Baseline characteristics**: control group: 37.7% male, mean age 38, 85.7% Caucasian, predicted FEV_1 86.4 (9.1). Intervention group: 31.7% male, mean age 38.6, 81.4% Caucasian, predicted FEV_1 85.7 (8.8) **Inclusion criteria**: patients ≥16 years of age (no upper age limit recorded) with ATS defined asthma for 6+ months, mild to moderate based on ICS use and pulmonary function, use of low to medium doses of ICS during the month before screening and a pre-BD FEV_1 between 60% and 90% predicted normal **Exclusion criteria**: participants with a significant medical condition that might put them at risk, influence their ability to participate in the study or influence study results. Participants with any malignancy (other than basal cell carcinoma) within the past 5 years, a clinically significant laboratory test abnormality or a clinically significant abnormal electrocardiogram (ECG) also were excluded. Patients requiring systemic corticosteroids in the previous month were excluded at screening
Interventions	**Run-in**: During the 4- to 5-week run-in period, eligible participants discontinued their current asthma therapy and received single-blind treatment with budesonide/formoterol 80/4.5 mcg twice daily and as needed rescue albuterol **Intervention (LABA stopped)**: 2 of the 5 treatment arms were relevant and are analysed in our review. The intervention group was the group in which LABA was stepped-down, budesonide 160 mcg × 2 inhalations was given once daily for 12 weeks, and rescue albuterol was taken if required **Control (LABA+ICS)**: budesonide/formoterol 80/4.5 mcg × 2 inhalations twice daily for 12 weeks. Rescue albuterol was taken if required
Outcomes	**Primary**: morning and evening peak expiratory flow (PEF) and morning and evening pre-dose FEV_1 **Secondary**: spirometry (FEV_1) at clinic visits at 2, 6 and 12 weeks, daytime and night-time symptom scores, night-time awakenings due to asthma, rescue medication use, patient withdrawals due to worsening asthma control (according to predefined criteria) , Asthma Quality of Life Questionnaire, standardised version (AQLQ(S)) results, diary card data, adverse events, vital signs, cortisol levels and physical examination findings

Notes	**Funding**: AstraZeneca **Study number**: AstraZeneca study code: D5896C00726, SD-039-0726; clinical trial registration number: NCT00652392 Symptom-free day: a day with no daytime or night-time asthma symptoms and no awakenings due to asthma Rescue-free day: a calendar day with no daytime or night-time rescue medication use Clinical exacerbation: an exacerbation requiring emergency treatment, hospitalisation or use of an asthma medication not allowed by the protocol

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Not sufficiently described in published reports, but previous contact with study sponsors confirmed standard practice with computerised codes
Allocation concealment (selection bias)	Low risk	Not sufficiently described in published reports, but previous contact with study sponsors confirmed concealed automated allocation system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy. Medications given by identical delivery devices to maintain study blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, double-dummy. Medications given by identical delivery devices to maintain study blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout < 20% in both groups, 99% included with imputation in the efficacy and safety analyses
Selective reporting (reporting bias)	Low risk	Full AQLQ results were not reported but had been previously been acquired by another review team, who shared the data
Other bias	Low risk	None identified

Godard 2008

Methods	**Design**: randomised, double-blind, parallel-group multi-centre trial Study period was 13 May 2002 to 6 November 2003. Trial included 124 centres in France. Duration of treatment was 24 weeks
Participants	**Population**: 475 eligible participants with well-controlled asthma after a run-in period of 8 weeks were randomly assigned to receive fluticasone propionate/salmeterol 250/50 mcg twice daily, fluticasone propionate/salmeterol 100/50 mcg twice daily or fluticasone propionate 250 mcg twice daily **Baseline characteristics**: control group: 51.9% male, mean age 46.5, 85.7% Caucasian, predicted FEV_1 87.8 (18.2). Intervention group: 48.7% male, mean age 42, 81.4% Caucasian, predicted FEV_1 90.8 (17.2) **Inclusion criteria**: male and female participants ≥ 18 years old with documented history of asthma (≥ 6 months), whose asthma was controlled with current treatment (1000 mg of inhaled beclomethasone dipropionate or equivalent and a long-acting $beta_2$-agonist) at a stable dose for at least 4 weeks **Exclusion criteria**: smoking history ≥ 10 pack-years, respiratory tract infection during the last 4 weeks before the initial clinic visit, acute asthma exacerbation requiring emergency room treatment or hospitalisation within 4 weeks before the initial clinic visit and/or use of oral/parenteral corticosteroids during the past 4 weeks (12 weeks for depot corticosteroids) or any change in their asthma maintenance treatment in the previous 4 weeks. Changes in asthma medication (excluding study rescue medication) or insufficient asthma control according to daily record card or ACQ and/or investigator's judgement regarding the suitability of a reduction in maintenance treatment
Interventions	**Run-in**: 8-Week run-in period during which all participants received open-label salmeterol/fluticasone propionate combination 50/250 mcg. All previous asthma control medications were discontinued with the exception of short-acting bronchodilator rescue medication used by the patient previously and antihistamines. At the end of the run-in period, asthma control was assessed and participants were randomly assigned if they fulfilled the weekly criteria for 'well-controlled' asthma (as defined in Gaining Optimal Asthma Control (GOAL) study criteria) during the last 2 weeks of the run-in period **Intervention (LABA stopped)**: 2 of the 3 treatment arms were relevant; these are analysed in our review. The intervention group was the group in which LABA was stepped-down: fluticasone propionate 250 mcg × twice daily for 24 weeks. Rescue short-acting bronchodilators were taken if required **Control (LABA+ICS)**: salmeterol/fluticasone propionate 50/250 mcg twice daily for 24 weeks. Rescue short-acting bronchodilators were taken if required
Outcomes	**Primary**: The primary endpoint was mean morning peak expiratory flow (PEF) over the first 12 weeks of treatment **Secondary**: morning PEF over the last 12 weeks of the treatment period, evening PEF, daily symptoms, short-acting bronchodilator use as rescue medication, exacerbations, forced expiratory volume in 1 second (FEV_1) and asthma control using the GOAL definitions of total and well-control
Notes	**Funding**: GlaxoSmithKline (GSK) **Study number**: GSK study code SAM40088 (SFCF4026) **Definitions**: moderate exacerbation: worsening of asthma leading to a prescription for short use of oral corticosteroids. Severe exacerbation: worsening of asthma leading to

Godard 2008 (*Continued*)

	hospitalisation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Not sufficiently described in published reports, but previous contact with study sponsors confirmed standard practice with computerised codes
Allocation concealment (selection bias)	Low risk	Not sufficiently described in published reports, but previous contact with study sponsors confirmed concealed automated allocation system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No specific details but described as double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No specific details but described as double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropout < 20% in both groups, somewhat lower in the LABA/ICS group. All randomly assigned participants were included in the ITT population
Selective reporting (reporting bias)	Low risk	All named outcomes were reported in the published report or were made available by study author or sponsor via a previous review team
Other bias	Low risk	None identified

GSK SAS40037

Methods	**Design**: randomised, double-blind, double-dummy, parallel-group multi-centre trial Study period was 29 October 2001 to 29 May 2003. Trial included 99 centres in the United States, of which 87 randomly assigned participants. Duration of treatment was 16 weeks
Participants	**Population**: 824 eligible participants with well-controlled asthma after a run-in period of 8 weeks were randomly assigned to receive fluticasone propionate/salmeterol 250/50 mcg twice daily, fluticasone propionate/salmeterol 100/50 mcg twice daily or fluticasone propionate 250 mcg twice daily **Baseline characteristics**: control group: 58% male, mean age 41, 83% Caucasian. Intervention group: 67% male, mean age 42, 81.4% Caucasian

	Inclusion criteria: male and female participants, 15 years of age or older, with a diagnosis of asthma, as defined by the ATS, for at least 6 months before the first visit. Each participant must have been treated with an allowed inhaled corticosteroid at a fixed dosing regimen (within an allowed total daily dose) for at least 4 weeks before the screening visit. All participants were required to have FEV_1 of 40% to 85% of their predicted normal value and $\geq$ 12% reversibility within 30 minutes following 2 to 4 puffs of albuterol inhaler at the screening visit Documentation of historical reversibility within 24 months was allowed **Exclusion criteria**: Participants were not allowed to participate if they had been diagnosed with life-threatening asthma, were hospitalised for asthma within the previous 6 months, had a concurrent respiratory disease or had intermittent or seasonal asthma alone. Participants also could not have had a respiratory tract infection or used antibiotics for treatment of a suspected or diagnosed respiratory tract infection within 14 days of visit 1
Interventions	**Run-in**: 2-Week run-in phase during which participants continued their current inhaled corticosteroid therapy, followed by an open-label treatment period during which those who did not achieve asthma control replaced this with fluticasone propionate/salmeterol 100/50 mcg twice daily. Those who achieved control during the open-label period were randomly assigned to 16 weeks of blinded treatment with fluticasone propionate/salmeterol 100/50 mcg twice daily, fluticasone propionate 100 mcg twice daily, salmeterol 50 mcg twice daily or montelukast 10 mg 4 times a day. Albuterol was allowed as a rescue short-acting bronchodilator for each group **Intervention (LABA stopped)**: 2 of the 3 treatment arms were relevant to our protocol; these are analysed in this review. The intervention group was the group in which LABA was stepped-down: fluticasone propionate 100 mcg × twice daily for 16 weeks **Control (LABA+ICS)**: fluticasone propionate/salmeterol 100/50 mcg twice daily for 16 weeks
Outcomes	**Primary**: mean change from baseline at endpoint in morning PEF **Secondary**: mean change from baseline at endpoint in morning predose FEV_1, percentage of symptom-free days, percentage of rescue-free days and participant-rated satisfaction with treatment
Notes	**Funding**: GlaxoSmithKline (GSK) **Study number**: GSK study code SAS40037

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Not sufficiently described in published reports, but previous contact with study sponsors confirmed standard practice with computerised codes
Allocation concealment (selection bias)	Low risk	Not sufficiently described in published reports, but previous contact with study sponsors confirmed concealed automated

GSK SAS40037 (*Continued*)

		allocation system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No specific details but described as double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No specific details but described as double-blind
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropout unbalanced and high in both groups; higher in ICS group (34%) than in LABA+ICS group (24%). All randomly assigned participants were included in the ITT analysis
Selective reporting (reporting bias)	Low risk	All named outcomes were reported in the published report or were made available by study author or sponsor via a previous review team
Other bias	Low risk	None identified

Koenig 2008

Methods	**Design**: randomised, double-blind, double-dummy, parallel-group multi-centre trial Study period was 29 October 2001 to 28 May 2003. Trial included 97 centres in the United States, of which 85 randomly assigned participants. Duration of treatment was 16 weeks
Participants	**Population**: 647 participants with stable asthma while taking fluticasone propionate/salmeterol 100/50 mcg twice daily were randomly assigned to receive fluticasone propionate 100 mcg twice daily, salmeterol 50 mcg twice daily or montelukast 10 mg once daily **Baseline characteristics**: control group: 39% male, mean age 40.4, 88% Caucasian. Intervention group: 43% male, mean age 42, 87% Caucasian **Inclusion criteria**: male or female participants $\geq$ 15 years of age with a diagnosis of asthma using the ATS definition. Eligible participants had to demonstrate prebronchodilator FEV_1 between 40% and 80% of predicted normal. Participants also had to demonstrate at visit 1 or provide historical evidence of reversible airway disease characterised by an increase in FEV_1 > 12% within 30 minutes after inhalation of albuterol, or 1 standard dose of nebulised albuterol. Eligible participants used 1 of the following ICS at a fixed daily dosing regimen for at least 4 weeks before screening: beclomethasone 160 to 240 mcg/d; budesonide 200 to 400 mcg/d; flunisolide 1000 mcg/d; fluticasone propionate MDI 176 to 220 mcg/d; fluticasone propionate dpi 200 mcg/d; triamcinolone acetonide 600 to 1000 mcg/d **Exclusion criteria**: life-threatening asthma, asthma instability, concurrent respiratory disease, intermittent and seasonal asthma or exercise-induced bronchospasm alone or any other concurrent condition/disease that would put safety of participants at risk.

	Concurrent use of medications that could affect the course of asthma or interact with study medications was prohibited. Systemic corticosteroid use was prohibited within 4 weeks of screening
Interventions	**Run-in**: 2-Week run-in phase during which participants continued their current inhaled corticosteroid therapy, followed by an open-label treatment period only for those who did not achieve asthma control. Inhaled corticosteroids were replaced with fluticasone propionate/salmeterol 100/50 mcg (Advair Diskus, GSK) twice daily. Those who achieved control during the open-label period were then randomly assigned to 16 weeks of blinded treatment with fluticasone propionate/salmeterol 100/50 mcg twice daily, fluticasone propionate 100 mcg twice daily, salmeterol 50 mcg twice daily or montelukast 10 mg 4 times a day. Albuterol was allowed as a rescue short-acting bronchodilator in all groups **Intervention (LABA stopped)**: 2 of the 4 treatment arms were relevant to our protocol; these are analysed in this review. The intervention group was the group in which LABA was stepped-down: fluticasone propionate 100 mcg twice daily for 16 weeks **Control (LABA+ICS)**: fluticasone propionate/salmeterol 100/50 mcg twice daily for 16 weeks
Outcomes	**Primary**: mean change from baseline at endpoint in morning PEF **Secondary**: mean change from baseline at endpoint in morning predose FEV_1, percentage of symptom-free days, percentage of rescue-free days, asthma symptom scores, nighttime awakenings, participant-related satisfaction on treatment questionnaire
Notes	**Funding**: GlaxoSmithKline (GSK) **Study number**: GSK study code SAS40036 **Definitions**: rescue-free day: day without use of rescue albuterol

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Not sufficiently described in published reports, but previous contact with study sponsors confirmed standard practice with computerised codes
Allocation concealment (selection bias)	Low risk	Not sufficiently described in published reports, but previous contact with study sponsors confirmed concealed automated allocation system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, double-dummy study

Koenig 2008 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number of participants who dropped out during the study was not given. Study authors stated that the ITT population was used, which consisted of all participants who were randomly assigned to treatment
Selective reporting (reporting bias)	Low risk	All named outcomes were reported in the published report or were made available by study author or sponsor via a previous review team
Other bias	Unclear risk	During the course of the study, participant recruitment was placed on hold pending analysis of data from the Salmeterol Multicenter Asthma Research Trial and was subsequently terminated, with approximately 161 participants per treatment group (target was 206 per group)

Reddel 2010

Methods	**Design**: block-randomised, double-blind, parallel-group, multi-centre study conducted at 3 centres in Australia Study period was from 28 March 2002 to 17 February 2006
Participants	**Population**: 82 participants with asthma were block randomly assigned to receive salmeterol/fluticasone 50/500 mcg twice daily or fluticasone 500 mcg twice daily alone **Inclusion criteria**: male or female, 18 to 80 years of age with a clinical diagnosis of asthma (according to ATS criteria) for 6 months who had been taking salmeterol and fluticasone for at least 4 weeks at a daily dose of 50/500 mcg twice a day by Diskus or by pressurised metered dose inhaler. Showed evidence of adequate unsupervised spirometric technique, had completed > 60% of run-in diary card sessions and had not experienced an exacerbation within the previous 4 weeks **Exclusion criteria**: current smoking or > 10 pack-year smoking history, significant chronic respiratory disease or evidence of extrathoracic airway obstruction, pregnancy or lactation, use of oral/parenteral corticosteroids or hospitalisation for asthma in the previous 3 months or respiratory tract infection within the previous 4 weeks. Those experiencing a severe exacerbation were withdrawn but could be re-enrolled 3 months after cessation of systemic corticosteroids. Treatment with asthma medications, other than study medications and corticosteroids for exacerbations, was not permitted
Interventions	**Run-in**: During the 4-week run-in period, participants received open-label salmeterol and fluticasone propionate 50/500 mcg twice daily via Diskus **Intervention (LABA stopped)**: fluticasone 500 mcg twice a day for 12 weeks **Control (LABA+ICS)**: salmeterol and fluticasone propionate 50/500 mcg twice daily via Diskus plus rescue beta$_2$-agonist for symptom relief

Outcomes	**Primary**: mean daily fluticasone propionate dose including ICS for exacerbations **Secondary**: minimum effective ICS dose, dose reduction failure (exacerbation), FEV_1, FVC, PD20 methacholine, ACQ, AQLQ, optimal asthma control, % sputum eosinophils and neutrophils, blood eosinophils, exacerbations, exhaled nitric oxide, asthma-free days, average rescue medication use per day, average morning and evening FEV_1 and PEF, adverse events
Notes	**Funding**: GlaxoSmithKline **Study number**: clinical trial registration number ACTRN12605000465651 (Australian and New Zealand Clinical Trial Registry). GSK Trial register: SAM40031 **Definitions**: moderate exacerbation: increase in rescue beta agonist use by 2 occasions and/or fall in PEF by $\geq$ 2 standard deviations from baseline mean on 2 of 3 consecutive days Severe exacerbation: increase in rescue beta agonist use by $\geq$ 2 occasions in a day compared with baseline, and fall in PEF $\geq$ 3 standard deviations from baseline mean on 2 of 3 consecutive days

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation (week 0) was conducted by GSK Australia by computer-generated schedule and was stratified by duration of SFC treatment (6 months and > 6 months) , with a permuted block design (block size of 4 randomisation numbers)
Allocation concealment (selection bias)	Low risk	Not sufficiently described in published reports, but previous contact with study sponsors confirmed concealed automated allocation system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identified by dose level and by a unique randomly assigned pack number to maintain blinding and concealment of randomisation allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Identified by dose level and by a unique randomly assigned pack number to maintain blinding and concealment of randomisation allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout low overall but somewhat unbalanced; much higher in ICS group (14%) than in LABA+ICS group (4%). 96% of participants were included in the analyses presented

Selective reporting (reporting bias)	Low risk	All named outcomes were reported in the published report or were made available by study author or study sponsor via a previous review team
Other bias	Low risk	None identified

Slankard 2011

Methods	**Design**: randomised, double-blind, parallel-group trial Start date of study: June 2007. Final data collection date: November 2010. Clinical trials portal lists this study as 'ongoing' but not recruiting participants Duration of treatment: 16 weeks
Participants	**Population**: 69 participants who had been genotyped were randomly assigned to continue on the same dose of LABA-ICS or to step down to ICS alone **Baseline characteristics**: individual group characteristics unknown **Inclusion criteria**: men or women $\geq$ 18 years of age, history of moderate or severe and persistent asthma, currently being treated with a long-acting beta$_2$-agonist and inhaled corticosteroid, $FEV_1 \geq 70\%$ at randomisation visit. Women of childbearing potential must be taking an effective form of contraception. Literate in English **Exclusion criteria**: active smoking or > 10 pack-year history of smoking, history of intubation for asthma within the past 10 years, pregnancy or breast feeding, major co-morbidity including severe cardiac disease, uncontrolled hypertension, poorly controlled diabetes, malignancy within the past 5 years (except non-melanoma skin lesions) and other pulmonary disease
Interventions	**Run-in**: 6-Week run-in phase during which participants continued their current inhaled ICS-LABA therapy **Intervention**: LABA stopped for 16 weeks **Control**: LABA+ICS for 16 weeks
Outcomes	**Primary**: absolute change from baseline at endpoint in morning PEF **Secondary**: absolute and percentage change in rescue inhaler use
Notes	**Funding**: unknown **Study number**: ClinicalTrials.gov Identifier: NCT00521222

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised; no additional details
Allocation concealment (selection bias)	Unclear risk	No details

Slankard 2011 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	No specific details but described as double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No specific details but described as double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No details of dropout or imputation
Selective reporting (reporting bias)	High risk	No data could be included in the meta-analysis, and several outcomes were not reported at all. Only a conference abstract was available
Other bias	Low risk	None identified

ACQ: asthma control questionnaire; **ATS:** American Thoracic Society; **AQLQ:** asthma quality of life questionnaire; **FEV_1:** forced expiratory volume in one second; **FVC:** forced expiatory volume; **ICS:** inhaled corticosteroids; **ITT:** intention to treat; **LABA:** long-acting beta$_2$-agonist; **PD20:** histamine provocation dose causing a 20% drop in FEV_1; **PEF:** peak expiratory flow.

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

Study	Reason for exclusion
Aalbers 2005	LABA was not stopped - wrong comparison
Bumbacea 2010	This paper was not about stepping down LABA - wrong comparison
Cowie 2007	LABA was not stepped down - wrong comparison
FitzGerald 2003	LABA was not stepped down - wrong comparison
Fowler 2002	ICS dose was higher in the step-down group - wrong comparison
GSK ADA109315	Not a LABA step-down study - wrong comparison. This was an analysis of healthcare utilisation and costs of stepping down LABA
GSK SMS30046	Cross-over study - wrong study design
Harrison 1997	LABA was not stepped down - wrong comparison
Ind 2004	LABA was not stepped down - wrong comparison

(*Continued*)

Liu 2007	Not a LABA step-down study - wrong comparison. Assessing usefulness of monitoring airway hyperresponsiveness to guide dose adjustment
Nathan 2009	LABA was not stepped down - wrong comparison
NCT01565031	No clear step-down strategy for LABA - wrong comparison
Obase 2013	ICS dose was stepped down - wrong comparison
Paggiaro 2011	LABA was not stepped down - wrong comparison
Papi 2012	LABA was not stepped down - wrong comparison
Self 1998	ICS dose was stepped down - wrong comparison
Shamsul 2007	2 step-down groups - wrong comparison
Zangrilli 2009	LABA was not stepped down - wrong comparison

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

NCT01437995

Trial name or title	Long-acting beta agonist step down study (LASST)
Methods	6-Week, multi-centre, blinded, randomised, double-masked, parallel-group comparative effectiveness study of approaches to stepping down therapy for patients with well-controlled asthma treated with combination ICS and LABA
Participants	**Inclusion criteria**: men and women 12 to 80 years of age with well-controlled asthma taking moderate dose of ICS/LABA based on an Asthma Control Test (ACT) score $\geq$ 20, absence of unscheduled visits or use of rescue prednisone for 4 weeks before enrolment and a prebronchodilator $FEV_1 \geq 70\%$ predicted **Exclusion criteria**: long-term oral steroid therapy, hospitalisation or urgent care visit within 4 weeks of screening visit, lung disease other than asthma including COPD, bronchiectasis, sarcoidosis or other lung disease. < 10 pack-years of tobacco use and abstinence, postbronchodilator FEV_1 < 70% predicted, near-fatal asthma (intubation or ICU admission for asthma) within 2 years of enrolment, high risk of near-fatal or fatal asthma, history of known premature birth less than 33 weeks or any significant level of respiratory care including prolonged oxygen administration or mechanical ventilation during the neonatal period, unstable cardiac disease (decompensated CHF, unstable angina, recent MI, atrial fibrillation, supraventricular or ventricular tachycardia, congenital heart disease or severe uncontrolled hypertension), other major chronic illnesses, drug allergies, pregnancy, lactation
Interventions	Stepping down from fluticasone/salmeterol diskus 250/50 mcg bd to fluticasone diskus 250 mcg bd without salmeterol

NCT01437995 (*Continued*)

Outcomes	Rate of treatment failure assessed by decline in peak flow or FEV_1, increased need for beta-agonists, requirement for non-scheduled medical care for asthma symptoms or prednisone taper Pulmonary function measures: (1) morning peak expiratory flow rate (from participants' daily diary cards) and (2) pre-BD FEV_1 and bronchodilator response Rate of episodes of poor asthma control (EPAC) defined by unscheduled medical care, hospitalisation, use of oral corticosteroids and/or increased use of rescue medications and/or decrease of 30% or more in morning PEFR
Starting date	March 2012
Contact information	Joy Saams, Registered Nurse
Notes	Estimated enrolment: 450. Estimated study completion date: June 2015

NCT02094937

Trial name or title	201135: a randomised, double-blind, multi-centre, parallel-group study to compare the efficacy and safety of fluticasone furoate (FF) 100 mcg once daily with fluticasone propionate (FP) 250 mcg twice daily (BD) and FP 100 mcg BD in well-controlled asthmatic participants stepped down from maintenance therapy with RELVAR inhaler (FF/VI) 100/25 mcg once daily in Japanese participants
Methods	Randomised, multi-centre, double-blind, placebo-controlled, parallel-group study
Participants	**Inclusion criteria**: men and women $\geq$ 18 years of age with a diagnosis of asthma as defined by the National Institutes of Health at least 1 year before screening visit. Asthma must be 'stable' as judged by the investigator with no change in asthma medication for at least 8 weeks before screening and an ACT score $\geq$ 20. Best prebronchodilator FEV_1 $\geq$ 80% of predicted normal value at screening visit. Using the middle-dose ICS/LABA, equivalent to twice-daily combination of fluticasone propionate and salmeterol 250 mcg for at least 12 weeks before registration visit. In addition, the prescription of the middle-dose ICS/LABA should not be changed at least 8 weeks before **Exclusion criteria**: history of life-threatening asthma, recent respiratory tract infection, exacerbation of asthma requiring oral corticosteroids in the previous 12 weeks, other respiratory disease, other significant co-morbidities, smoker or history of smoking $\geq$ 10 pack-years
Interventions	4 experimental arms. Arms of interest to this review are fluticasone furoate/vilanterol 100/25 mcg and the comparison arm of those receiving fluticasone furoate 100 mcg bd alone
Outcomes	Time to withdrawal due to poorly controlled asthma during weeks 8 to 20. Proportion of participants with well-controlled asthma at the end of week 20, mean change from baseline in clinic visit trough FEV_1 at the end of period 2, mean change from baseline in the percentage of symptom-free 24-hour periods during week 20, mean change from baseline in percentage of rescue-free 24-hour periods during period 2, mean change from baseline in Asthma Control Test (ACT) score during weeks 8 to 20, proportion of participants with ACT score $\geq$ 20 at the end of week 20
Starting date	March 2014
Contact information	US GSK Clinical Trials Call Center

NCT02094937 (*Continued*)

Notes	Estimated study completion date: June 2015 Sponsored by GlaxoSmithKline

DATA AND ANALYSES

Comparison 1. Stopped LABA vs continued LABA+ICS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Exacerbation: systemic corticosteroids	4	1257	Odds Ratio (M-H, Random, 95% CI)	1.74 [0.83, 3.65]
2 Asthma control: ACQ	3	645	Mean Difference (IV, Random, 95% CI)	0.24 [0.13, 0.35]
3 Serious adverse events	5	1342	Odds Ratio (M-H, Random, 95% CI)	0.82 [0.28, 2.42]
4 Asthma-related quality of life	2	359	Std. Mean Difference (IV, Random, 95% CI)	0.36 [0.15, 0.57]
5 Exacerbation: hospital admission or emergency department visit	5		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
6 Adverse events (all cause)	5	1339	Odds Ratio (M-H, Random, 95% CI)	0.83 [0.66, 1.05]
7 Withdrawals (all)	5	1352	Odds Ratio (M-H, Random, 95% CI)	1.95 [1.47, 2.58]

Comparison 2. Subgroup analysis: type of LABA

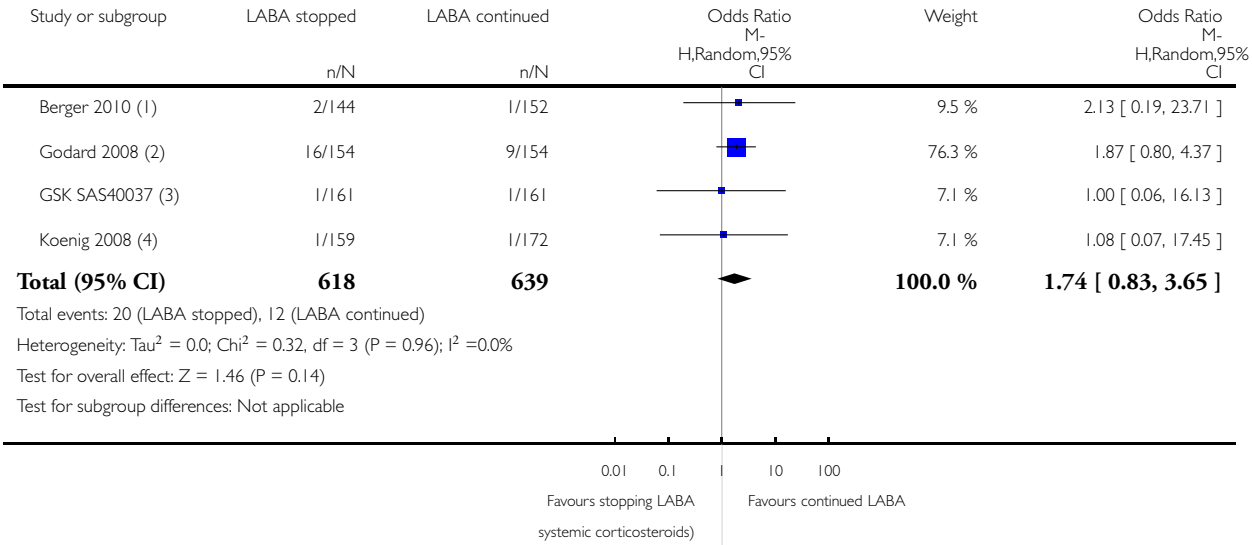
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Exacerbation: requiring systemic corticosteroids	4	1257	Odds Ratio (M-H, Random, 95% CI)	1.74 [0.83, 3.65]
1.1 Formoterol	1	296	Odds Ratio (M-H, Random, 95% CI)	2.13 [0.19, 23.71]
1.2 Salmeterol	3	961	Odds Ratio (M-H, Random, 95% CI)	1.70 [0.78, 3.72]
2 Asthma control: ACQ	3	645	Mean Difference (IV, Random, 95% CI)	0.24 [0.13, 0.35]
2.1 Formoterol	1	290	Mean Difference (IV, Random, 95% CI)	0.32 [0.15, 0.49]
2.2 Salmeterol	2	355	Mean Difference (IV, Random, 95% CI)	0.19 [0.05, 0.33]
3 Serious adverse events	5	1342	Odds Ratio (M-H, Random, 95% CI)	0.82 [0.28, 2.42]
3.1 Formoterol	1	299	Odds Ratio (M-H, Random, 95% CI)	0.35 [0.04, 3.40]
3.2 Salmeterol	4	1043	Odds Ratio (M-H, Random, 95% CI)	1.05 [0.31, 3.60]

Analysis 1.1. Comparison 1 Stopped LABA vs continued LABA+ICS, Outcome 1 Exacerbation: systemic corticosteroids.

Review: Stopping long-acting beta$_2$-agonists (LABA) for adults with asthma well controlled by LABA and inhaled corticosteroids

Comparison: 1 Stopped LABA vs continued LABA+ICS

Outcome: 1 Exacerbation: systemic corticosteroids



(1) "A clinical exacerbation was defined as an exacerbation requiring emergency treatment, hospitalization, or use of an asthma medication not allowed by the protocol" (assumed to include

(2) Requiring oral corticosteroids

(3) "Any use of systemic corticosteroids" (From Brozek 2012. obtained from study sponsor)

(4) Data for Koenig 2008 and SAS40037 have been incorporated with permission from Brozek et al (provided to them by the study sponsor)

Analysis 1.2. Comparison 1 Stopped LABA vs continued LABA+ICS, Outcome 2 Asthma control: ACQ.

Review: Stopping long-acting beta$_2$-agonists (LABA) for adults with asthma well controlled by LABA and inhaled corticosteroids

Comparison: 1 Stopped LABA vs continued LABA+ICS

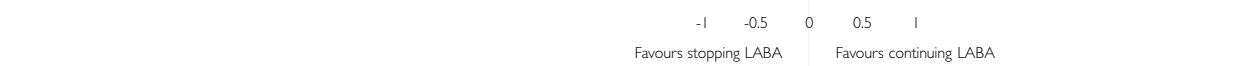
Outcome: 2 Asthma control: ACQ

Study or subgroup	LABA stopped N	Mean(SD)	LABA continued N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Berger 2010 (1)	139	0.38 (0.811)	151	0.06 (0.632)		40.9 %	0.32 [0.15, 0.49]
Godard 2008	141	0.8 (0.6)	142	0.6 (0.7)		50.2 %	0.20 [0.05, 0.35]
Reddel 2010 (2)	35	1.13 (0.86)	37	1.01 (0.69)		8.9 %	0.12 [-0.24, 0.48]
Total (95% CI)	**315**		**330**			**100.0 %**	**0.24 [0.13, 0.35]**

Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.56, df = 2 (P = 0.46); I^2 =0.0%

Test for overall effect: Z = 4.41 (P = 0.000011)

Test for subgroup differences: Not applicable



(1) Data for Berger 2010 and Reddel 2010 have been incorporated with permission from Brozek et al (provided to them by the study sponsor)

(2) Visit 4 (week 12) data before ICS were titrated

Analysis 1.3. Comparison 1 Stopped LABA vs continued LABA+ICS, Outcome 3 Serious adverse events.

Review: Stopping long-acting beta$_2$-agonists (LABA) for adults with asthma well controlled by LABA and inhaled corticosteroids

Comparison: 1 Stopped LABA vs continued LABA+ICS

Outcome: 3 Serious adverse events

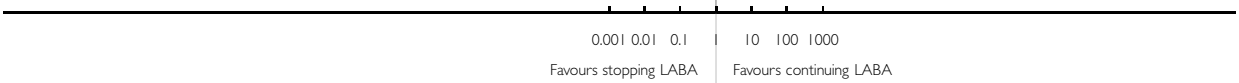
Study or subgroup	LABA stopped n/N	LABA continued n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Berger 2010	1/145	3/154		22.7 %	0.35 [0.04, 3.40]
Godard 2008	1/154	3/154		22.7 %	0.33 [0.03, 3.20]
GSK SAS40037	2/161	1/161		20.2 %	2.01 [0.18, 22.42]
Koenig 2008	0/159	0/172			Not estimable
Reddel 2010 (1)	3/41	2/41		34.5 %	1.54 [0.24, 9.73]
Total (95% CI)	**660**	**682**		**100.0 %**	**0.82 [0.28, 2.42]**

Total events: 7 (LABA stopped), 9 (LABA continued)

Heterogeneity: Tau^2 = 0.0; Chi^2 = 2.15, df = 3 (P = 0.54); I^2 =0.0%

Test for overall effect: Z = 0.36 (P = 0.72)

Test for subgroup differences: Not applicable



(1) Data for the full 52 weeks including ICS dose tapering

Analysis 1.4. Comparison 1 Stopped LABA vs continued LABA+ICS, Outcome 4 Asthma-related quality of life.

Review: Stopping long-acting beta$_2$-agonists (LABA) for adults with asthma well controlled by LABA and inhaled corticosteroids

Comparison: 1 Stopped LABA vs continued LABA+ICS

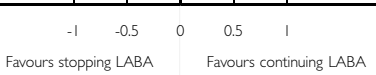
Outcome: 4 Asthma-related quality of life

Study or subgroup	LABA stopped N	Mean(SD)	LABA continued N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Berger 2010 (1)	136	0.27 (0.89)	151	-0.06 (0.9)		79.9 %	0.37 [0.13, 0.60]
Reddel 2010 (2)	35	1.61 (1.54)	37	1.18 (1.03)		20.1 %	0.33 [-0.14, 0.79]
Total (95% CI)	**171**		**188**			**100.0 %**	**0.36 [0.15, 0.57]**

Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.02, df = 1 (P = 0.88); I^2 =0.0%

Test for overall effect: Z = 3.37 (P = 0.00074)

Test for subgroup differences: Not applicable



(1) Data for Berger 2010 were measured on the Juniper AQLQ (higher is better) and have been incorporated with permission from Brozek et al (provided to them by the study sponsor)

(2) Marks Quality of Life Questionnaire - lower values better. Visit 4 (week 12) data before ICS were titrated

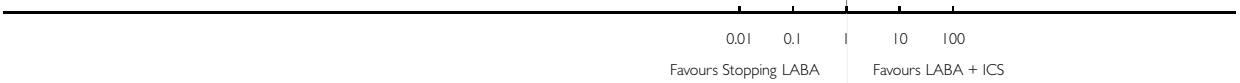
Analysis 1.5. Comparison 1 Stopped LABA vs continued LABA+ICS, Outcome 5 Exacerbation: hospital admission or emergency department visit.

Review: Stopping long-acting beta$_2$-agonists (LABA) for adults with asthma well controlled by LABA and inhaled corticosteroids

Comparison: 1 Stopped LABA vs continued LABA+ICS

Outcome: 5 Exacerbation: hospital admission or emergency department visit

Study or subgroup	LABA stopped n/N	Continued LABA+ICS n/N	Odds Ratio M-H,Random,95% CI	Odds Ratio M-H,Random,95% CI
Berger 2010	0/145	0/154		Not estimable
Godard 2008	0/154	0/154		Not estimable
GSK SAS40037	0/161	0/161		Not estimable
Koenig 2008 (1)	0/159	0/172		Not estimable
Reddel 2010	0/41	0/41		Not estimable



(1) The absence of hospital admissions for asthma was confirmed with the study sponsors by Brozek et al

Analysis 1.6. Comparison 1 Stopped LABA vs continued LABA+ICS, Outcome 6 Adverse events (all cause).

Review: Stopping long-acting beta$_2$-agonists (LABA) for adults with asthma well controlled by LABA and inhaled corticosteroids

Comparison: 1 Stopped LABA vs continued LABA+ICS

Outcome: 6 Adverse events (all cause)

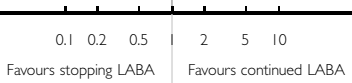
Study or subgroup	LABA stopped n/N	LABA continued n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Berger 2010	76/144	90/152		24.0 %	0.77 [0.49, 1.22]
Godard 2008	42/154	48/154		21.1 %	0.83 [0.51, 1.35]
GSK SAS40037	84/161	77/161		26.4 %	1.19 [0.77, 1.84]
Koenig 2008	76/159	100/172		26.8 %	0.66 [0.43, 1.02]
Reddel 2010 (1)	37/41	39/41		1.7 %	0.47 [0.08, 2.75]
Total (95% CI)	**659**	**680**		**100.0 %**	**0.83 [0.66, 1.05]**

Total events: 315 (LABA stopped), 354 (LABA continued)

Heterogeneity: Tau^2 = 0.00; Chi^2 = 4.18, df = 4 (P = 0.38); I^2 =4%

Test for overall effect: Z = 1.53 (P = 0.13)

Test for subgroup differences: Not applicable



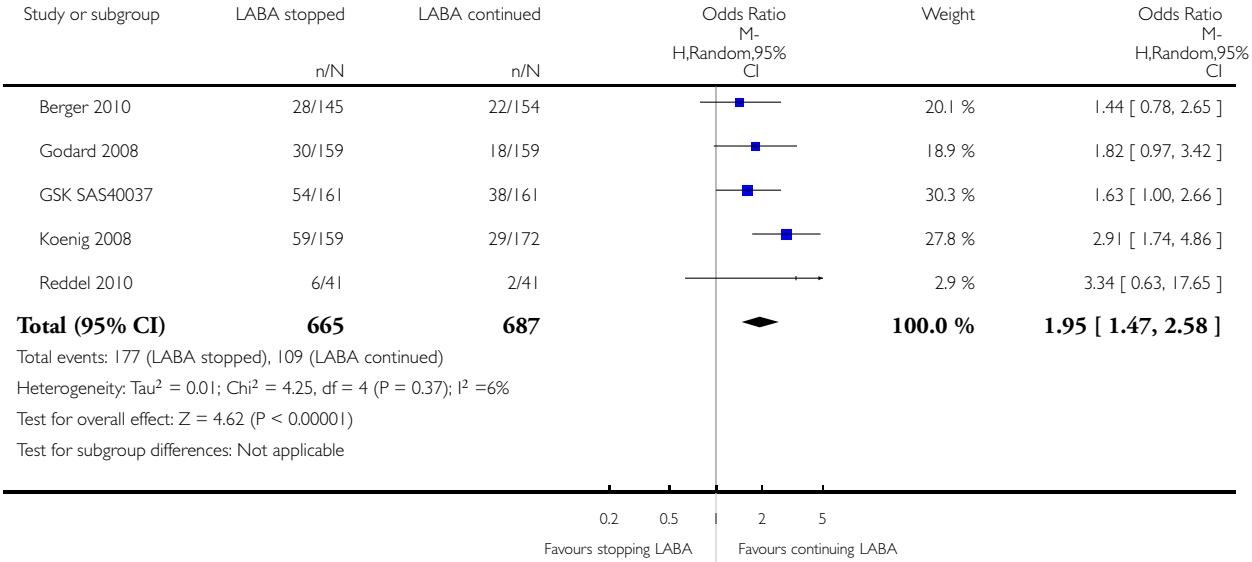
(1) Data for the full 52 weeks including ICS dose tapering

Analysis 1.7. Comparison 1 Stopped LABA vs continued LABA+ICS, Outcome 7 Withdrawals (all).

Review: Stopping long-acting beta$_2$-agonists (LABA) for adults with asthma well controlled by LABA and inhaled corticosteroids

Comparison: 1 Stopped LABA vs continued LABA+ICS

Outcome: 7 Withdrawals (all)

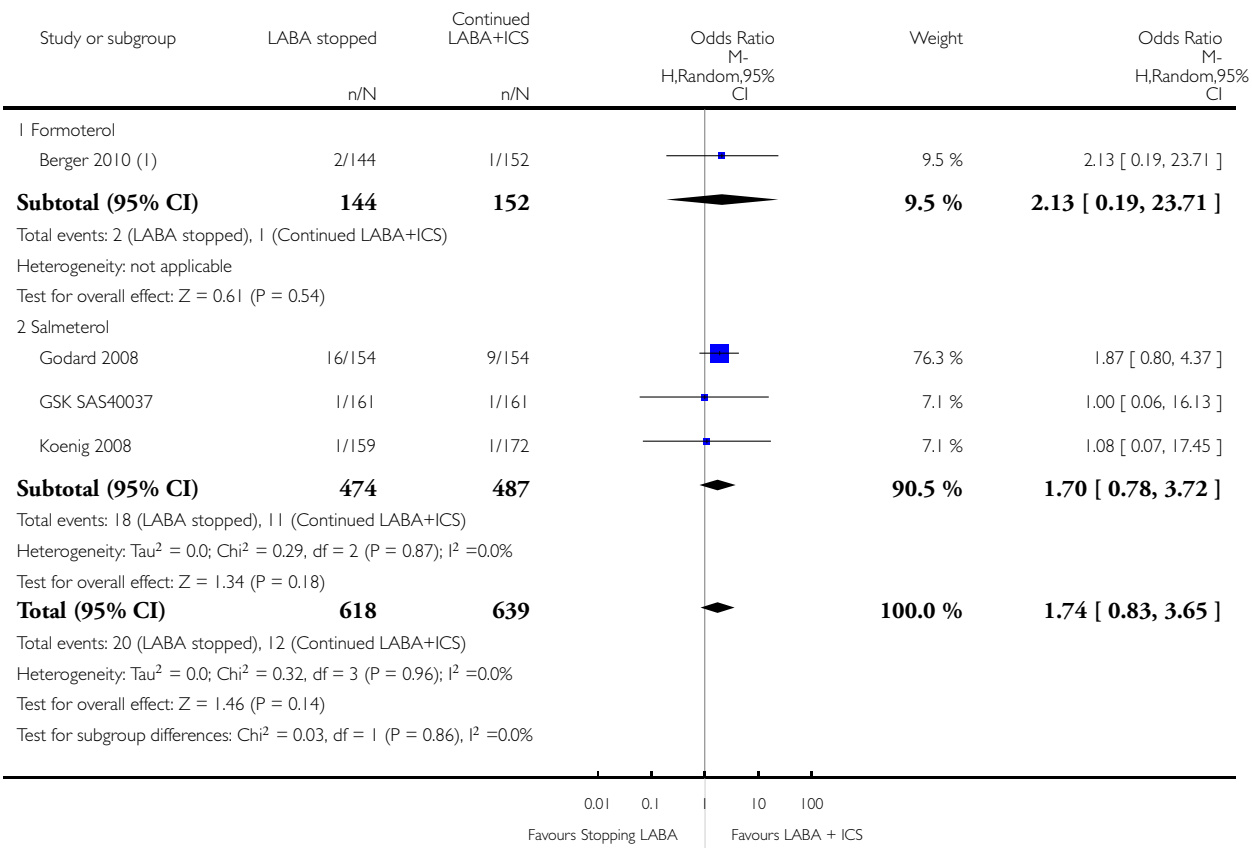


Analysis 2.1. Comparison 2 Subgroup analysis: type of LABA, Outcome 1 Exacerbation: requiring systemic corticosteroids.

Review: Stopping long-acting beta$_2$-agonists (LABA) for adults with asthma well controlled by LABA and inhaled corticosteroids

Comparison: 2 Subgroup analysis: type of LABA

Outcome: 1 Exacerbation: requiring systemic corticosteroids



(1) Data for Koenig 2008 and SAS40037 provided to Brozek et al from the study sponsor and reproduced with permission

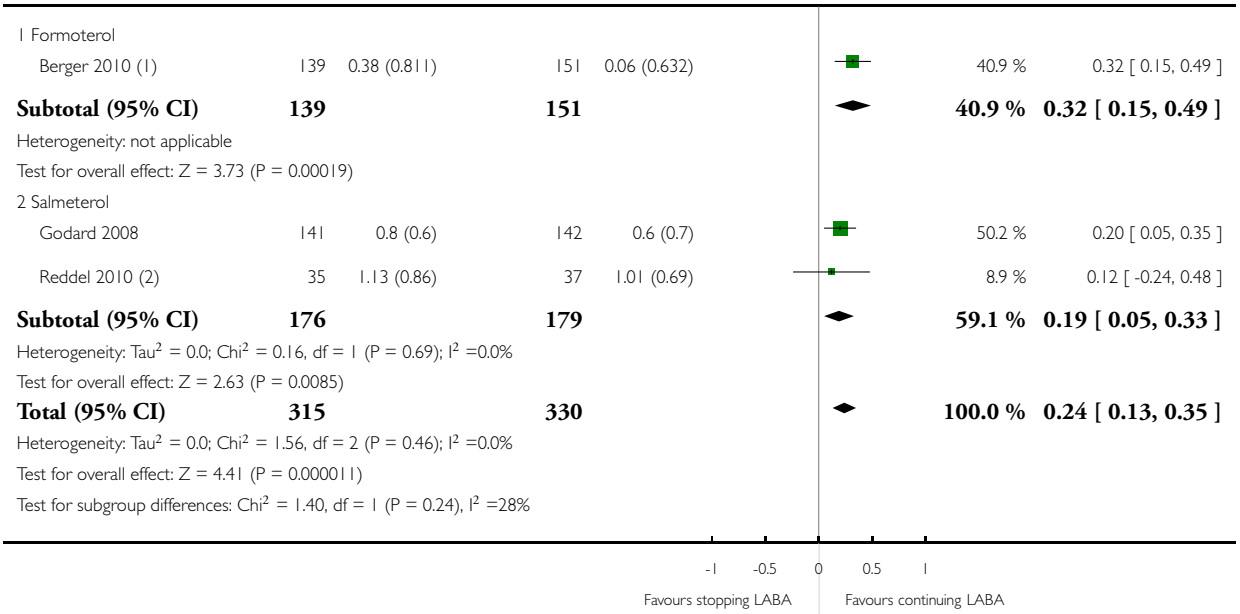
Analysis 2.2. Comparison 2 Subgroup analysis: type of LABA, Outcome 2 Asthma control: ACQ.

Review: Stopping long-acting beta$_2$-agonists (LABA) for adults with asthma well controlled by LABA and inhaled corticosteroids

Comparison: 2 Subgroup analysis: type of LABA

Outcome: 2 Asthma control: ACQ

Study or subgroup	LABA stopped N	Mean(SD)	LABA continued N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Formoterol							
Berger 2010 (1)	139	0.38 (0.811)	151	0.06 (0.632)		40.9 %	0.32 [0.15, 0.49]
Subtotal (95% CI)	**139**		**151**			**40.9 %**	**0.32 [0.15, 0.49]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.73 (P = 0.00019)							
2 Salmeterol							
Godard 2008	141	0.8 (0.6)	142	0.6 (0.7)		50.2 %	0.20 [0.05, 0.35]
Reddel 2010 (2)	35	1.13 (0.86)	37	1.01 (0.69)		8.9 %	0.12 [-0.24, 0.48]
Subtotal (95% CI)	**176**		**179**			**59.1 %**	**0.19 [0.05, 0.33]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.16, df = 1 (P = 0.69); I^2 =0.0%							
Test for overall effect: Z = 2.63 (P = 0.0085)							
Total (95% CI)	**315**		**330**			**100.0 %**	**0.24 [0.13, 0.35]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.56, df = 2 (P = 0.46); I^2 =0.0%							
Test for overall effect: Z = 4.41 (P = 0.000011)							
Test for subgroup differences: Chi^2 = 1.40, df = 1 (P = 0.24), I^2 =28%							



(1) Data for Berger 2010 and Reddel 2010 have been incorporated with permission from Brozek et al (provided to them by the study sponsor)

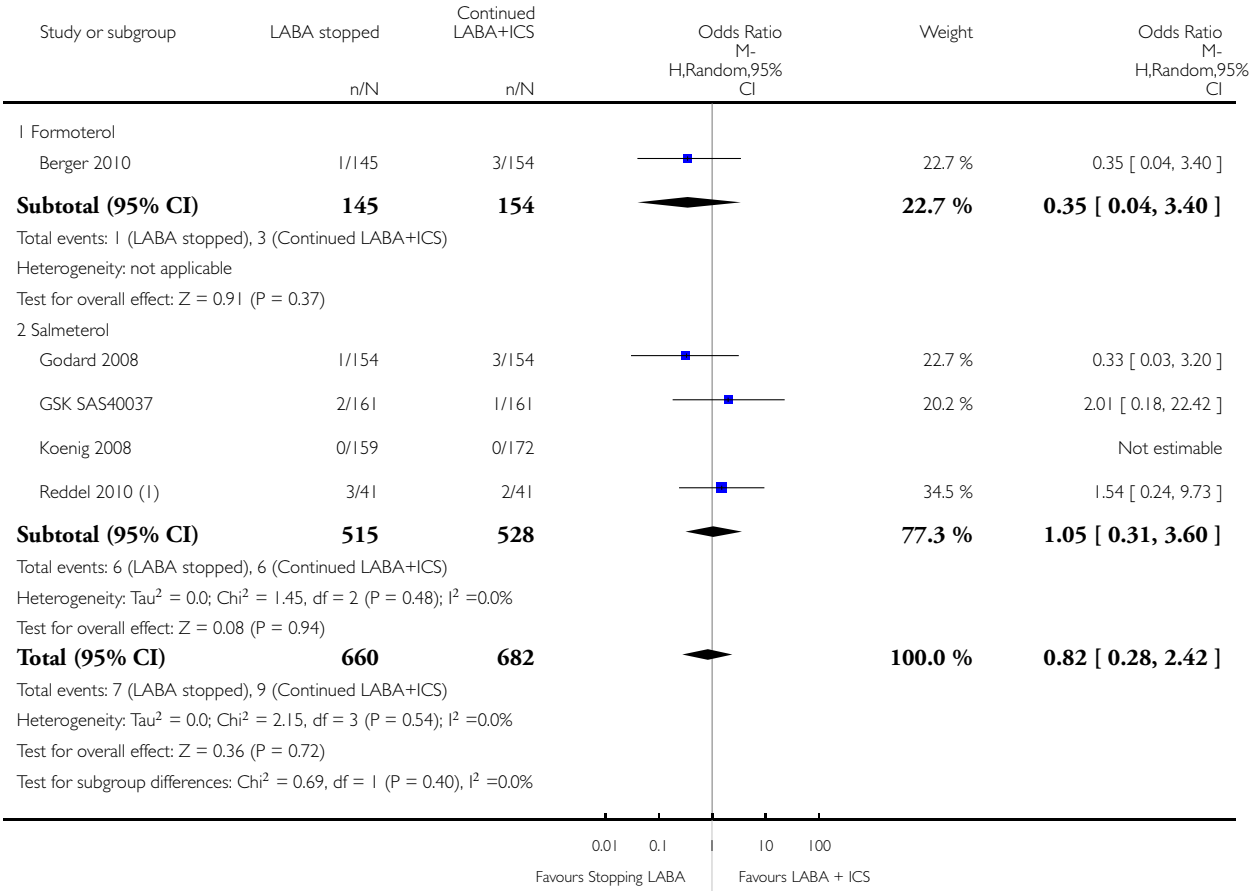
(2) Visit 4 (week 12) data before ICS were titrated

Analysis 2.3. Comparison 2 Subgroup analysis: type of LABA, Outcome 3 Serious adverse events.

Review: Stopping long-acting beta$_2$-agonists (LABA) for adults with asthma well controlled by LABA and inhaled corticosteroids

Comparison: 2 Subgroup analysis: type of LABA

Outcome: 3 Serious adverse events



(1) Data for the full 52 weeks including ICS dose tapering

ADDITIONAL TABLES

Table 1. All included studies - summary characteristics

Study ID	Other ID (s)	Country (centres)	Total N	Study design	Duration	Age, years	LABA	ICS

Table 1. All included studies - summary characteristics (*Continued*)

Berger 2010	SD-039-0726 D5896C0072 NCT006523	USA (116)	752	R, DB, PC	12 weeks	16+	Formoterol 9 mcg bd	Budesonide 320 mcg qd (intervention) 160 mcg bd (control)
Godard 2008	SAM40088 SFCF4026	France (124)	476	R, DB	24 weeks*	18+	Salmeterol 50 mcg bd	Fluticasone propionate 250 mcg bd
GSK SAS40037	SAS40037	USA (87)	824	R, DB, PC	16 weeks	15+	Salmeterol 50 mcg bd	Fluticasone propionate 100 mcg bd
Koenig 2008	SAS40036	USA (85)	647	R, DB	16 weeks	15+	Salmeterol 50 mcg bd	Fluticasone propionate 100 mcg bd
Reddel 2010	SAM40031 AC-TRN1260500	Australia (3)	82	R, DB	12 weeks	18+	Salmeterol 50 mcg bd	Fluticasone propionate 500 mcg bd
Slankard 2011	None	USA	69	R, DB	16 weeks	18+	Salmeterol 50 mcg bd	Unclear

Participants were allowed to continue use of their normal rescue inhaler.

*Primary outcome peak flow reported at 12 weeks.

N: number randomly assigned; **LABA:** long-acting beta$_2$-agonists; **ICS:** inhaled corticosteroids; R: randomly assigned; **DB:** double-blind; **PC:** placebo-controlled; qd: once daily; **bd:** twice daily.

APPENDICES

Appendix 1. Sources and search methods for the Cochrane Airways Group Specialised Register (CAGR)

Electronic searches: core databases

Database	Frequency of search
CENTRAL	Monthly
MEDLINE (Ovid)	Weekly
EMBASE (Ovid)	Weekly
PsycINFO (Ovid)	Monthly
CINAHL (EBSCO)	Monthly
AMED (EBSCO)	Monthly

Handsearches: core respiratory conference abstracts

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

MEDLINE search strategy used to identify trials for the CAGR

Asthma search

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

Filter to identify RCTs

1. exp "clinical trial [publication type]"/
2. (randomised or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. Animals/
10. Humans/
11. 9 not (9 and 10)
12. 8 not 11

The MEDLINE strategy and RCT filter are adapted to identify trials in other electronic databases.

Appendix 2. Search strategy to identify trial reports from the CAGR

#1 AST:MISC1
#2 MeSH DESCRIPTOR Asthma Explode All
#3 asthma*:ti,ab
#4 #1 or #2 or #3
#5 MeSH DESCRIPTOR Adrenergic beta-Agonists
#6 beta* NEAR agonist*
#7 LABA*:ti,ab
#8 *formoterol
#9 Foradil
#10 Oxis
#11 salmeterol
#12 vilanterol
#13 Serevent
#14 Seretide or Advair or Viani or Symbicort or Inuvair or Dulera or Adoair or Breo or Relvar

#15 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14
#16 withdraw*:ti,ab
#17 down-titrat*:ti,ab
#18 discontinu*:ti,ab
#19 stop*:ti,ab
#20 cease*:ti,ab
#21 cessat*:ti,ab
#22 (step-down or "step down"):ti,ab
#23 (reduc* or decreas*) NEAR (dose*):ti,ab
#24 #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23
#25 #4 and #15 and #24
[*Note: in search line #1 MISC1 denotes the field in which the reference has been coded for condition, in this case, asthma]*

CONTRIBUTIONS OF AUTHORS

Shaleen Ahmad (SA) and Kayleigh Kew (KK) sifted the search and extracted data independently. KK entered data into the analyses, and all review authors had input on grading evidence quality. SA wrote up the results, with comments and edits from KK and Rebecca Normansell (RN). All review authors contributed to the discussion and approved the final version of this document.

DECLARATIONS OF INTEREST

Shaleen Ahmad: none known.

Kayleigh Kew: none known.

Rebecca Normansell: none known.

SOURCES OF SUPPORT

Internal sources

- The authors declare that no internal sources of funding were received for this systematic review, UK.
- Kayleigh Kew, UK.

Kayleigh was supported by St George's, University of London

External sources

- National Institute for Health Research, UK.

Evidence to guide care in adults and children with asthma, 13/89/14

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We were not able to carry out subgroup analyses for dose of inhaled corticosteroids because all studies reporting primary outcomes used doses classified as 'low' in GINA 2014. In addition, we were unable to carry out subgroup analyses for inhaler type because no studies gave LABA and ICS in separate inhalers. No studies were rated high for risk of bias for blinding, and no unpublished data were included in the analyses, so there was no need to carry out the planned sensitivity analyses.

We had planned to supplement the main systematic review of effectiveness and safety with a brief economic analysis, but we found no relevant studies.