

Differential effects of maintenance long-acting β -agonist and inhaled corticosteroid on asthma control and asthma exacerbations

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Background: Combination therapy with long-acting β -agonists (LABAs)/inhaled corticosteroids (ICSs) has become established as effective maintenance treatment for asthma.

Objective: To compare and contrast the efficacy and safety of LABAs/ICSs against different maintenance ICS strategies in adults with asthma.

Methods: Cochrane systematic reviews of randomized controlled trials (to April 2004) were identified that compared the addition of LABA to ICS against 3 inhaled corticosteroid strategies: (1) a similar dose ($n = 4312$ subjects), (2) a higher dose ($n = 4951$), and (3) a similar dose in steroid-naïve subjects ($n = 968$). The outcomes evaluated were asthma exacerbations, asthma control, and adverse effects. Pediatric studies were excluded.

Results: The addition of LABA to ICSs significantly reduced the risk of exacerbations compared with a similar ICS dose, number needed to treat = 18. The effects of LABA/ICSs on exacerbations compared with the other maintenance inhaled corticosteroid strategies were not statistically significant. LABA added to inhaled corticosteroids led to significant improvements in asthma control compared with all 3 maintenance ICS strategies. There was an increased risk of tremor with LABA/ICSs that reached significance for initial therapy, number needed to harm = 21, and compared with higher ICS doses, number needed to harm = 74.

Conclusion: Maintenance asthma therapy with LABA/ICSs has differential effects on asthma control and asthma exacerbations.

Clinical implications: The greatest benefit and least harm of LABAs comes when they are added to a similar ICS dose in adults with symptomatic asthma. (*J Allergy Clin Immunol* 2007;119:344-50.)

Key words: Asthma, long-acting beta-agonist, inhaled corticosteroid, systematic review

Combination therapy with inhaled corticosteroids (ICSs) and long-acting β -agonists (LABAs) has become established as effective maintenance treatment for asthma. LABA given as monotherapy is associated with poorer outcomes.¹⁻³ Therefore, both national and international guidelines recommend LABA only be given in combination with ICS. Most guidelines recommend commencing LABA when asthma is inadequately controlled on ICS; however, there is variation at which ICS dose to commence LABA.⁴⁻⁸ There is also emerging evidence of efficacy of LABA/ICS as initial maintenance therapy for asthma.⁹ To evaluate the optimal placement of LABA/ICS in maintenance asthma therapy, we sought to compare the relative efficacy and safety of LABA/ICS using the results of systematic reviews of randomized controlled trials (RCTs) that compared the use of LABA and ICS therapy against different maintenance ICS strategies in adults with asthma.

There is also a need to provide some balance in the literature regarding the outcomes used to evaluate LABA/ICS therapy. In Cochrane Reviews, all outcomes are presented, but conclusions are based primarily on asthma exacerbations. In many primary papers, the bronchodilatory benefits of combination therapy are emphasized. We have developed a composite score to assess asthma control specifically for use in meta-analyses and applied it to assess the role of long-acting β_2 -agonists as add-on therapy to inhaled steroids. We have used this to assess the differential effects of LABA/ICS on asthma exacerbations and asthma control.

METHODS

The Cochrane Database of Systematic Reviews of randomized trials was searched using the terms *asthma AND ((corticosteroid OR steroid) OR beclometh* OR triamcin* OR flutic* OR budes* OR betameth* OR flunis*) AND ((long AND (beta* OR*agonist* OR bronchodilator)) OR salmeterol OR eformoterol OR formoterol)*. This search identified 94 systematic reviews. Three completed systematic reviews, including RCTs to April 2004, fitted the study inclusion criteria that evaluated the addition of a LABA to ICSs compared with ICS alone. These reviews examined LABA/ICS compared with a similar ICS dose in steroid-naïve subjects with inadequately controlled asthma ($n = 968$ subjects included in meta-analysis),¹⁰ compared with a similar maintenance ICS dose in inadequately controlled asthma ($n = 4312$ subjects included in meta-analysis),¹¹ and

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TABLE I. Characteristics of LABA/ICS systematic reviews*

Citation	No. of trials	No. of subjects included in meta-analysis	Intervention ICS†	Intervention LABA	Comparison
LABA/ICS vs ICS alone (ICS-naïve) Similar ICS (ICS-naïve) comparison ¹⁰	9	968	ICS (400 > 800 µg/d)	LABA (formoterol, n = 2; salmeterol, n = 7)	ICS alone (similar dose)
LABA/ICS vs ICS alone Similar ICS comparison ¹¹	20	4312	ICS (200-400 µg/d)	LABA (formoterol, n = 11; salmeterol, n = 13)‡	ICS alone (similar dose)
LABA/ICS vs higher dose ICS Higher ICS comparison ¹²	26	4951	ICS (200-1000 µg/d)	LABA (formoterol, n = 7; salmeterol n = 20)‡	ICS alone (400-2000 µg/d; higher dose)

*All participants were adults with inadequately controlled asthma with mild to moderate airway obstruction.

†ICS dose expressed as beclomethasone equivalent µg/d.

‡Some trials included more than 1 comparison.

Abbreviations used

- ICS: Inhaled corticosteroid
- LABA: Long-acting β-agonist
- NNH: Number needed to harm
- NNT: Number needed to treat
- OCS: Oral corticosteroid
- PEF: Peak expiratory flow
- RCT: Randomized controlled trial
- RR: Relative risk
- SMD: Standardized mean difference
- WMD: Weighted mean difference

compared with a higher maintenance ICS dose in inadequately controlled asthma (4951 subjects included in meta-analysis)¹² (Table I and this article's Table E1 in the Online Repository at www.jacionline.org).

Data were extracted from the meta-analyses, and efficacy and harm estimates were calculated for each ICS strategy. The outcomes included were exacerbations requiring oral corticosteroids (OCS), indices of asthma control, and adverse effects. Pediatric studies were specifically excluded because there were insufficient pediatric studies to examine the effect across all 3 systematic reviews.

Asthma control was assessed as a composite score using 3 relevant outcomes that evaluated the change from baseline in morning peak expiratory flow (PEF; L/min), reduction in β-agonist use (puffs/d), and percent symptom-free days. Each of these outcomes was combined as discrete subgroups weighted equally and pooled to create a composite asthma control score using a standardized mean difference (SMD) for each ICS strategy. To maintain statistical integrity, the number of subjects for the intervention and control groups in each study was divided by the number of subgroups that the study was in for each meta-analysis. The direction for rescue β-agonist use was reversed to represent the reduction rather than improvement in β-agonist use to enable all outcomes to be in the same direction. Sensitivity analyses were conducted to assess the effects of other potential outcome combinations, pooling different studies in the analyses, and different variance estimates.

Our choice of which outcomes to include in the meta-analysis was determined by the asthma control construct, feasibility, and

sensitivity analyses. The outcomes that were reported in the most number of studies, with the most number of subjects, and that were reported in the same way were included in the final score (see this article's Tables E2-E4 in the Online Repository at www.jacionline.org). A sensitivity analysis identified that the same results were evident whether we included only studies that reported all 3 outcomes or all studies reporting at least 1 of the outcomes, demonstrating the robustness of the asthma control composite score (Figs 1-3). We chose to include the latter because this led to a greater number of subjects and a more precise estimate of effect. The component variables were weighted on the basis of their variance and sample size, as is standard meta-analytic technique. The magnitude of the SMD was similar across each of the component variables of asthma control, such that the use of different measurement scales did not allow 1 component to dominate the control score. These sensitivity analyses confirmed that the asthma control variable derived by meta-analysis was robust.

Exacerbations and adverse effects were assessed using the relative risk (RR) from the meta-analyses for each ICS strategy. Significant categorical outcomes were reported as the number needed to treat (NNT) or number needed to harm (NNH) calculated for each ICS strategy from the RR and control group event rates from the meta-analyses.

The data for this analysis were extracted from the pooled results reported from the outcomes in the included reviews. These included the RR with 95% CI for dichotomous outcomes, a weighted mean difference (WMD) with 95% CI for continuous outcomes using the same unit of measure, and a SMD with 95% CI for continuous outcomes using different units of measure. The RR is the probability of experiencing an outcome when treated compared with the probability of experiencing that outcome if untreated, with values of <1 indicating a favorable treatment effect. For a WMD, each trial is given a weight based on the inverse-variance method of meta-analysis resulting in a combined mean difference and 95% CI. The SMD is calculated from the mean difference divided by a SD.¹³ The composite asthma control score was combined using a SMD with random-effects (DerSimonian-Laird) model.¹⁴

RESULTS

Exacerbations

Long-acting β-agonist/ICS combination therapy was superior to ICS alone in preventing exacerbations

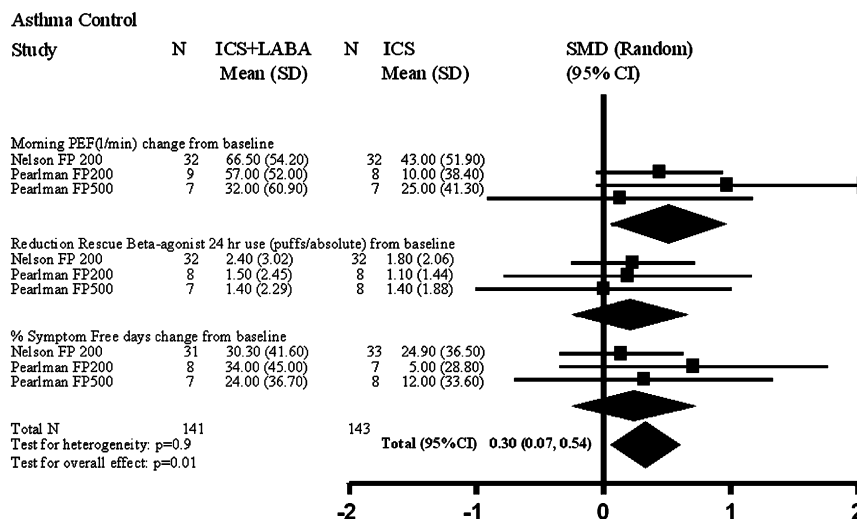


FIG 1. LABA/ICS vs similar ICS dose (ICS-naive)¹⁰ metanalysis including studies reporting all 3 outcomes. FP, Fluticasone propionate.

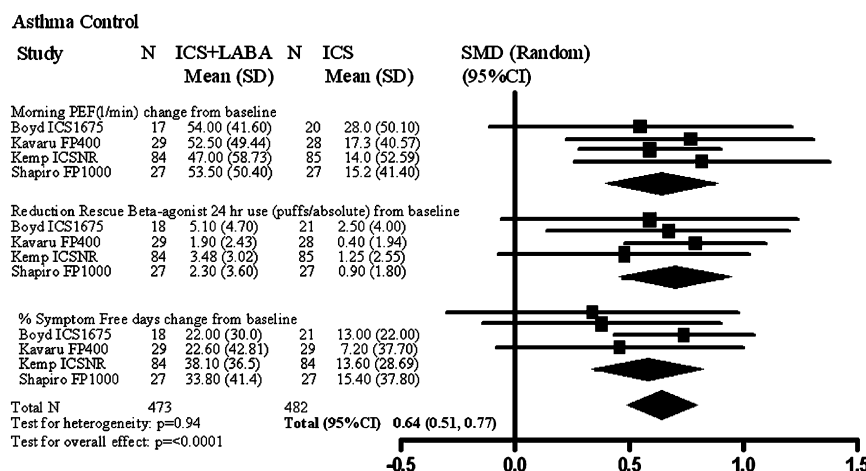


FIG 2. LABA/ICS vs similar ICS dose¹¹ metanalysis including studies reporting all 3 outcome. ICSNR, Inhaled corticosteroid type not reported.

requiring OCS compared with a similar ICS dose (Table II, Fig 4). Treatment of 18 people with LABA/ICS combination therapy prevented 1 person from experiencing a severe exacerbation compared with a similar ICS dose alone (NNT [95% CI] = 18 [13-32]; Table II). When comparing LABA/ICS to a higher ICS dose, there was no statistically significant group difference on the risk of exacerbations requiring OCS. Similarly, when the combination of LABA/ICS was compared with ICS alone, in steroid-naive patients with asthma, no group difference on exacerbation was observed (Fig 4).

Asthma control

Asthma control improved significantly with LABA/ICS combination therapy compared with all ICS dose strategies (Fig 4). In comparison with a similar or higher ICS dose strategy, there were significant improvements

across all outcomes contributing to asthma control: morning PEF (L/min), rescue β -agonist use, and percent symptom-free days (Table III). In steroid-naive people with asthma, there were significant improvements in morning PEF (L/min) and a nonsignificant improvement in percent symptom-free days and reduction in rescue β -agonist use for the LABA/ICS combination group (Table III).

Sensitivity analysis

Sensitivity analyses were conducted that included (1) assessing all available outcomes for inclusion; (2) including only studies reporting all 3 control outcomes of morning PEF, rescue β -agonist use, and percent symptom-free days; and (3) the influence of the SMDs of each variable on the included outcomes. Morning PEF was included in preference to FEV₁ because it was reported

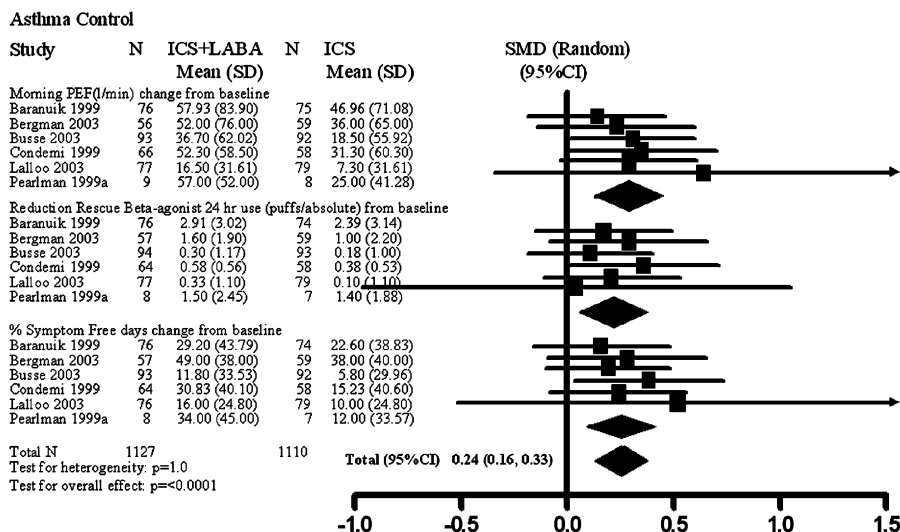


FIG 3. LABA/ICS vs higher ICS dose¹² metanalysis including studies reporting all 3 outcomes.

TABLE II. The effects of the addition of LABAs to ICS across different ICS regimens on exacerbations requiring OCS

ICS regimen	RR (95%CI)	n	Intervention n (%)	Control n (%)	NNT (95%CI)
Similar (ICS-naive)	1.19 (0.75-1.88)	514	35 (13.6%)	29 (11.3%)	Not significant
Similar	0.80 (0.73-0.89)	3625	423 (23.3%)	518 (28.6%)	18 (13-32)
Higher	0.88 (0.76-1.01)	4140	295 (14.1%)	334 (16.3%)	Not significant

with greater consistency in the systematic reviews. Similarly, percent symptom-free days and overall (24-hour) rescue β -agonist use were reported in all 3 systematic reviews. The asthma control variables were chosen on the basis of consistency of reporting (see Tables E2-E4 in this article's [Online Repository](#) at www.jacionline.org). Deriving the asthma control variable using meta-analysis that included only those studies that reported all 3 outcomes gave similar results to using all of the available data (Table III). The magnitude of the SMDs was found to be similar for the individual outcomes and for the pooled result for the similar and higher ICS dose strategies, but tended to be higher for morning PEF in steroid-naive subjects (Table III).

Safety

The addition of LABA to ICS therapy led to an increase in tremor. This was not significant compared with a similar ICS dose strategy. For every 21 steroid-naive subjects with asthma who received ICS/LABA combination therapy (NNH [95% CI] = 21 [5-53]), and every 74 people compared with a higher ICS dose strategy (NNH [95% CI] = 74 [33-242]), 1 person experienced tremor (Table IV). There was no difference in withdrawals caused by adverse events or occurrence of headache compared with all 3 ICS strategies (Table IV) and no difference in total withdrawals compared with a similar ICS dose in ICS-naive subjects or a higher ICS dose. There were significantly fewer total withdrawals compared with a

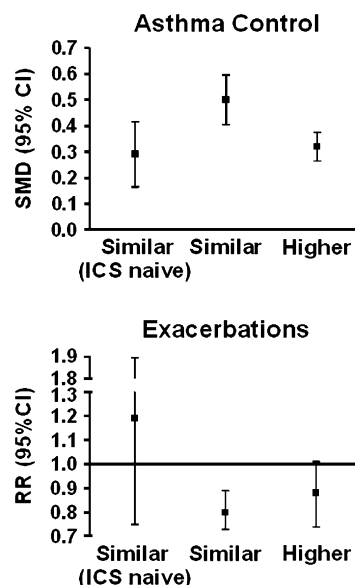


FIG 4. Efficacy of LABA/ICS on asthma control and exacerbations. Similar (ICS-naive): LABA/ICS vs similar dose ICS alone in steroid-naive inadequately controlled asthma.¹⁰ Asthma control: N trials = 5; N subjects = 968. Exacerbations: N trials = 3; N subjects = 514. Similar: LABA/ICS vs a similar maintenance dose ICS alone in inadequately controlled asthma.¹¹ Asthma control: N trials = 13; N subjects = 4312. Exacerbations: N trials = 12; N subjects = 3625. Higher: LABA/ICS vs a higher maintenance dose ICS alone in inadequately controlled asthma.¹² Asthma control: N trials = 14; N subjects = 4951. Exacerbations: N trials = 13; N subjects = 4140. A positive SMD favors LABA/ICS; a negative SMD favors ICS.

TABLE III. Efficacy for the addition of LABAs to different ICS strategies compared with ICS alone on asthma control variables

Outcome	Similar (ICS-naive)				Similar				Higher			
	n*	SMD (95% CI)	P value	Weight	n*	SMD (95% CI)	P value	Weight	n*	SMD (95% CI)	P value	Weight
Change from baseline												
Morning peak flow (L/min)	438	0.44 (0.25, 0.63)	<.001	44.82%	2741	0.54 (0.41, 0.67)	<.001	56.43%	2773	0.36 (0.27, 0.44)	<.001	55.8%
Rescue β -agonist use (puffs/24 h)	436	0.18 (-0.04, 0.39)	.10	45.47%	1071	0.42 (0.22, 0.62)	<.001	26.62%	1031	0.22 (0.09, 0.34)	<.001	21.02%
% Symptom-free days	94	0.25 (-0.16, 0.66)	.23	9.70%	500	0.55 (0.36, 0.73)	<.001	16.95%	1147	0.33 (0.21, 0.44)	<.001	23.18%
Asthma control (morning PEF + β_2 use + % symptom-free days)	968	0.29 (0.17, 0.42)	<.001	100%	4312	0.50 (0.40, 0.59)	<.001	100%	4951	0.32 (0.27, 0.38)	<.001	100%
Asthma control (sensitivity analysis: including only those trials reporting all 3 outcomes)	284	0.30 (0.07, 0.54)	.01		955	0.64 (0.51, 0.77)	<.001		2237	0.24 (0.16, 0.33)	<.001	

*Adjusted number of subjects included in this analysis.

TABLE IV. Risk of side effects with the addition of LABAs to ICS compared with different ICS strategies

Review	Outcome	RR (95% CI)	n	Intervention, n (%)	Control, n (%)	NNH (95% CI)
Similar (ICS-naive)	Tremor	5.05 (1.33-19.17)	339	12 (7.1%)	2 (1.2%)	21 (5-53)
	Headache	1.92 (0.54-6.85)	306	6 (3.9%)	3 (2.0%)	Not significant
	Withdrawals because of adverse events	1.71 (0.68-4.27)	765	11 (2.9%)	6 (1.6%)	Not significant
	Total withdrawals	0.89 (0.64-1.23)	798	57 (14.3%)	64 (16.0%)	Not significant
Similar	Tremor	2.77 (0.73-10.46)	1795	25 (27.9%)	6 (0.7%)	Not significant
	Headache	1.07 (0.79-1.44)	2279	71 (5.9%)	63 (5.8%)	Not significant
	Withdrawals because of adverse events	1.2 (0.88-1.65)	4960	86 (3.4%)	66 (2.7%)	Not significant
	Total withdrawals	0.87 (0.77-0.98)	5566	411 (14.0%)	438 (16.7%)	NNT (95% CI) 47 (27-300)
Higher	Tremor	2.96 (1.6-5.45)	3731	50 (2.5%)	12 (0.7%)	74 (33-242)
	Headache	0.96 (0.83-1.11)	4594	271 (11.2%)	239 (11.0%)	Not significant
	Withdrawals because of adverse events	0.93 (0.70-1.23)	6248	87 (2.8%)	93 (3.0%)	Not significant
	Total withdrawals	0.92 (0.82-1.03)	7481	509 (13.1%)	518 (14.4%)	Not significant

similar ICS dose alone (RR [95% CI] = 0.87 [0.77-0.98]; Table IV).

DISCUSSION

This synthesis of the level 1 evidence shows a differential effect of the addition of LABA to ICS maintenance therapy on the key clinical outcomes of asthma exacerbations and asthma control. LABA/ICS improved asthma control in each setting tested; however, a beneficial effect on asthma exacerbations was seen only with the addition of LABA to ICS compared with remaining with the same ICS dose. In steroid-naive subjects, there was no benefit of LABA/ICS over ICS alone on asthma exacerbations. The addition of LABA resulted in an increased risk of tremor.

However, this risk was outweighed by the benefits of LABA/ICS combination therapy and the reduced need to increase or maintain high-dose ICSs and their associated side effects.¹⁵ The greatest benefit of LABA/ICS combination therapy occurred when they were compared with a similar ICS dose in adults with poorly controlled asthma.

The placement of LABA/ICS in recommendations for maintenance asthma therapy is of great interest to clinicians, policy makers, and the pharmaceutical industry. This work examines the results of RCTs that have been evaluated by systematic review using the Cochrane Airways Review Group methodology.¹⁶ These procedures ensure that the high quality evidence in a RCT is synthesized using measures to minimize bias.¹⁷ There are a variety of different strategies available with LABA/ICS for asthma. It can be difficult for clinicians to evaluate

multiple interventions and multiple outcomes to recommend the best therapy when studies emphasize different outcomes in their results. This is a particular issue for LABA, because they are potent bronchodilators and have important positive effects related to bronchodilation, but may have negative effects on other outcomes such as airway inflammation.¹⁸ We therefore sought to achieve a simple but accurate representation of treatment effect by comparing the results of key outcomes across different treatment strategies. This approach was found to be a successful way to evaluate ICS doses in asthma¹⁵ and was used as part of a successful strategy to reduce the excessive doses of ICS used in Australia.¹⁹

We also sought to report the effects of treatment on asthma control and report the novel assessment of asthma control using meta-analysis. Asthma control has emerged as an important treatment variable in asthma.^{20,21} It is now a recognized aim of therapy and is increasingly being incorporated into asthma management guidelines. Asthma control is a composite variable that represents domains including symptoms, lung function, and short-acting β -agonist requirements. In individual patients, it can be assessed by questionnaires that contain items that address these domains.²² For the purposes of this systematic review, we used a novel approach and developed a composite variable that contained each of these items: β -agonist use, PEF, and symptom-free days. We used conventional meta-analytical technique to combine these items into a single variable of asthma control. Because each variable used a different measurement scale, the results were expressed as a SMD. This converted effect sizes into SD units and allowed a comparison across scales,¹³ with results expressed in dimensionless SD units.

Several different asthma control measures are available for use in individual patients and clinical trials. The measure we have developed is suitable for use in the meta-analysis of clinical trials. Our control score addresses similar domains to the individual control scores by targeting the domains of peak flow, rescue bronchodilator use, and symptoms. It is therefore consistent with the concept of asthma control as a multidimensional variable. The scaling of our score differs significantly from individual scores. The individual score uses category scales that are summed to give a total score. In some circumstances, the score can be related to specific clinical assessments²⁰⁻²² and in a sense is calibrated against clinical judgment. Our score is scaled using SMD units for the specific purpose of allowing comparison across interventions. It is not suitable for individual patient assessment, but has been designed to permit the assessment of asthma control in the meta-analysis of several RCTs, and allow the comparison of therapies across trials.

There was a consistent effect of improved asthma control with the addition of LABA. When LABA were added to a similar or higher dose ICS in corticosteroid users, each of the control subdomains showed significant improvement. In corticosteroid-naïve asthma, the same trends were seen; however, the effect was less striking, with only the PEF subdomain showing significance.

When comparing exacerbation rates, the CI for steroid-naïve subjects was large, indicating an inadequate sample size to eliminate benefit or harm with the addition of LABA. Similarly, when comparing LABA/ICS with a higher dose ICS alone, the wide 95% CI only marginally ruled out a significant reduction in exacerbation rates for LABA/ICS. Since the publication of these systematic reviews, further RCTs have been published comparing LABA/ICS to a similar ICS dose in steroid-naïve subjects and a similar maintenance ICS dose.²³⁻²⁸ The results of these RCTs support the results of the systematic reviews included in this analysis.

The studies did not address the effects of LABA/ICS on asthma mortality. This is an important issue² that has recently resulted in a black box warning for the use of LABA in asthma.³ Although the total sample size in this analysis was large, asthma death is a rare event that requires evaluation in very large population samples.² Our results add to the debate by highlighting differential effects of LABA on asthma outcomes that will need to be considered when recommending therapy in asthma.

There remains an additional treatment option that has not been evaluated in systematic reviews. This compares low-dose ICS with high-dose ICS in combination with LABA. The Formoterol and Corticosteroid Establishing Therapy study²⁹ evaluated this option in people taking an initial ICS dose of 1600 $\mu\text{g}/\text{d}$ and found a significant reduction in asthma exacerbations (RR [95% CI] = 0.50 [0.36-0.68]) when budesonide 800 $\mu\text{g}/\text{LABA}$ was compared with budesonide 200 $\mu\text{g}/\text{d}$. This also appeared to improve asthma control variables, although the lack of reported variance for the measures has prevented meta-analysis of these results.

The results of this study, as shown in Fig 4, allow a rapid assessment of the relative efficacy of LABA/ICS against different ICS comparison strategies. Systematic reviews of asthma therapy have seldom evaluated asthma control as a variable because of inconsistent measurement and/or reporting of key variables across different trials. The strategy used in this study provides a means to examine this concept in meta-analyses in the future. In conclusion, LABA/ICS combination therapy consistently improves measures of asthma control and reduces exacerbations in some settings. The greatest benefits appear when added to the same dose of ICS compared with remaining with the same ICS dose.

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