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# Inhaled Reliever Therapies for Asthma
## A Systematic Review and Meta-Analysis

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**IMPORTANCE** The optimal inhaled reliever therapy for asthma remains unclear.

**OBJECTIVE** To compare short-acting β agonists (SABA) alone with SABA combined with inhaled corticosteroids (ICS) and with the fast-onset, long-acting β agonist formoterol combined with ICS for asthma.

**DATA SOURCES** The MEDLINE, Embase, and CENTRAL databases were searched from January 1, 2020, to September 27, 2024, without language restrictions.

**STUDY SELECTION** Pairs of reviewers independently selected randomized clinical trials evaluating (1) SABA alone, (2) ICS with formoterol, and (3) ICS with SABA (combined or separate inhalers).

**DATA EXTRACTION AND SYNTHESIS** Two reviewers independently extracted data and assessed risk of bias. Random-effects meta-analyses synthesized outcomes. GRADE (Grading of Recommendations Assessment, Development, and Evaluation) was used to evaluate the certainty of evidence.

**MAIN OUTCOMES AND MEASURES** Asthma symptom control (5-item Asthma Control Questionnaire; range, 0-6, lower scores indicate better asthma control; minimum important difference [MID], 0.5 points), asthma-related quality of life (Asthma Quality of Life Questionnaire; range, 1-7, higher scores indicate better quality of life; MID, 0.5 points), risk of severe exacerbations, and risk of serious adverse events.

**RESULTS** A total of 27 randomized clinical trials (N = 50 496 adult and pediatric patients; mean age, 41.0 years; 20 288 male [40%]) were included. Compared with SABA alone, both ICS-containing relievers were associated with fewer severe exacerbations (ICS-formoterol risk ratio [RR], 0.65 [95% CI, 0.60-0.72]; risk difference [RD], −10.3% [95% CI, −11.8% to −8.3%]; ICS-SABA RR, 0.84 [95% CI, 0.73-0.95]; RD, −4.7% [95% CI, −8.0% to −1.5%]) with high certainty. Compared with SABA alone, both ICS-containing relievers were associated with improved asthma control (ICS-formoterol RR improvement [MID] in total score, 1.07 [95% CI, 1.04-1.10]; RD, 4.1% [95% CI, 2.3%-5.9%]; ICS-SABA RR, 1.09 [95% CI, 1.03-1.15]; RD, 5.4% [95% CI, 1.8%-8.5%]) with high certainty. In an indirect comparison with ICS-SABA, ICS-formoterol was associated with fewer severe exacerbations (RR, 0.78 [95% CI, 0.66-0.92]; RD, −5.5% [95% CI, −8.4% to −2.0%]) with moderate certainty. Compared with SABA alone, ICS-formoterol (RD, −0.6% [95% CI, −1.3% to 0%]) was not associated with increased risk of serious adverse events (high certainty) and ICS-SABA (RD, 0% [95% CI, −1.1% to 1.2%]) was not associated with increased risk of serious adverse events (moderate certainty).

**CONCLUSIONS AND RELEVANCE** In this network meta-analysis of patients with asthma, ICS combined with formoterol and ICS combined with SABA were each associated with reduced asthma exacerbations and improved asthma control compared with SABA alone.

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Supplemental content

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Asthma has a global prevalence of 262 million people and is characterized by airway inflammation and variable airflow obstruction.[1] Reliever inhalers, including bronchodilator-only relievers (short-acting β agonists [SABA]), such as albuterol, or inhaled corticosteroids (ICS) with either SABA or formoterol, are indicated for patients with asthma to acutely relieve symptoms of dyspnea, wheezing, or cough.[1] Although the Global Initiative for Asthma (GINA)[1] and the National Asthma Education and Prevention Program[2] recommend ICS-formoterol as the preferred reliever over SABA alone, the US Food and Drug Administration (FDA) recently approved ICS-SABA as a reliever inhaler; the optimal asthma reliever remains unclear.[3] Furthermore, guideline recommendations do not sufficiently differentiate between ICS-SABA and SABA-alone relievers, and the relative benefits of ICS-formoterol compared with ICS-SABA on clinical outcomes remain unclear.[1,2] This systematic review evaluated inhaled relievers for improving outcomes in asthma.

### Key Points

**Question** In people with asthma, compared with short-acting β agonists (SABA) alone, is the combination of SABA with inhaled corticosteroids (ICS-SABA) and the combination of formoterol with inhaled corticosteroids (ICS-formoterol) associated with better asthma outcomes?

**Findings** In this systematic review and network meta-analysis that included 27 randomized clinical trials (50 496 adult and pediatric patients), compared with SABA alone, ICS-SABA was associated with a 4.7% reduction in risk of severe exacerbations and ICS-formoterol was associated with a 10.3% reduction in severe exacerbations, without an increase in adverse events.

**Meaning** Both combined ICS with SABA and ICS with formoterol were associated with lower risks of severe asthma exacerbations compared with SABA alone.

## Methods

This prospectively registered systematic review (PROSPERO CRD42023486453) is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (eMethods 1 in Supplement 1).

### Search Strategy and Selection Criteria

We systematically searched the MEDLINE, Embase, and CENTRAL databases from January 1, 2020, to September 27, 2024, for published and unpublished randomized clinical trials (RCTs) reported in any language that evaluated eligible inhaled reliever therapies for any type of asthma (see eMethods 2 in Supplement 1 for search strategies used for each database). Additionally, studies included in prior relevant systematic reviews were evaluated for inclusion.[4,5] To identify additional eligible studies, we searched reference lists of included studies and the articles citing them using Web of Science (all databases). Eligible inhaled reliever therapies included: (1) bronchodilator-only relievers (SABA); (2) fast-onset, long-acting β agonist alone; (3) ICS and fast-onset, long-acting β agonist; and (4) ICS and SABA. Eligible trials compared different reliever therapies and had similar levels of maintenance therapy between clinical trial groups (defined by GINA 2024 step classifications).[1]

### Study Selection and Data Extraction

Two reviewers (D.G.R., D.M.F.) screened titles and abstracts and reviewed full texts independently using Covidence (Veritas Health). Two reviewers (D.G.R., D.M.F.) independently extracted data using standardized and prepiloted extraction forms. Reviewers resolved disagreements through discussion and, if necessary, through discussion with a third reviewer (D.K.C.). We collected study bibliographic information, trial design, patient characteristics, intervention and comparator characteristics, outcomes according to randomized group, and sources of funding. See eMethods 3 in Supplement 1 for additional methods details.

### Outcomes

Outcomes were selected and prioritized based on input from a multistakeholder guideline development group, including clinicians (internists, pediatricians, nurse practitioners, physician assistants), asthma experts (allergists-immunologists and pulmonologists), and patient and caregiver partners (people with asthma and their family or caregivers). Outcomes consisted of asthma symptom control, asthma-related quality of life, severe asthma exacerbations (defined as use of systemic corticosteroids, emergency department visits, and/or hospitalizations) and their individual components, adverse events (overall, serious adverse events, treatment discontinuations due to adverse events), and overall mortality.

### Risk-of-Bias Assessment

Following a similar approach to the data extraction process, 2 reviewers (D.G.R., D.M.F.) assessed the risk of bias for each outcome of each study using a modified Cochrane Risk of Bias tool version 2 (RoB 2.0) for RCTs.[6] We further classified assessments with some concerns regarding risk of bias as some concerns, probably high and some concerns, probably low. If at least 1 domain was high or probably high risk for bias, we considered the study outcome to be at high risk of bias. Potential examples for classifying a study outcome as overall high risk of bias included a lack of allocation concealment, high rates of missing data, and the use of subjective outcome measurements in an unblinded setting.

### Evaluating Evidence Certainty

We evaluated the certainty (quality) of the evidence using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach,[7,8] with certainty being classified as high, moderate, low, or very low. Evidence from RCTs starts at high certainty and may be rated down for risk of bias, imprecision, inconsistency, indirectness, publication bias, intransitivity (the potential imbalance of effect modifiers among studies forming an indirect comparison), and incoherence (the potential disagreement between direct and indirect evidence).[7,8] Bias was assessed by considering the contribution and consistency of studies at high vs low risk of bias,



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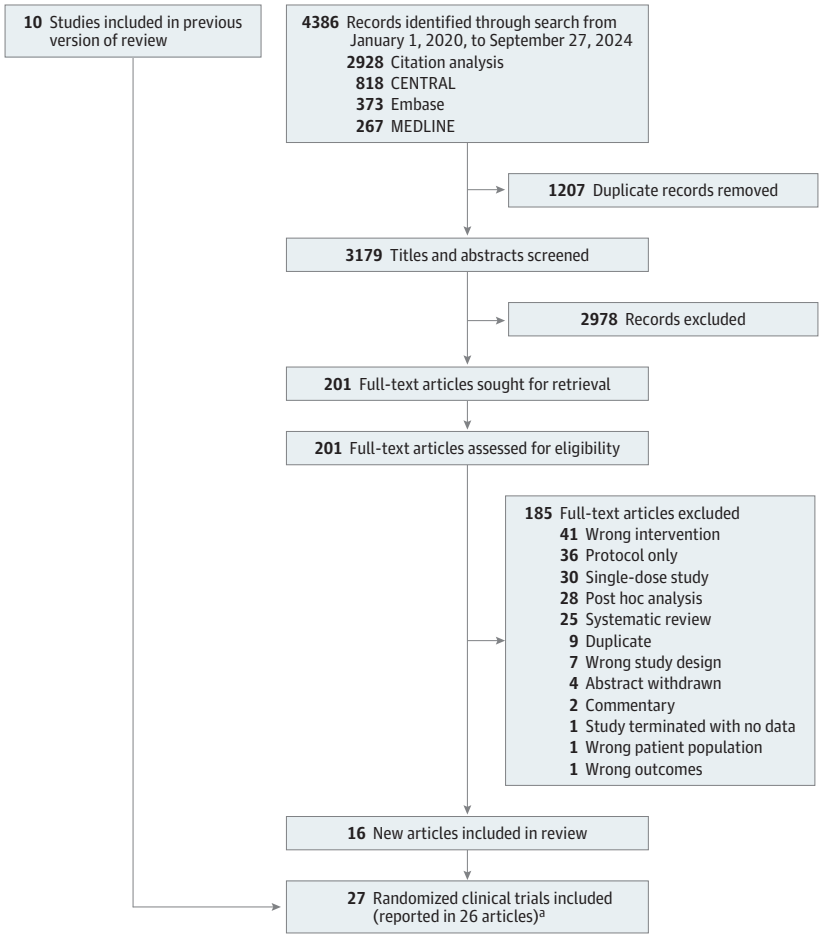
Figure 1. Study Selection and Flowchart for Systematic Review and Meta-Analysis of Asthma Relievers




[a]One publication reports 2 separate randomized clinical trials.[32]

imprecision and inconsistency were assessed by comparing the individual and pooled estimates and CIs to small effect thresholds established by our linked guideline panel,[7-9] and indirectness was assessed by evaluating whether the studies addressed the review question. We evaluated for intransitivity by evaluating for imbalanced distribution of credible effect modifiers comprising comparisons among the networks and comparing estimates from unadjusted models with those produced by models adjusted for covariates (eg, GINA 2024 steps[1]). We assessed incoherence by assessing the consistency and contribution of direct and indirect estimates to the network estimates using node-splitting models.

## Data Synthesis

We used the R meta package (R Foundation) to calculate pairwise effect estimates for each pairwise comparison using restricted maximum likelihood random-effects meta-analyses (eMethods 3 in Supplement 1). Following GRADE guidance, we used linear transformation to the most commonly used scale if multiple instruments measured the same outcome.[9]

We used the R netmeta package (R Foundation) to perform frequentist random-effects network meta-analyses using restricted maximum likelihood estimators (eMethods 3 in Supplement 1). We calculated absolute risks using the median risk among participants assigned to bronchodilator-only relievers (SABA) and ICS-SABA as baseline risks in the included trials in primary analyses (eMethods 3 in Supplement 1).[10] For severe exacerbation estimates, recognizing the difference in exacerbation risk between groups of patients, we generated absolute risk estimates for different GINA 2024 steps (based on the classification of asthma maintenance therapies in accordance with the GINA 2024 guidelines[1]), with GINA step 1 patients representing a lower-risk group and GINA step 4 patients representing a higher-risk group. For all continuous outcomes, we conducted responder analyses by modeling risk differences and 95% CIs for achieving at least the minimum important difference (MID) for each scale (5-item Asthma Control Questionnaire [ACQ-5]: 0.5-point decrease; Asthma Quality of Life Questionnaire [AQLQ]: 0.5-point increase). We calculated the effective sample size for each indirect comparison from the network meta-analysis.[11]

We assessed publication bias by inspecting funnel plots for small study effects, evaluating the relationship between study findings and funding, and through a review of trial registries (using Cochrane CENTRAL, which includes ClinicalTrials.gov and the World Health Organization's International Clinical



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Table. Characteristics of Included Trials in the Systematic Review and Meta-Analysis of Asthma Inhaled Reliever Therapies (N = 27)[a]

| Source | Randomized participants, No. | Age, mean (SD) [range], y | No. (%) | | Follow-up, wk | GINA step[b] | Interventions and comparators (No. randomized per group) |
|---|---|---|---|---|---|---|---|
| | | | Male | Female | | | |
| Israel et al,[14] 2022 (PREPARE) | 1201 | 47.7 (13.7) [18-75] | 196 (16) | 1005 (84) | 65 | 3 | Any SABA (601)<br>Beclomethasone dipropionate, 80 µg + any SABA (600) |
| Papi et al,[15] 2022 (MANDALA) | 3132 | 49.4 (16.4) [≥4] | 1102 (35) | 2030 (75) | 24 | 4 | Albuterol, 180 µg (1059)<br>Budesonide/albuterol, 180/80-160 µg (2073) |
| NCT03924635[16] | 42 | 49.2 (15.8) [≥18] | 15 (36) | 27 (64) | 24 | 3 | Budesonide/formoterol, 100-200/6 µg (24)<br>Salbutamol, 100 µg (18) |
| Beasley et al,[17] 2019 (Novel START) | 675 | 35.6 (14.1) [18-75] | 307 (46) | 368 (54) | 52 | 1 | Albuterol, 200 µg (227)<br>Budesonide/formoterol, 200/6 µg (222) |
| O'Byrne et al,[18] 2018 (SYGMA 1) | 3849 | 39.6 (16.6) [≥12] | 1496 (39) | 2353 (61) | 52 | 1 | Terbutaline, 0.5 mg (1280)<br>Budesonide/formoterol, 200/6 µg (1279) |
| Lazarinis et al,[19] 2014 | 66 | 28.4 (11.1) [≥12] | 30 (45) | 36 (55) | 6 | 1 | Terbutaline, 0.5 mg (22)<br>Budesonide/formoterol, 200/6 µg (23) |
| Takeyama et al,[20] 2014 | 63 | 40.0 (NR) [16-80] | 23 (37) | 40 (63) | 48 | 4 | Salbutamol, 100 µg (31)<br>Budesonide/formoterol, 160/4.5 µg (32) |
| Atienza et al,[21] 2013 (SAKURA) | 2091 | 45.7 (14.5) [≥16] | 677 (32) | 1413 (68) | 52 | 3 | Terbutaline, 0.4 mg (1042)<br>Budesonide/formoterol, 160/4.5 µg (1049) |
| Papi et al,[22] 2013 | 1714 | 48.0 (NR) [≥18] | 657 (38) | 1057 (62) | 48 | 2 | Salbutamol, 100 µg (857)<br>Beclomethasone dipropionate/formoterol, 100/6 µg (857) |
| Patel et al,[23] 2013 (SMART) | 303 | 42.0 (14.1) [16-65] | 94 (31) | 209 (69) | 24 | 4 | Salbutamol, 100 µg (152)<br>Budesonide/formoterol, 200/6 µg (151) |
| Martinez et al,[24] 2011 (TREXA) | 288 | 10.8 (3.1) [6-18] | 159 (55) | 129 (45) | 44 | 1 or 2 | Albuterol, 180 µg (146)<br>Beclomethasone, 80 µg + albuterol, 180 µg (142)[c] |
| Ställberg et al,[25] 2008 (SHARE) | 1776 | 43.5 (NR) [≥12] | 733 (41) | 1043 (59) | 52 | 3 | Terbutaline, 0.25-0.5 mg (456)<br>Budesonide/formoterol, 80-160/4.5 µg (887) |
| Bousquet et al,[26] 2007 | 2309 | 39.5 (NR) [≥12] | 877 (38) | 1432 (62) | 24 | 4 | Terbutaline, 0.5 mg (1155)<br>Budesonide/formoterol, 160/4.5 µg (1154) |
| Kuna et al,[27] 2007 | 3335 | NR [≥12] | 1415 (42) | 1920 (58) | 24 | 3 | Terbutaline, 0.5 mg (2228)<br>Budesonide/formoterol, 160/4.5 µg (1107) |
| Papi et al, 2007[28] (BEST) | 466 | 38.8 (13.6) [18-65] | 192 (41) | 274 (59) | 26 | 1 | Albuterol, 100 µg (119)<br>Beclomethasone/albuterol, 250/100 µg (124) |
| Cheung et al,[29] 2006 | 211 | 44.7 (13.4) [≥18] | 105 (50) | 106 (50) | 3 | 2 | Salbutamol, 100 µg (211)<br>Formoterol, 4.5 µg (211) |
| Haahtela et al,[30] 2006 (SOMA) | 93 | 35.7 (11.4) [15-63] | 28 (30) | 65 (70) | 24 | 1 | Formoterol, 4.5 µg (48)<br>Budesonide/formoterol, 160/4.5 µg (45) |
| Rabe et al,[31] 2006 | 3394 | 42.3 (NR) [≥12] | 1345 (40) | 2049 (60) | 52 | 3 | Terbutaline, 0.4 mg (1141)<br>Formoterol, 4.5 µg (1140)<br>Budesonide/formoterol, 160/4.5 µg (1113) |
| Chuchalin et al,[32] 2005 (1) | 675 | 23.5 (NR) [≥6] | 402 (60) | 273 (40) | 52 | 1 | Terbutaline, 0.5 mg (342)<br>Formoterol, 4.5 µg (333) |

(continued)

Trials Registry Platform) for completed trials without publication or reporting of results.[12]

eMethods 3 in Supplement 1 details the subgroup (risk of bias, age, therapy intensity [defined by the GINA 2024 step



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Table. Characteristics of Included Trials in the Systematic Review and Meta-Analysis of Asthma Inhaled Reliever Therapies (N = 27)[a] (continued)

| Source | Randomized participants, No. | Age, mean (SD) [range], y | No. (%) | | Follow-up, wk | GINA step[b] | Interventions and comparators (No. randomized per group) |
|---|---|---|---|---|---|---|---|
| | | | Male | Female | | | |
| Chuchalin et al,[32] 2005 (2) | 455 | 25.0 (NR) [≥6] | 232 (51) | 223 (49) | 52 | 2 | Terbutaline, 0.5 mg (227)<br>Formoterol, 4.5 µg (228) |
| O'Byrne et al,[33] 2005 | 2760 | 35.7 (NR) [4-80] | 1231 (45) | 1529 (55) | 52 | 3 | Terbutaline, 0.4 mg (909)<br>Budesonide/formoterol, 80/4.5 µg (925) |
| Vogelmeier et al,[34] 2005 | 2143 | 45.0 (NR) [≥12] | 879 (41) | 1264 (59) | 54 | 4 | Salbutamol, 100 µg (1076)<br>Budesonide/formoterol, 160/4.5 µg (1067) |
| Jain et al,[35] 2004 | 60 | NR | NR | NR | 26 | NR | Albuterol, 200 µg (31)<br>Formoterol, 4.5 µg (29) |
| Pauwels et al,[36] 2003 (RELIEF) | 18 124 | 39.0 (NR) [≥6] | 7793 (43) | 10 331 (57) | 24 | 2 | Salbutamol, 200 µg (9060)<br>Formoterol, 4.5 µg (9064) |
| Ind et al,[37] 2002 | 357 | 47.0 (NR) [≥18] | 143 (40) | 214 (60) | 12 | 1 | Terbutaline, 0.5 mg (181)<br>Formoterol 4.5 µg (176) |
| Villa et al,[38] 2002 | 552 | NR [6-17] | NR | NR | 26 | NR | Terbutaline, 0.25 mg (276)<br>Formoterol, 4.5 µg (276) |
| Tattersfield et al,[39] 2001 | 362 | 47.0 (NR) [≥18] | 157 (43) | 205 (57) | 12 | 2 | Terbutaline, 0.5 mg (180)<br>Formoterol, 4.5 µg (182) |

Abbreviations: GINA, Global Initiative for Asthma; NR, not reported; SABA, short-acting β agonist.

[a] Smoking status, reported in 10 trials (37%), was 0%-19% current, 8%-42% prior, and 44%-87% never.

[b] GINA step is based on the classification of asthma maintenance therapies in accordance with the GINA 2024 guidelines.[1] GINA steps range from 1 to 5, with higher steps representing more intense asthma maintenance therapies.

[c] Interventions administered using separate inhalers.

classifications[1]], and asthma type [type 2 high vs non-type 2 high, defined using baseline peripheral blood eosinophil count]), with credibility appraised using the Instrument for assessing the Credibility of Effect Modification Analyses[13] and sensitivity analyses. Sensitivity analyses were based on the use of imputation of missing SDs using established Cochrane guidance (eMethods 3 in Supplement 1), reliever strategies using combined or separate inhalers, and between-study variance estimators.

We used R version 4.3.2 (R Foundation) for pairwise and network meta-analyses and Stata version 18 (StataCorp) for sample size calculations.

## Results

The systematic search yielded 3179 unique citations and 201 potentially relevant full articles. Of these, 26 articles[14-39] reporting 27 unique RCTs (50 496 patients) were included (**Figure 1**). The **Table** summarizes characteristics of the included trials. Participants in the 27 RCTs had a mean age of 41.0 years (range of means, 10.8-49.4 years) and the median percentage of male participants was 41% (range, 16%-60%). The treatment duration of the included RCTs was a median of 26 weeks (range, 3-65 weeks). All included RCTs of fast-onset, long-acting β agonists (alone or combined with an ICS) as a reliever therapy evaluated formoterol. Two trials (7%) evaluated patient populations composed entirely of people aged 18 years or younger (pediatrics).[24,38] Consistent associations were found between adult and pediatric studies for all outcomes. All included trials were conducted in outpatient settings. No included clinical trials evaluated levalbuterol. For all RCTs, prescription of oral corticosteroids for severe exacerbations was based on physician discretion.

Of 138 assessments of risk of bias for study outcomes, 113 (82%) had a low overall risk of bias (eResults 1 and 2 in Supplement 1). Visual inspection of funnel plots, comparison of direct and indirect estimates, and evaluation of potential effect modifier distributions across studies showed no strong evidence of small study effects, network incoherence, or intransitivity (eResults 3-5 in Supplement 1). Network plots and league tables are shown in eResults 5 and 6 in Supplement 1.

### Outcomes

#### Severe Exacerbations

A total of 22 RCTs,[14-18,20-28,31-34,36,37,39] including 45 117 patients, provided data for the outcome of severe asthma exacerbations (**Figures 2** and **3**; eResults 7 in Supplement 1). Compared with bronchodilator-only relievers, high-certainty evidence showed that ICS-formoterol was associated with lower risk of severe exacerbations (risk ratio [RR], 0.65 [95% CI, 0.60-0.72]; risk difference [RD], −10.3% [95% CI, −11.8% to −8.3%]). High-certainty evidence demonstrated that ICS-SABA (RR, 0.84 [95% CI, 0.73-0.95]; RD, −4.7% [95% CI, −8.0% to −1.5%]) was associated with lower risk of severe exacerbations. Similar associations for asthma-related hospitalizations and emergency department visits were observed (eResults 5 in Supplement 1). Compared with ICS-SABA, moderate-certainty evidence showed that ICS-formoterol was associated with lower risk of severe exacerbations (RR, 0.78 [95% CI, 0.66-0.92]; RD, −5.5% [95% CI, −8.4% to −2.0%]; GINA step 4). However, these absolute RDs became smaller in lower-risk patient populations (RD, −1.9% [95% CI, −3.0% to −0.7%]; GINA step 1) (**Figure 4**).

#### Asthma Symptom Control

A total of 22 RCTs,[14-24,26-34,39] including 25 233 patients, were identified for analyses of asthma symptom control measured using the ACQ-5 (scores range from 0-6, with lower scores indicating better asthma control). Compared with bronchodilator-only relievers, high-certainty evidence



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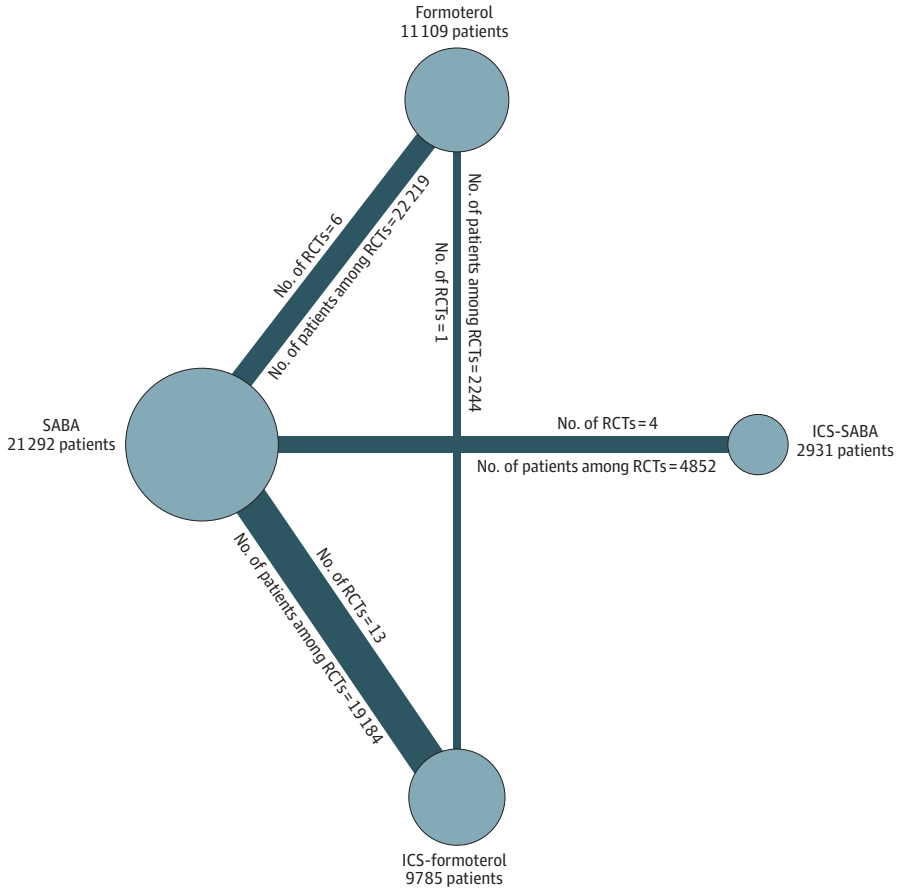
Figure 2. Network Meta-Analysis Map for Severe Exacerbation Outcomes With Bronchodilator-Only Reliever or Anti-Inflammatory Relievers[a]



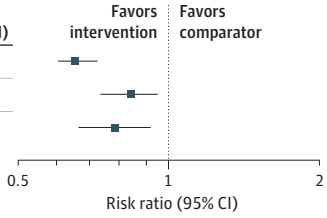

Graphical representation of network for all included RCTs. Connecting lines represent head-to-head comparisons between reliever therapies, indicated by nodes. The thickness of lines between nodes is proportional to the number of RCTs comparing the treatments. The size of the nodes is proportional to the number of patients in each treatment.

ICS indicates inhaled corticosteroids; RCTs, randomized clinical trials; and SABA, short-acting β agonists.

[a]ICS with either SABA or formoterol.

Figure 3. Network Meta-Analysis Results for Severe Exacerbation Outcomes With Bronchodilator-Only Reliever or Anti-Inflammatory Relievers[a]

| Comparison | No. of patients | No. of trials | Certainty of evidence | Network risk ratio for severe asthma exacerbations (95% CI) |
|---|---|---|---|---|
| ICS-formoterol vs SABA | 19 184 | 13 | High | 0.65 (0.60-0.72) |
| ICS-SABA vs SABA | 4852 | 4 | High | 0.84 (0.73-0.95) |
| ICS-formoterol vs ICS-SABA | 3949[b] | 22[b] | Moderate | 0.78 (0.66-0.92) |




Severe asthma exacerbations defined as use of systemic corticosteroids, emergency department visits, and/or hospitalizations. The network risk ratio incorporates data from both direct and indirect evidence and thus the network risk ratio may have a larger effective sample size than what is listed in the columns. High-certainty evidence indicates that a large randomized trial is unlikely to change the interpretation. Moderate-certainty evidence indicates that a large randomized trial may importantly change the estimate.

ICS indicates inhaled corticosteroids; and SABA, short-acting β agonists.

[a]ICS with either SABA or formoterol.

[b]Values represent the number of contributing trials in the network and a conservative estimate of the effective sample size.

showed ICS-formoterol (mean difference, −0.09 [95% CI, −0.13 to −0.05]; RR corresponding to ≥0.5-point improvement [MID] in total score, 1.07 [95% CI, 1.04-1.10]; RD, 4.1% [95% CI, 2.3%-5.9%]) and ICS-SABA (mean difference, −0.12 [95% CI, −0.19 to −0.04]; RR corresponding to ≥0.5-point improvement [MID] in total score, 1.09 [95% CI, 1.03-1.15]; RD, 5.4% [95% CI, 1.8%-8.5%]) were associated with improvements in asthma symptom control. These effect sizes were small and potentially unimportant to patients. Low-certainty evidence suggested little to no difference between ICS-SABA and ICS-formoterol in asthma symptom control (Figure 4).



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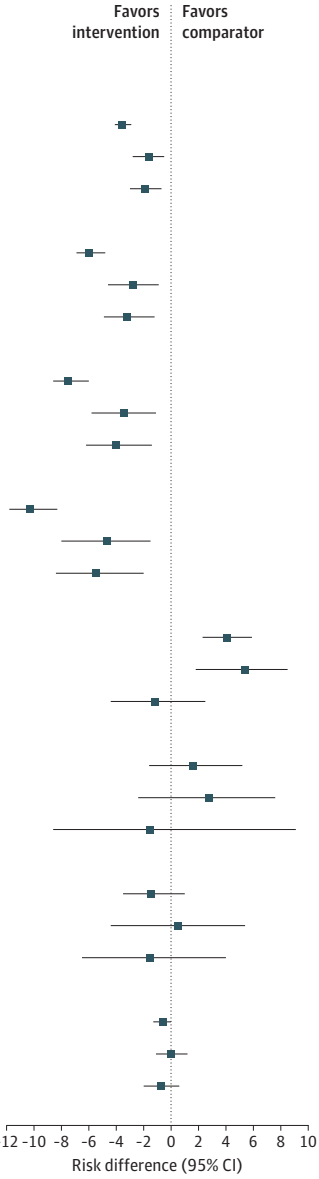
Figure 4. Summary of Network Meta-Analysis Comparisons of Bronchodilator-Only Reliever or Anti-Inflammatory Relievers[a] and Asthma Outcomes

| Group and comparison | No. of patients (No. of trials) | Patients in intervention group with outcome, % | Patients in comparator group with outcome, % | Certainty of evidence | Network risk difference (95% CI) |
|---|---|---|---|---|---|
| Severe exacerbations | | | | | |
| GINA step 1 | | | | | |
| ICS-formoterol vs SABA | 19 184 (13) | 6.7 | 10.3 | High | -3.6 (-4.1 to -2.9) |
| ICS-SABA vs SABA | 4852 (4) | 8.7 | 10.3 | High | -1.6 (-2.8 to -0.5) |
| ICS-formoterol vs ICS-SABA | 3949[b] (22) | 6.8 | 8.7 | Moderate | -1.9 (-3.0 to -0.7) |
| GINA step 2 | | | | | |
| ICS-formoterol vs SABA | 19 184 (13) | 11.2 | 17.2 | High | -6.0 (-6.9 to -4.8) |
| ICS-SABA vs SABA | 4852 (4) | 14.4 | 17.2 | High | -2.8 (-4.6 to -0.9) |
| ICS-formoterol vs ICS-SABA | 3949[b] (22) | 11.2 | 14.4 | Moderate | -3.2 (-4.9 to -1.2) |
| GINA step 3 | | | | | |
| ICS-formoterol vs SABA | 19 184 (13) | 14.0 | 21.5 | High | -7.5 (-8.6 to -6.0) |
| ICS-SABA vs SABA | 4852 (4) | 18.1 | 21.5 | High | -3.4 (-5.8 to -1.1) |
| ICS-formoterol vs ICS-SABA | 3949[b] (22) | 14.1 | 18.1 | Moderate | -4.0 (-6.2 to -1.4) |
| GINA step 4 | | | | | |
| ICS-formoterol vs SABA | 19 184 (13) | 19.2 | 29.5 | High | -10.3 (-11.8 to -8.3) |
| ICS-SABA vs SABA | 4852 (4) | 24.8 | 29.5 | High | -4.7 (-8.0 to -1.5) |
| ICS-formoterol vs ICS-SABA | 3949[b] (22) | 19.3 | 24.8 | Moderate | -5.5 (-8.4 to -2.0) |
| Improvement in asthma symptom control (ACQ-5)[c,d] | | | | | |
| ICS-formoterol vs SABA | 17 596 (13) | 61.0 | 56.9 | High | 4.1 (2.3 to 5.9) |
| ICS-SABA vs SABA | 4733 (4) | 62.3 | 56.9 | High | 5.4 (1.8 to 8.5) |
| ICS-formoterol vs ICS-SABA | 3792[b] (22) | 61.1 | 62.3 | Low | -1.2 (-4.4 to 2.5) |
| Improvement in asthma-related quality of life (AQLQ)[d,e] | | | | | |
| ICS-formoterol vs SABA | 6351 (3) | 54.0 | 52.4 | Moderate | 1.6 (-1.6 to 5.2) |
| ICS-SABA vs SABA | 3337 (2) | 55.2 | 52.4 | Moderate | 2.8 (-2.4 to 7.6) |
| ICS-formoterol vs ICS-SABA | 2188[b] (5) | 48.9 | 50.4 | Low | -1.5 (-8.6 to 9.1) |
| Overall adverse events[f] | | | | | |
| ICS-formoterol vs SABA | 8716 (7) | 47.9 | 49.4 | Moderate | -1.5 (-3.5 to 1.0) |
| ICS-SABA vs SABA | 3127 (1) | 49.9 | 49.4 | Moderate | 0.5 (-4.4 to 5.4) |
| ICS-formoterol vs ICS-SABA | 2301[b] (12) | 48.4 | 49.9 | Moderate | -1.5 (-6.5 to 4.0) |
| Serious adverse events[g] | | | | | |
| ICS-formoterol vs SABA | 15 534 (11) | 3.5 | 4.1 | High | -0.6 (-1.3 to 0) |
| ICS-SABA vs SABA | 4875 (4) | 4.1 | 4.1 | Moderate | 0 (-1.1 to 1.2) |
| ICS-formoterol vs ICS-SABA | 3820[b] (21) | 3.4 | 4.1 | Moderate | -0.7 (-2.0 to 0.6) |




The network estimates incorporate data from both direct and indirect evidence and thus the estimates may have a larger effective sample size than what is listed in the columns. Baseline risks for comparators were derived using the median risk among participants assigned to the comparator in the included trials. The risks of severe exacerbations stratified by GINA 2024 steps reflect a continuum of severity; however, many factors beyond GINA 2024 step classification, including recent history of severe exacerbation, contribute to the future risk of exacerbation. As a result, some patients may be classified in 1 category, but their absolute risk and absolute treatment effects may be optimally reflected by another estimate. Thus, the absolute treatment effects presented should not be rigidly interpreted and should be considered as a spectrum of potential risks. GINA steps are based on the classification of asthma maintenance therapies in accordance with the GINA 2024 guidelines.[1] GINA steps range from 1 to 5, with higher GINA steps representing more intense asthma maintenance therapies.

ACQ-5 indicates 5-item Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroids; and SABA, short-acting β agonists.

[a]ICS with either SABA or formoterol.

[b]Values represent the number of contributing trials in the network and a conservative estimate of the effective sample size.

[c]The ACQ-5 is a patient-reported questionnaire measuring asthma symptom control. Scores range from 0 to 6, with lower scores indicating greater asthma control. The minimum important difference for the ACQ-5 is 0.5 points.

[d]Directionality is reversed compared with other outcomes, as larger values favor the intervention.

[e]The AQLQ is a patient-reported questionnaire measuring asthma-related quality of life. Scores range from 1 to 7, with higher scores indicating greater quality of life. The minimum important difference for the AQLQ is 0.5 points.

[f]oveal adverse events defined as any adverse event reported by trial authors.

[g]Serious adverse events, defined by the US Food and Drug Administration, are adverse events that led to (1) death, (2) life-threatening states, (3) hospitalization, (4) disability or permanent damage, (5) congenital anomalies or birth defects, or (6) required intervention to prevent permanent impairment or damage.



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### Asthma-Related Quality of Life

A total of 5 RCTs,[15,18,24,27,34] including 9688 patients, were identified for asthma-related quality of life analyses. As measured using the AQLQ (scores range from 1-7, with higher scores indicating better quality of life), compared with bronchodilator-only relievers, moderate-certainty evidence showed ICS-formoterol (mean difference, 0.04 [95% CI, −0.04 to 0.13]; RR corresponding to ≥0.5-point improvement [MID] in total score, 1.03 [95% CI, 0.97-1.10]; RD, 1.6% [95% CI, −1.6% to 5.2%]) and ICS-SABA (mean difference, 0.07 [95% CI, −0.06 to 0.19]; RR corresponding to ≥0.5-point improvement [MID] in total score, 1.05 [95% CI, 0.95-1.15]; RD, 2.8% [95% CI, −2.4% to 7.6%]) were likely associated with greater asthma-related quality of life. These point estimates are likely consistent with improvements in asthma-related quality of life, albeit by small amounts that may be unimportant to patients. Low-certainty evidence suggested little to no difference between ICS-SABA and ICS-formoterol in asthma-related quality of life (Figure 4).

## Safety Outcomes

There were no associations of increased risk of harm between inhaler groups (Figure 4). Twelve RCTs (31 228 patients)[15-19,21,22,29,32,33,36] were included in these analyses for any adverse event (moderate certainty). Twenty-three RCTs (41 933 patients)[14-19,21-24,27,28,30-39] were included in analyses of serious adverse events (ICS-formoterol vs SABA alone, high certainty; ICS-SABA vs SABA alone, moderate certainty). Among the 15 studies (65%)[14,15,17,18,21-24,27,28,30,31,36,37,39] that reported specific causes of serious adverse events, the 2 most commonly reported were cardiovascular events (ICS-formoterol vs SABA alone: RD, −0.2% [95% CI, −0.5% to 0.1%]; ICS-SABA vs SABA alone: RD, −0.2% [95% CI, −0.7% to 0.4%]) and pneumonia (ICS-formoterol vs SABA alone: RD, 0.1% [95% CI, −0.1% to 0.2%]; ICS-SABA vs SABA alone: RD, 0.2% [95% CI, −0.5% to 0.8%]) (eResults 8 in Supplement 1). Twenty-one RCTs (26 539 patients)[15,17-19,21-23,25-34,37-39] were included in analyses for inhaler discontinuations due to an adverse event (ICS-formoterol vs SABA alone: RD, −0.7% [95% CI, −1.2% to −0.3%], high certainty; ICS-SABA vs SABA alone: RD, 0.3% [95% CI, −0.8% to 1.4%], moderate certainty). A total of 15 RCTs (40 425 patients)[14,15,17-19,21-23,26,27,31,32,34,36] informed analyses for mortality (ICS-formoterol vs SABA alone: RD, 0% [95% CI, −0.1% to 0.1%], high certainty; ICS-SABA vs SABA alone: RD, 0.1% [95% CI, −0.3% to 0.4%], high certainty).

## Other Analyses

In subgroup analyses, results were consistent by risk of bias, patient age, therapy intensity, and asthma type (eResults 9 in Supplement 1). Results were consistent using different imputation methods, data analysis approaches, and inhaler type (combined vs separate) (eResults 9 in Supplement 1).

# Discussion

This systematic review and meta-analysis of 27 RCTs including 50 496 adult and pediatric patients with asthma provided high-certainty evidence that, compared with bronchodilator-only relievers, anti-inflammatory reliever treatment with ICS-formoterol and ICS-SABA (combined or separate inhalers) was associated with reduced risks of severe exacerbations and modest improvements in asthma symptom control. Compared with bronchodilator-only relievers, both anti-inflammatory reliever strategies were associated with no statistically significant difference in adverse event risk. Compared with ICS-SABA, ICS-formoterol was likely associated with lower risks of severe exacerbations, but may not be associated with improvements in asthma symptoms or asthma-related quality of life.

This systematic review differs from previous reviews[4,5] in the following ways: first, compared with prior reviews, the current review used a comprehensive search strategy to identify relevant RCTs evaluating inhaled reliever therapies, included 12 trials[16,19,24,28,29,32,35-39] not covered in previous reviews, and included clinical trials for the recently FDA-approved ICS-SABA studies.[14,15] Second, this review selected clinical trials that compared different reliever strategies with the same maintenance strategies in the compared groups. Third, this review assessed patient-important outcomes. Fourth, this review did not include surface under the cumulative ranking curve for its conclusions. Surface under the cumulative ranking curve results may be less valid than the analyses used for these results. Full elaboration of the implications of the study results to clinical practice, policy, and asthma mechanistic understanding is beyond the scope of this meta-analysis.

## Limitations

This review has limitations. First, none of the identified RCTs directly compared ICS-formoterol with ICS-SABA (combined or separate inhalers) as reliever inhalers. Estimate imprecision reduced certainty about these results and findings reported here could change with a large RCT directly comparing these 2 inhalers. Second, although the included RCTs evaluated severe exacerbations as a composite of asthma-related hospitalizations, asthma-related emergency department visits, and oral corticosteroid use, few clinical trials (9 of 22) reported the effects of inhaled reliever therapies on the individual outcomes. Estimates from the small number of RCTs that reported each component separately were consistent with results for the composite outcome. Third, only 2 of the included RCTs were limited to pediatric populations.[24,38] Fourth, none of the included trials reported on whether ipratropium use was allowed in combination with albuterol. Fifth, similar to other reviews, assessing publication bias involved the assessment of funnel plots. Using funnel plots, which assess for small study effects, to infer publication bias without additional data relies on untestable assumptions.

# Conclusions

In this meta-analysis of patients with asthma, ICS combined with formoterol and ICS combined with SABA were each associated with reduced asthma exacerbations and improved asthma control compared with SABA alone.



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*Acquisition, analysis, or interpretation of data:* Rayner, Ferri, Guyatt, Brignardello-Petersen, Foroutan, Sumino, Perry, Nyenhuis, Israel, Rivera-Spoljaric, McCabe, Rangel, Press, Hall, Sue-Wah-Sing, Melendez, Orr, Winders, Gardner, Przywara, Rank, Bacharier, Mosnaim, Chu.
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