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Association of Inhaled Corticosteroids and Long-Acting β-Agonists as Controller and Quick Relief Therapy With Exacerbations and Symptom Control in Persistent Asthma
A Systematic Review and Meta-analysis

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IMPORTANCE Combined use of inhaled corticosteroids and long-acting β-agonists (LABAs) as the controller and the quick relief therapy termed *single maintenance and reliever therapy* (SMART) is a potential therapeutic regimen for the management of persistent asthma.

OBJECTIVE To conduct a systematic review and meta-analysis of the effects of SMART in patients with persistent asthma.

DATA SOURCES AND STUDY SELECTION The databases of MEDLINE via OVID, EMBASE, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews were searched from database inception through August 2016 and updated through November 28, 2017. Two reviewers selected randomized clinical trials or observational studies evaluating SMART vs inhaled corticosteroids with or without a LABA used as the controller therapy and short-acting β-agonists as the relief therapy for patients aged 5 years or older with persistent asthma and reporting on an outcome of interest.

DATA EXTRACTION AND SYNTHESIS Meta-analyses were conducted using a random-effects model to calculate risk ratios (RRs), risk differences (RDs), and mean differences with corresponding 95% CIs. Citation screening, data abstraction, risk assessment, and strength of evidence grading were completed by 2 independent reviewers.

MAIN OUTCOMES AND MEASURES Asthma exacerbations.

RESULTS The analyses included 16 randomized clinical trials (N = 22 748 patients), 15 of which evaluated SMART as a combination therapy with budesonide and formoterol in a dry-powder inhaler. Among patients aged 12 years or older (n = 22 524; mean age, 42 years; 14 634 [65%] were female), SMART was associated with a reduced risk of asthma exacerbations compared with the same dose of inhaled corticosteroids and LABA as the controller therapy (RR, 0.68 [95% CI, 0.58 to 0.80]; RD, −6.4% [95% CI, −10.2% to −2.6%]) and a higher dose of inhaled corticosteroids and LABA as the controller therapy (RR, 0.77 [95% CI, 0.60 to 0.98]; RD, −2.8% [95% CI, −5.2% to −0.3%]). Similar results were seen when SMART was compared with inhaled corticosteroids alone as the controller therapy. Among patients aged 4 to 11 years (n = 341; median age, 8 [range, 4-11] years; 69 [31%] were female), SMART was associated with a reduced risk of asthma exacerbations compared with a higher dose of inhaled corticosteroids as the controller therapy (RR, 0.55 [95% CI, 0.32 to 0.94]; RD, −12.0% [95% CI, −22.5% to −1.5%]) or the same dose of inhaled corticosteroids and LABA as the controller therapy (RR, 0.38 [95% CI, 0.23 to 0.63]; RD, −23.2% [95% CI, −33.6% to −12.1%]).

CONCLUSIONS AND RELEVANCE In this meta-analysis of patients with persistent asthma, the use of single maintenance and reliever therapy compared with inhaled corticosteroids as the controller therapy (with or without a long-acting β-agonist) and short-acting β-agonists as the relief therapy was associated with a lower risk of asthma exacerbations. Evidence for patients aged 4 to 11 years was limited.

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Among patients with persistent asthma that remains suboptimally controlled with the use of inhaled corticosteroids, US guidelines suggest a stepwise approach to modifying therapy that includes increasing the dose of inhaled corticosteroids or adding adjunctive therapies.[1] Inhaled long-acting β-agonists (LABAs) are the preferred adjunctive therapy for patients aged 12 years or older and are considered 1 of several potential adjunctive therapies for patients aged 5 to 11 years.

When inhaled corticosteroids and LABA are used as controller therapies, the doses are scheduled on a daily basis and the patient continues to use short-acting β-agonists (SABAs) for as-needed quick relief of symptoms (**Box**). Given the fast onset of action with the LABA formoterol,[2] it has been hypothesized that the combined use of inhaled corticosteroids and formoterol as needed instead of SABAs would provide quick symptom relief and also deliver steroid sooner during the course of symptom deterioration, thereby effectively managing asthma symptoms and reducing exacerbation risk.

The use of a combination of inhaled corticosteroids and LABA inhaler as both the controller and quick relief therapy is a strategy that has been termed *single inhaler therapy* or *single maintenance and reliever therapy* (SMART) and is recommended for asthma management by international guidelines.[3-5] However, currently there are no combinations of inhaled corticosteroids and LABA approved for combined controller and quick relief therapy in the United States.

The objective of this review was to systematically identify and analyze data from trials that compared use of SMART among patients with persistent asthma vs inhaled corticosteroids with or without a LABA used as controller therapy and SABAs as reliever therapy among patients aged 5 years or older.

Methods

A standard protocol was developed and followed and can be found online in its entirety.[6] This article represents 1 of 6 research questions posed in the protocol. Two questions examined the effect of intermittent inhaled corticosteroids among children with recurrent wheezing or among children and adults with persistent asthma and 3 questions evaluated the comparative effectiveness of long-acting muscarinic antagonists vs standard inhaled controllers among patients with uncontrolled and persistent asthma. The final full report addressing all 6 research questions is available on the Agency for Healthcare Research and Quality website.[7]

Data Sources and Searches

We searched MEDLINE via OVID (including in-process and other nonindexed citations), EMBASE, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews via OVID from database inception through August 2016 and updated through November 28, 2017 (**Figure 1** and eAppendix 1 in the Supplement). The bibliographic database searches were supplemented with backward-citation tracking of relevant publications.

Key Points

Question What is the efficacy associated with using inhaled corticosteroids and long-acting β-agonists (LABAs) together as both the controller and the quick relief therapy termed *single maintenance and reliever therapy* (SMART) in patients with persistent asthma?

Findings In this meta-analysis that included 22 524 patients aged 12 years or older and 341 children aged 4 to 11 years with persistent asthma, SMART was associated with a significantly lower risk of asthma exacerbations compared with a higher dose of inhaled corticosteroids and LABA as controller therapy, absolute risk difference, −2.8% for the older age group and −12.0% for the younger age group, although less robust data were available for this group.

Meaning SMART was associated with better clinical outcomes than conventional approaches in patients with persistent asthma.

Box. Key Definitions

Inhaled Corticosteroids
The prescribed use of inhaled corticosteroids is not the same on a daily basis. As prescribed, intermittent dosing of inhaled corticosteroids may specify variations in the dose or frequency of administration. The determinant of intermittent dosing of inhaled corticosteroids may be the patient's decision based on need, an index of worsening asthma, or some other predefined criteria.

Inhaled Corticosteroids as Controller
Medications recommended to be taken daily on a long-term basis to achieve and maintain control of persistent asthma.

Quick Relief
Medications to be used on an as-needed basis for acute symptom relief. Commonly referred to as rescue therapy.

Single Maintenance and Reliever Therapy (SMART)
Use of inhaled corticosteroids and long-acting β-agonists together as both the controller and the quick relief therapy.

Additional searches included ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform for ongoing studies and those completed with reported results. The scientific resource center of the Agency for Healthcare Research and Quality also requested data from manufacturers.

Study Selection

Studies were included that evaluated patients aged 5 years or older with persistent asthma and compared SMART vs either inhaled corticosteroids alone or inhaled corticosteroids with LABA as the sole controller therapy and used SABA for reliever therapy. We required studies to assess 1 of the following outcomes: asthma exacerbations (systemic use of corticosteroids, hospitalization, emergency department [ED] visits, intensive care admission or intubation, or as defined by the study); all-cause or asthma-specific mortality; spirometry reported as peak, trough, or area under the curve; forced

expiratory volume in the first second of expiration (FEV_1); forced vital capacity (FVC); ratio of FEV_1 to FVC; asthma control assessed by the Asthma Control Test or the 5-item Asthma Control Questionnaire (ACQ-5); asthma-related quality of life assessed by the Asthma Quality of Life Questionnaire; and health care use (additional medication use, additional health care use related to the intervention). A patient response was defined as a reduction in the ACQ-5 score by 0.5 points or greater.[8] A minimally important difference in FEV_1 was defined as a change of 0.2 L.[9]

Studies considered for inclusion were randomized clinical trials (RCTs) (parallel or crossover design), prospective or retrospective observational cohort studies, and case-control studies. Crossover trials were included if the outcomes measured after the first treatment period were available and if the washout period was a minimum of 6 weeks for inhaled corticosteroids and 4 weeks for LABA. We did not apply restrictions in publication language or date.

Four independent investigators (D.M.S., E.R.W., E.N., W.L.B.) screened titles and abstracts to determine if the citation met eligibility criteria. Full-text publication review occurred when 2 of the reviewers agreed that a citation met the eligibility criteria. Disagreements were resolved through consensus in consultation with a third reviewer (D.M.S.). We contacted corresponding authors for clarification when needed to assess the inclusion criteria. Abstracts and meeting presentations were matched to their corresponding full-text publication and reviewed for supplemental data.

### Data Extraction and Risk of Bias Assessment

One investigator (E.R.W. or E.N.) abstracted data into standardized collection forms and created tables for the evidence and outcomes. A second investigator (E.R.W. or E.N.) verified entries. For crossover trials, data from period 1 were abstracted when available, otherwise we contacted authors for period 1 outcomes.

Two independent reviewers (D.M.S., E.R.W., E.N., or W.L.B.) assessed risk of bias using the Cochrane Collaboration risk of bias tool[10] for RCTs. The individual domains included (1) random-sequence generation, (2) allocation sequence concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, (5) completeness of outcome data, (6) selective reporting, and (7) other sources of bias. Two investigators (D.M.S., E.R.W., E.N., or W.L.B.) independently classified each domain as either low, unclear, or high risk of bias.

Data Synthesis and Analysis

Data synthesis was based on pharmacological class rather than an individual drug. Studies were categorized as follows based on the comparator studied and in each case included a SABA reliever: inhaled corticosteroids alone as the controller therapy, both inhaled corticosteroids and LABA as the controller therapy, or either inhaled corticosteroids alone or inhaled corticosteroids and LABA together as the controller therapy. Studies were grouped and analyzed separately based on whether the estimated daily dose of inhaled

Figure 1. Flow Diagram of Literature Search
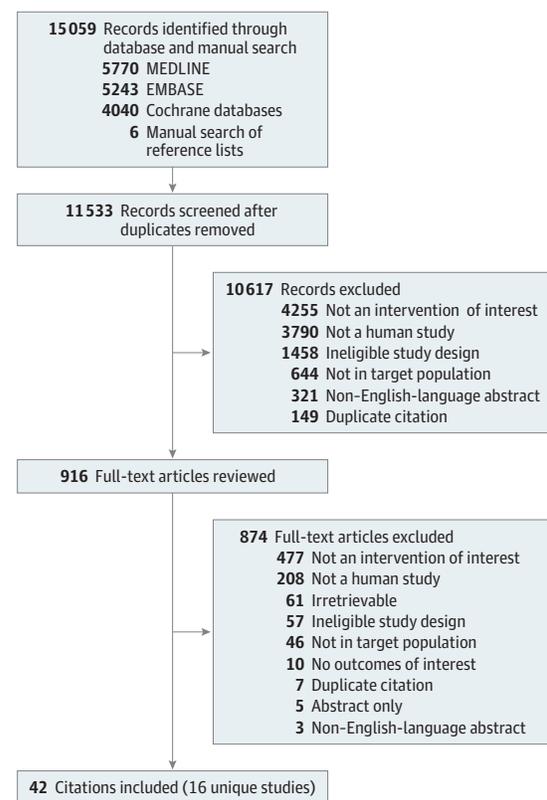
corticosteroids[1] in the comparator group was the same, higher, or lower than the intervention group. Some studies met criteria for more than 1 of these groups when multiple groups were reported. This article reports the results of SMART vs inhaled corticosteroids with or without a LABA at the same or higher dose of inhaled corticosteroids. The results of SMART vs a control group that allowed both inhaled corticosteroids alone or inhaled corticosteroids and LABA together as the controller therapy, or a lower comparative dose of inhaled corticosteroids appear in the full report.[7]

Data synthesis also was based on age categories consistent with the previously used age cut points of 5 to 11 years and 12 years or older.[1] Studies that fit into more than 1 predefined age category were included in the main analysis if they were the only source of data. These studies were added to the age category consistent with the reported mean or median age of the study as a sensitivity analysis. If a study fit into more than 1 age category and reported results separately for the different age subgroups, those subgroups were considered for the main analyses.

All analyses were performed using the meta package in R (version 3.4.3; R Project for Statistical Computing). We conducted a meta-analysis of the RCTs using the Hartung-Knapp[11,12] random-effects model to estimate risk ratio (RR) and risk difference with corresponding 95% CIs for binary outcomes and mean difference with corresponding 95% CIs for continuous outcomes. For binary outcomes

with rare events (<5%), odds ratios and 95% CIs were calculated using the method of Peto in place of an RR.[13] Because of debate regarding the routine use of the Hartung-Knapp method,[14] recommendations suggest conducting standard random-effects analyses as a sensitivity analysis.[15] Therefore, we reanalyzed each end point using the DerSimonian and Laird random-effects model to determine if any of the conclusions were sensitive to model choice.

Additional sensitivity analyses were performed whereby studies considered to have at least 1 of 7 domains rated with high risk of bias (eg, those that did not blind participants or personnel) were removed and the analyses were rerun. The presence of statistical heterogeneity was assessed using the Cochrane P value (P < .10 was considered significant) and the degree of heterogeneity was assessed using the I^2 statistic and a value greater than 50% was considered substantial.[16] We planned to assess publication bias using funnel plot inspection and tests of plot asymmetry when 10 or more trials were pooled.[17] However, none of the pooled analyses reached this threshold.

Strength of Evidence

Two senior investigators (D.M.S. and W.L.B.) assessed strength of evidence independently and via discussion arrived at the final grading based on 5 required domains: risk of bias, consistency, directness, precision, and publication bias. The strength of evidence for each outcome was designated as high, moderate, low, or insufficient (definitions appear in eAppendix 2 in the Supplement).[18]

Results

Forty-two citations represent 16 RCTs[19-35] (N = 22 748 patients), 15 of which evaluated SMART as a combination therapy with budesonide and formoterol in a dry-powder inhaler. Characteristics of the included studies appear in eTables 1 through 4 in the Supplement. For the comparison of SMART with other therapies, 4 RCTs[17-20] evaluated inhaled corticosteroids alone as the controller therapy[19-22] and 14 RCTs[20,23-35] evaluated inhaled corticosteroids and LABA as the controller therapy. All studies included SABA as the relief therapy for patients aged 5 years or older with persistent asthma and reported an outcome of interest. All but 1 trial[26] evaluated SMART as a combination of budesonide and formoterol in a dry-powder inhaler.

Risk of Bias

The risk of bias assessment for each included trial and the summative assessment by domain appear in eFigures 1 and 2 in the Supplement. Most RCTs had a low risk of bias for random-sequence generation (13 [81.3%]), allocation concealment (10 [62.5%]), incomplete reporting of data (14 [87.5%]), and other types of bias (16 [100%]). Of the 16 studies, 6 (37.5%) had a high risk of bias because of the blinding methods used for participants, personnel, and study outcomes. Most RCTs had an unclear risk of bias in the domain of selective outcome reporting (9 [56.2%]).

SMART vs Inhaled Corticosteroids Alone as Controller

Three RCTs[19,21,22] compared SMART vs the same comparative daily dose of inhaled corticosteroids alone as the controller therapy among patients aged 12 years or older. Sovani et al[19] enrolled patients with suboptimally controlled persistent asthma and required patients to have evidence of poor adherence to medications; therefore, the results are described separately from the other 2 trials. The remaining 2 trials enrolled symptomatic patients, one[22] with mild to moderate persistent asthma and the other[21] with moderate to severe persistent asthma.

One RCT[20] provided a comparison of SMART vs a higher dose of inhaled corticosteroids alone as the controller therapy among patients aged 4 to 80 years with persistent symptomatic asthma. This trial also included a preplanned subgroup analysis among patients aged 4 to 11 years (median age, 8 [range, 4-11] years).[31]

All trials compared SMART vs budesonide controller and SABA quick relief. Among patients aged 12 years or older, SMART was associated with a decreased risk of asthma exacerbations defined as a composite of those requiring use of systemic corticosteroids, hospitalization, or ED visit compared with the same dose of inhaled corticosteroids alone as the controller therapy (RR, 0.64 [95% CI, 0.53 to 0.78]; risk difference, −8.1% [95% CI, −11.5% to −4.5%]) and compared with a higher comparative dose of inhaled corticosteroids (RR, 0.59 [95% CI, 0.49 to 0.71]; risk difference, −11.0% [95% CI, −14.8% to −7.2%]; Table 1).[8,36,38] Each of these results was based on a single RCT.

Compared with the same dose of inhaled corticosteroids alone, single trials demonstrated that SMART was associated with improved FEV$_1$ (mean difference, 0.10 [95% CI, 0.07 to 0.13]) and decreased need for rescue medication inhalations per day (mean difference, −0.34 [95% CI, −0.51 to −0.17]). All-cause mortality was rare in the single trial reporting this outcome. One death (0.1%) occurred in the SMART group and 2 deaths (0.2%) occurred in the inhaled corticosteroids group (odds ratio, 0.51 [95% CI, 0.05 to 4.92]; risk difference, −0.1% [95% CI, −0.7% to 0.4%]), none of which were asthma-specific deaths. No other outcomes of interest were reported.

Among patients aged 4 to 11 years, an analysis of a similar composite for asthma exacerbations (including increases in asthma medications with or without a peak expiratory flow [PEF] component) suggests a reduced risk in the association with SMART based on a subgroup analysis in a single trial (Table 2). No significant association of SMART with the risk of mild asthma exacerbations was seen.

SMART vs Inhaled Corticosteroids and LABA Controller

Fourteen RCTs[20,23-35] compared SMART vs inhaled corticosteroids and LABA as the controller therapy and SABA as the quick relief. Nine trials[20,23-30] (n = 12 902) used the same comparative dose of inhaled corticosteroids in both groups and all but 1 RCT[20] fit into the age group of 12 years or older. O'Byrne et al[20] enrolled patients aged 4 to 80 years and provided subgroup data[31] for patients aged 4 to 11 years.

Five trials[29,32-35] (n = 7605) compared SMART vs a higher dose of inhaled corticosteroids and LABA controller therapy.

Table 1. Summary of Findings and Strength of Evidence in Studies Comparing SMART vs Inhaled Corticosteroids With or Without a LABA as Controller Therapy Among Patients Aged 12 Years or Older (n = 22 524)[a]

Outcome	Included Studies[b]	SMART Group		Control Group[d]		Absolute Risk Difference (95% CI), %[e]	Effect Size (95% CI)	Strength of Evidence[f]
		No. of Patients	Outcome[c]	No. of Patients	Outcome[c]			
SMART vs Same Dose of Inhaled Corticosteroids Alone as Controller Therapy								
Asthma exacerbations: required use of systemic corticosteroids, hospitalization, or ED visit	21	947	137	943	212	−8.1 (−11.5 to −4.5)	RR, 0.64 (0.53 to 0.78)	Moderate
Death								
All cause	21	947	1	943	2	−0.1 (−0.7 to 0.4)	OR, 0.51 (0.05 to 4.92)	Insufficient
Specific to asthma	21	947	0	943	0	No events occurred		Insufficient
Spirometry: FEV_1, L	21	947	2.54 (NR)	943	2.44 (NR)		MD, 0.10 (0.07 to 0.13)	Moderate
Health care use: rescue medication, puffs/d	22	355	1.04 (NR)	342	1.48 (NR)		MD, −0.34 (−0.51 to −0.17)	Low
SMART vs Higher Dose of Inhaled Corticosteroids as Controller								
Asthma exacerbations: required use of systemic corticosteroids, hospitalization, or ED visit	20	925	148	909	245	−11.0 (−14.8 to −7.2)	RR, 0.59 (0.49 to 0.71)	Low
SMART vs Same Dose of Inhaled Corticosteroids and LABA as Controller Therapy								
Asthma exacerbations								
Required use of systemic corticosteroids, hospitalization, or ED visit	23-27	4226	263	4257	385	−6.4 (−10.2 to −2.6)	RR, 0.68 (0.58 to 0.80)	High
Mild	24-26	3008	2166	3029	2328	−4.6 (−15.9 to 6.6)	RR, 0.94 (0.81 to 1.09)	Moderate
Death								
All cause	23-25,27	3374	2	3408	5	−0.1 (−0.2 to 0.1)	OR, 0.43 (0.04 to 4.49)	Moderate
Specific to asthma	23-25,27	3374	0	3408	0	No events occurred		Insufficient
Asthma control								
Asthma Control Test score[g]	30	32	6.9 (1.93)	31	0.6 (2.61)		MD, 6.30 (5.15 to 7.45)	Insufficient
5-Item Asthma Control Questionnaire[h]								
Score	24,25,28	2177	NA	2198	NA		MD, −0.16 (−0.39 to 0.06)	Low
Patient response[i]	24	1049	587	1042	511	6.9 (2.6 to 11.2)	RR, 1.14 (1.05 to 1.24)	Moderate
Spirometry								
FEV_1, L	24-27,30	2177	NA	3215	NA		MD, 0.04 (0 to 0.09)	Low
FEV_1, % predicted	27	133	5.5 (17.0)	141	3.7 (21.3)		MD, 1.8 (−2.8 to 6.4)	Moderate
FVC, L	28	15	7.6 (7.4)	15	5.7 (9.1)		MD, 1.9 (−4.3 to 8.1)	Moderate
	26	852	0.11 (0.6)	849	0.12 (0.6)		MD, −0.01 (−0.07 to 0.04)	Low
Health care use								
Rescue medication, puffs/d	24-26	3014	NA	3032	NA		MD, −0.16 (−0.45 to 0.14)	Low

(continued)

Table 1. Summary of Findings and Strength of Evidence in Studies Comparing SMART vs Inhaled Corticosteroids With or Without a LABA as Controller Therapy Among Patients Aged 12 Years or Older (n = 22 524)[a] (continued)

Outcome	Included Studies[b]	SMART Group No. of Patients	SMART Group Outcome[c]	Control Group[d] No. of Patients	Control Group[d] Outcome[c]	Absolute Risk Difference (95% CI), %[e]	Effect Size (95% CI)	Strength of Evidence[f]
SMART vs Higher Dose of Inhaled Corticosteroids and LABA as Controller Therapy								
Asthma exacerbations								
Required use of systemic corticosteroids, hospitalization, or ED visit	32,33	2254	202	3371	394	−2.8 (−5.2 to −0.3)	RR, 0.77 (0.60 to 0.98)	High
Mild	Comparison 1[33,j]	1103	674	1099	687	−1.4 (−5.5 to 2.7)	RR, 0.97 (0.91 to 1.04)	Moderate
	Comparison 2[33,k]	1103	674	1119	660	0.2 (−2.0 to 6.2)	RR, 1.04 (0.97 to 1.11)	
Death								
All cause	32-34	2321	3	3436	1	0.1 (0 to 0.2)	OR, 5.19 (0.32 to 85.45)	Moderate
Specific to asthma	32-34	2321	0	3436	0	No events occurred		Insufficient
Asthma control: 5-item Asthma Control Questionnaire score[h]	32	1144	1.84 (NR)	1145	1.89 (NR)		MD, −0.02 (−0.07 to 0.04)	High
	Comparison 1[33,j]	1068	NR	1060	NR		MD, −0.02 (−0.08 to 0.05)	
	Comparison 2[33,k]	1068	NR	1074	NR		MD, 0.03 (−0.03 to 0.09)	
Spirometry: FEV$_1$, L	Comparison 1[33,j]	1103	2.69 (NR)	1103	2.66 (NR)		MD, 0.01 (−0.03 to 0.04)	Moderate
	Comparison 2[33,k]	1103	2.69 (NR)	1103	2.67 (NR)		MD, 0.01 (−0.03 to 0.04)	
Quality of life: Asthma Quality of Life Questionnaire score[l]	Comparison 1[33,j]	1103	NR	1103	NR		MD, 0.01 (−0.07 to 0.08)	Moderate
	Comparison 2[33,k]	1103	NR	1103	NR		MD, −0.02 (−0.09 to 0.06)	
Health care use: rescue medication, puffs/d	32	1144	0.95 (NR)	1145	1.01 (NR)		MD, −0.04 (−0.12 to 0.04)	High
	Comparison 1[33,j]	1068	1.02 (NR)	1119	1.05 (NR)		MD, −0.03 (−0.12 to 0.06)	
	Comparison 2[33,k]	1068	1.02 (NR)	1099	0.96 (NR)		MD, 0.07 (−0.02 to 0.16)	

Abbreviations: ED, emergency department; FEV$_1$, forced expiratory volume in the first second of expiration; FVC, forced vital capacity; LABA, long-acting β-agonist; MD, mean difference; NA, not available; NR, not reported; OR, odds ratio; RR, risk ratio; SMART, single maintenance and reliever therapy.

[a] The mean age of patients was 42 years and 14 634 (65%) were female.

[b] Meta-analyses were performed when 3 or more studies reported on the same outcome. When data were available for 2 or fewer studies, the results from each study are individually shown. Thus, the groups are treated as a separate comparison with individual results shown.

[c] Outcome data are expressed as mean (SD) or No. of patients with an event. The mean outcome values represent the mean change from baseline for each study group. The mean difference represents the between-group difference in change from baseline.

[d] The control group used a short-acting β-agonist as the reliever therapy.

[e] Indicates between-group risk (SMART group minus control group).

[f] Based on domains of risk of bias, consistency, directness, precision, and publication bias. Additional information appears in eAppendix 2 in the Supplement. Some rows do not have an evidence rating because ratings were given for each outcome as a whole rather than for the individual studies.

[g] Patient self-administered tool for assessing overall asthma control; range, 5 (worse) to 25 (better control). The minimally important difference is a 3-point change.[36]

[h] Patient self-administered tool for assessing overall asthma control; range, 0 (worse) to 6 (better control). The minimally important difference is a 0.5-point change.[8]

[i] Defined as an improved score by at least 0.5 points.

[j] SMART vs combination budesonide and formoterol.[33]

[k] SMART vs combination fluticasone and salmeterol.[33]

[l] Patient self-administered tool for assessing asthma-specific quality of life; range, 1 (severe impairment) to 7 (no impairment). The minimally important difference is a 0.5-point change.[37,38]

Table 2. Summary of Findings and Strength of Evidence in Studies Comparing SMART vs Inhaled Corticosteroids With or Without a LABA as Controller Therapy Among Patients Aged 4 to 11 Years (n = 341)ᵃ

Outcome	Included Studies	SMART Group		Control Groupᵇ		Absolute Risk Difference (95% CI), %ᶜ	Risk Ratio (95% CI)	Strength of Evidenceᵈ
		No. of Patients	No. With Event	No. of Patients	No. With Event			
SMART vs Higher Dose of Inhaled Corticosteroids as Controller Therapy								
Asthma exacerbations								
Required use of systemic corticosteroids, hospitalization, ED visit, increase in inhaled corticosteroids or other asthma medication, or having PEF <70%	31	118	17	106	28	−12.0 (−22.5 to −1.5)	0.55 (0.32 to 0.94)	Low
Required use of systemic corticosteroids, hospitalization, ED visit, or increase in inhaled corticosteroid or other asthma medication	31	118	10	106	21	−11.3 (−20.7 to −2.2)	0.43 (0.21 to 0.87)	Low
Mild	31	118	74	106	77	−9.9 (−21.7 to 2.4)	0.86 (0.72 to 1.04)	Low
SMART vs Same Dose of Inhaled Corticosteroids and LABA as Controller Therapy								
Asthma exacerbations								
Required use of systemic corticosteroids, hospitalization, ED visit, increase in inhaled corticosteroids or other asthma medication, or having PEF <70%	31	118	17	117	44	−23.2 (−33.6 to −12.1)	0.38 (0.23 to 0.63)	Low
Required use of systemic corticosteroids, hospitalization, ED visit, or increase in inhaled corticosteroid or other asthma medication	31	118	10	117	36	−22.3 (−31.9 to −12.3)	0.28 (0.14 to 0.53)	Low
Mild	31	118	74	117	98	−21.1 (−31.6 to −9.8)	0.75 (0.64 to 0.88)	Low

Abbreviations: ED, emergency department; LABA, long-acting β-agonist; PEF, peak expiratory flow; SMART, single maintenance and reliever therapy.
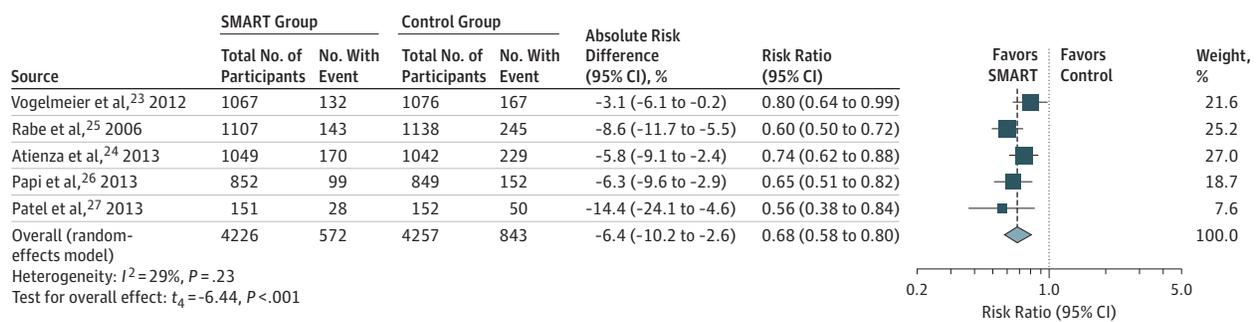
ᵃ The median age of patients was 8 (range, 4-11) years and 69 (31%) were female.

ᵇ The control group used a short-acting β-agonist as the reliever therapy.

ᶜ Indicates between-group risk (SMART group minus control group).

ᵈ Based on domains of risk of bias, consistency, directness, precision, and publication bias. Additional information appears in eAppendix 2 in the Supplement.
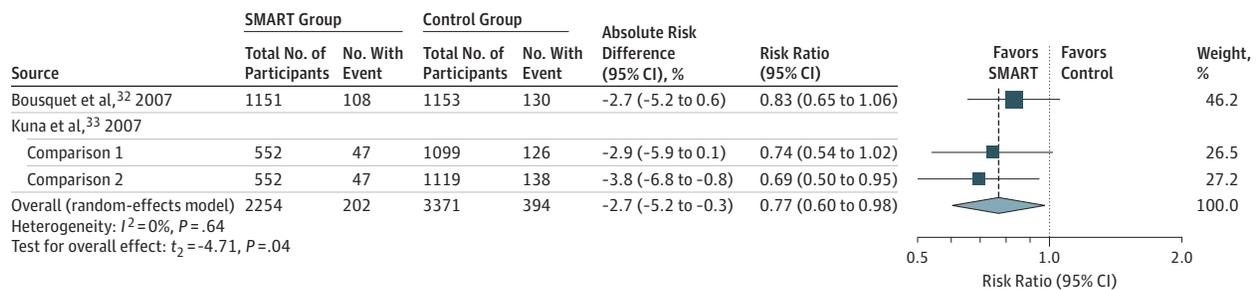
Figure 2. Association of SMART With Exacerbations Requiring Systemic Corticosteroids, Hospitalization, or ED Visits Among Patients Aged 12 Years or Older vs the Same Dose of Inhaled Corticosteroids and LABA Controller Therapy

Source	SMART Group		Control Group		Absolute Risk Difference (95% CI), %	Risk Ratio (95% CI)	Weight, %
	Total No. of Participants	No. With Event	Total No. of Participants	No. With Event			
Vogelmeier et al,[23] 2012	1067	132	1076	167	−3.1 (−6.1 to −0.2)	0.80 (0.64 to 0.99)	21.6
Rabe et al,[25] 2006	1107	143	1138	245	−8.6 (−11.7 to −5.5)	0.60 (0.50 to 0.72)	25.2
Atienza et al,[24] 2013	1049	170	1042	229	−5.8 (−9.1 to −2.4)	0.74 (0.62 to 0.88)	27.0
Papi et al,[26] 2013	852	99	849	152	−6.3 (−9.6 to −2.9)	0.65 (0.51 to 0.82)	18.7
Patel et al,[27] 2013	151	28	152	50	−14.4 (−24.1 to −4.6)	0.56 (0.38 to 0.84)	7.6
Overall (random-effects model)	4226	572	4257	843	−6.4 (−10.2 to −2.6)	0.68 (0.58 to 0.80)	100.0

Heterogeneity: $I^2 = 29\%$, $P = .23$
Test for overall effect: $t_4 = -6.44$, $P < .001$

The box sizes are proportional to study weight and the horizontal lines indicate 95% CIs. The I^2 value indicates the percentage of variability across the pooled estimates attributable to statistical heterogeneity (range, 0%-100%), and the P value for heterogeneity is a test of heterogeneity across all studies ($P < .10$ indicates likely variation across pooled estimates related to statistical heterogeneity). ED indicates emergency department; LABA, long-acting β-agonist; SMART, single maintenance and reliever therapy.

Figure 3. Association of SMART With Exacerbations Requiring Systemic Corticosteroids, Hospitalization, or ED Visits Among Patients Aged 12 Years or Older vs a Higher Dose of Inhaled Corticosteroids and LABA Controller Therapy

Source	SMART Group		Control Group		Absolute Risk Difference (95% CI), %	Risk Ratio (95% CI)	Weight, %
	Total No. of Participants	No. With Event	Total No. of Participants	No. With Event			
Bousquet et al,[32] 2007	1151	108	1153	130	−2.7 (−5.2 to 0.6)	0.83 (0.65 to 1.06)	46.2
Kuna et al,[33] 2007							
Comparison 1	552	47	1099	126	−2.9 (−5.9 to 0.1)	0.74 (0.54 to 1.02)	26.5
Comparison 2	552	47	1119	138	−3.8 (−6.8 to −0.8)	0.69 (0.50 to 0.95)	27.2
Overall (random-effects model)	2254	202	3371	394	−2.7 (−5.2 to −0.3)	0.77 (0.60 to 0.98)	100.0

Heterogeneity: $I^2 = 0\%$, $P = .64$
Test for overall effect: $t_2 = -4.71$, $P = .04$

The box sizes are proportional to study weight and the horizontal lines indicate 95% CIs. The I^2 value indicates the percentage of variability across the pooled estimates attributable to statistical heterogeneity (range, 0%-100%), and the P value for heterogeneity is a test of heterogeneity across all studies ($P < .10$ indicates likely variation across pooled estimates related to statistical heterogeneity). ED indicates emergency department; LABA, long-acting β-agonist; SMART, single maintenance and reliever therapy.

Four[29,32-34] of these 5 trials included patients aged 12 years or older (mean age range, 38-45 years). The other trial by Lundborg et al[35] studied patients aged 6 years or older. However, this trial[35] used formoterol instead of SABA as the quick relief therapy in the control group; therefore, the trial was not pooled with the others.

One trial[30] further specified persistent asthma severity as moderate to severe. Nine trials enrolled patients with symptomatic asthma,[20,23-25,28,30,32-34] 2 trials[29,35] enrolled patients regardless of presence of asthma symptoms, and 4 trials[24,26,28,30] specified that enrolled patients had uncontrolled asthma. Most trials used budesonide and formoterol in a dry-powder inhaler in both groups. Two trials compared combined budesonide and formoterol in a dry-powder inhaler and quick relief with combined fluticasone and salmeterol.[23,28] One trial[26] compared combined beclomethasone and formoterol in both groups.

Among patients aged 12 years or older, asthma exacerbations were most commonly defined as a composite requiring use of systemic corticosteroids, hospitalization, or an ED visit. SMART was associated with a lower risk of asthma exacerbations compared with the same dose of inhaled corticosteroids and LABA controller therapy (RR, 0.68 [95% CI, 0.58 to 0.80]; risk difference, −6.4% [95% CI, −10.2% to −2.6%]; Figure 2) and a higher dose of inhaled corticosteroids and LABA controller therapy (RR, 0.77 [95% CI, 0.60 to 0.98], risk difference, −2.7% [95% CI, −5.2% to −0.3%]; Figure 3).

No significant association of SMART with risk of mild exacerbation was seen (RR, 0.94 [95% CI, 0.81 to 1.09]; risk difference, −0.05 [95% CI, −0.16 to 0.07]; eFigure 3 in the Supplement). There was no association between SMART and all-cause mortality regardless of comparative dose of inhaled corticosteroids (2/3374 [0.06%] for SMART vs 5/3408 [0.15%] for the same dose of inhaled corticosteroids; 3/2321 [0.13%] for SMART vs 1/3436 [0.03%] for a higher dose of inhaled corticosteroids; eFigures 4-5 in the Supplement). There were no asthma-specific deaths.

No significant association of SMART with asthma symptom control measured by the ACQ-5 was seen compared with the same dose of inhaled corticosteroids and LABA controller therapy (eFigure 6 in the Supplement) or with a higher dose of inhaled corticosteroids (Table 1). However, in a single trial,

SMART was associated with an improved ACQ-5 response rate vs the same dose of inhaled corticosteroids and LABA controller therapy (RR, 1.14 [95% CI, 1.05 to 1.24]; risk difference, 6.9% [95% CI, 2.6% to 11.2%]).

There was no significant association of SMART with changes in FEV_1, FVC, or percentage of predicted FEV_1 (Table 1 and eFigure 7 in the Supplement) vs inhaled corticosteroids and LABA controller therapy at either the same or a higher dose of inhaled corticosteroids. Two trials evaluated asthma-related quality of life using the Asthma Quality of Life Questionnaire and found no significant association with SMART vs a higher dose of inhaled corticosteroids and LABA controller therapy (Table 1). SMART was not associated with lower use of rescue medication as inhalations per day vs either the same or a higher dose of inhaled corticosteroids and LABA controller therapy (Table 1 and eFigure 8 in the Supplement).

Among patients aged 4 to 11 years, a subgroup analysis from a single RCT reported that SMART was associated with a lower risk of asthma exacerbations using 3 different composite definitions vs the same dose of inhaled corticosteroids alone as the controller therapy (Table 2).

Sensitivity Analysis

The results of the sensitivity analyses, whereby all outcomes were reanalyzed using different methods appear in eTable 5 in the Supplement. Three analyses were shown to be sensitive to model choice and the 95% CIs were more narrow than the base-case analysis, resulting in statistically significant findings.

When analyzed using the DerSimonian-Laird random-effects model and compared with the same dose of inhaled corticosteroids and LABA controller therapy, SMART was associated with a significant improvement in mild asthma exacerbations (RR, 0.94 [95% CI, 0.88 to 1.00]; eTable 5 in the Supplement; mean difference in asthma control assessed by the ACQ-5 score, −0.16 [95% CI, −0.24 to −0.09]; mean difference in rescue medication use, −0.16 [95% CI, −0.29 to −0.03 puffs/day]). All other outcomes remain unchanged.

When the studies rated as having a high risk of bias were removed during the sensitivity analyses, the overall findings remained consistent (eTable 6 in the Supplement).

Discussion

This systematic review supports the combined use of inhaled corticosteroids and LABA as both the controller and quick relief therapy (SMART) among patients aged 12 years or older compared with using either the same or a higher dose of inhaled corticosteroids alone as the controller therapy or the same or a higher dose of inhaled corticosteroids and LABA as the controller therapy with SABA as the quick relief therapy for patients aged 12 years or older with persistent asthma. Current evidence regarding children aged 4 to 11 years is limited but also suggests similar efficacy associated with SMART.

Persistent asthma severity was not usually defined further in the studies; however, all of the studies required patients to be taking inhaled corticosteroids prior to enrollment and many patients also were taking an LABA. Based on

reported mean doses of inhaled corticosteroids prior to enrollment, most patients were taking medium to high doses of inhaled corticosteroids and thus represent patients with asthma severity that is worse than mild persistent asthma.

Efficacy associated with SMART among patients aged 12 years or older is primarily based on a composite outcome including asthma exacerbations requiring systemic corticosteroids, hospitalization, or ED visits. SMART was associated with reduced RRs regardless of the comparator. Although it is recommended that trials report the individual components of a composite outcome,[39] this was rarely done. Some insight is provided from the comparison of SMART vs the same dose of inhaled corticosteroids and LABA controller therapy for which SMART was associated with a reduced risk in a similar magnitude for each of the 3 components of the composite outcome.

Other outcomes including all-cause mortality were rare and there were no asthma-specific deaths among the patients studied. Trials typically lasted 6 to 12 months and thus may be limited in the analysis of such long-term outcomes. Several postmarketing trials mandated by the US Food and Drug Administration that were designed to evaluate the safety of LABA used in combination with inhaled corticosteroids in patients with asthma, albeit traditional dosing not SMART, have not detected any concern regarding serious asthma-related events.[40-42] This has recently prompted the Food and Drug Administration to remove the black box warning regarding asthma-related deaths from all medications that contain both inhaled corticosteroids and LABA.[43]

Current guidelines recommend that asthma management goals not only include risk reduction of asthma exacerbations but also improvement in asthma control.[1] Among patients aged 12 years or older, measures of asthma control were much less frequently available for analysis. Spirometry was represented mostly by FEV_1. Even though SMART was associated with significantly increased FEV_1 compared with the same comparative dose of inhaled corticosteroids, the difference did not reach the minimally important difference of 0.2 L.[9] Continuous composite measures of asthma symptom control (eg, Asthma Control Test and the ACQ-5) did not support improvement in asthma symptom control with SMART more often than not despite a single trial that found SMART was associated with increased chances of having a response on the ACQ-5 (achievement of a minimally important difference of 0.5).[38,44-46]

There are several hypotheses regarding why changes in symptom control were negligible in this review. Based on a systematic review of the literature, some have concluded that a within-patient minimally important difference of 0.5 for the ACQ-5 score is not achievable in studies when controller therapies are added to inhaled corticosteroids.[38] Bateman et al[38] noted that the development of the ACQ-5 was largely based on a population of patients that had not taken steroids or were taking inhaled corticosteroids alone, and initial derivation of the questionnaire was based on physician-perceived improvement in patient symptoms. SMART delivers a fast-acting LABA; therefore, it is reasonable to expect patients to obtain symptom relief in place of a SABA. However, unlike traditional dosing of inhaled corticosteroids and LABA, SMART delivers

inhaled corticosteroids sooner during symptom deterioration, which may in part have a role in improvement of other outcomes such as asthma exacerbations.

Despite the lack of symptom control found in this review, a retrospective analysis of 5 trials included in this review found that ACQ-5 scores continued to improve over 6 to 12 months of therapy during the trials, regardless of the treatment group.[46] The rates of controlled asthma according to various ACQ-5 cut points also were similar regardless of intervention group and continued to improve over the course of the trials.[46] The data support improved asthma control as measured through validated composite scores with SMART.

SMART was not associated with changes in asthma-related quality of life; however, this outcome was rarely reported and should be a target for future studies evaluating this intervention. In addition, no significant association between SMART and changes in the need for rescue medication inhalations was seen across the various comparators in this review, and only favored SMART vs a higher dose of inhaled corticosteroids alone as the controller therapy, albeit not reaching the minimally important difference of 0.8 inhalations per day.[9]

Composite asthma exacerbations were the only outcomes available for analysis among patients aged 4 to 11 years based on data from a subgroup analysis of a single trial.[20,31] Even though a composite outcome for asthma exacerbations was used, it was broader than the literature base for patients aged 12 years or older and included asthma exacerbations requiring systemic steroids, hospitalization, ED visit, a change in PEF to less than 70%, or an increase in inhaled corticosteroids or other asthma medications.

Although lung function can document reduced airflow associated with asthma exacerbations, PEF is less sensitive than FEV_1.[39] Furthermore, not all reductions in PEF will result in medical intervention as was found in the 1 trial[20] in which 87% of the asthma exacerbations meeting the PEF criterion were retrospectively found not to lead to medical intervention. When the PEF component of the composite outcome was removed, a significant association in favor of SMART was still found; however, the criterion of an increase in inhaled corticosteroids or other medication remained.[20] Even in younger children, this characteristic is not 1 of the recommended definitions of asthma exacerbations.[39]

Taken together, the strength of evidence for asthma exacerbation outcomes among patients aged 4 to 11 years was low and more limited than the evidence in support of SMART among patients aged 12 years or older. Future research is needed to confirm the similar efficacy of SMART seen in the prior trial on asthma exacerbations as well as to evaluate other important outcomes such as asthma control and quality of life.

Applicability

The target population for this review included patients aged 5 years or older with persistent asthma. Consistent with the National Asthma Education and Prevention Program's Expert Panel Report 3 guidelines, this systematic review aimed to evaluate patients aged 5 years or older and separately analyzed patients aged 4 to 11 years and aged 12 years or older. The

evidence base for patients aged 4 to 11 years was limited to a single subgroup analysis (n = 341) from a single trial and included patients as young as 4 years of age with uncontrolled asthma while receiving inhaled corticosteroids alone.

However, even though this study was the only source of evidence for this age group, the data were included because the mean age was within the target range. Several of the trials fitting the age category of 12 years or older involved mainly older patients (mean ages in the 40s) and thus reflect adult populations rather than adolescents. The majority of trials required patients to either have uncontrolled asthma or required use of rescue SABA during the run-in period. Although SABA use is 1 criterion to measure impairment associated with asthma control, others such as nighttime awakenings, spirometry, and interference with activities of daily living are also suggested.

All but 1 trial evaluated the combination of inhaled corticosteroids and LABA as budesonide and formoterol delivered as a dry-powder inhaler; therefore, the results of this systematic review are most reflective of this particular inhaler. Combination budesonide and formoterol is only available in the United States as a metered-dose inhaler. Data suggest that budesonide and formoterol delivered via a metered-dose inhaler is therapeutically equivalent to the dry-powder inhaler based on morning PEF measured in patients aged 12 years or older with suboptimal asthma control while using inhaled corticosteroids alone.[47] However, specific trials evaluating the metered-dose inhaler in SMART were not available.

Limitations

This study has several limitations. First, this review did not evaluate adverse events associated with administering SMART because it was not within the scope of the review. However, when selecting appropriate therapy for patients, decision makers should consider known harms and costs of these drug therapies.

Second, although there were many subgroups of interest, individual analyses could not be conducted due to the lack of reported data, which limits the ability of decision makers to further individualize recommendations. Third, some trials included in this review were determined to have medium risk of bias specifically due to the open-label nature of the study design. Fourth, due to the number of outcomes that were evaluated, some statistically significant associations may represent type I error.

Fifth, there is still debate surrounding the most appropriate statistical model to use within meta-analyses. Due to its more favorable handling of between-study heterogeneity, an a priori decision was made to use a random-effects model with a Hartung-Knapp estimator.[48] However, the Hartung-Knapp estimator has received criticism and some recommend conducting a sensitivity analysis using standard random-effects analyses, such as the DerSimonian-Laird estimator.[14,15] When each end point was reanalyzed using this method, the 95% CIs for a few outcomes were narrowed whereby they did not cross unity. However, because the changes seen did not reach the level of clinical relevance, the conclusions remain unchanged.

Conclusions

In this meta-analysis of patients with persistent asthma, the use of single maintenance and reliever therapy compared with inhaled corticosteroids as the controller therapy (with or without a long-acting β-agonist) and short-acting β-agonists as the relief therapy was associated with a lower risk of asthma exacerbations. Evidence for patients aged 4 to 11 years was limited.

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