Comparative Effectiveness Review
Number 194

Intermittent Inhaled Corticosteroids and Long-Acting Muscarinic Antagonists for Asthma

Agency for Healthcare Research and Quality
Effective Health Care Program

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Addendum

An updated search was conducted for studies to address Key Questions (KQs) 1c and 2a-c. These KQs were related to the combined use of inhaled corticosteroids and long-acting beta agonists as controller and quick relief therapy and to the use of long-acting muscarinic antagonists as add-on therapy to inhaled corticosteroids. The original search was conducted in August 2016 using the earliest date for each database. This update was made on November 28, 2017. No new studies met inclusion criteria.

Key Messages

Purpose of Review

To assess the efficacy of intermittent inhaled corticosteroids in different populations of patients with asthma and to assess whether adding long-acting muscarinic antagonists improves outcomes for patients with uncontrolled, persistent asthma.

Key Messages

- In children less than 5 years old with recurrent wheezing, intermittent use of inhaled corticosteroids during an upper respiratory tract infection decreases asthma exacerbations
- In patients 12 years and older with persistent asthma:
  - using inhaled corticosteroids intermittently may be as effective as using them as a controller medication
  - using inhaled corticosteroids and long-acting beta-agonists together as controller and quick relief therapy reduces asthma exacerbations compared to using inhaled corticosteroids alone or with long-acting beta agonist as a controller
- In patients 12 years and older with uncontrolled, persistent asthma, adding long-acting muscarinic antagonist to:
  - inhaled corticosteroids reduces exacerbations and improves lung function
  - inhaled corticosteroids and long-acting beta-agonist controllers improves asthma control and lung function

This report is based on research conducted by the University of Connecticut Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2015-00012-I). The National Institutes of Health (NIH) National Heart, Lung, and Blood Institute (NHLBI) sponsored the report. The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ or NIH/NHLBI. Therefore, no statement in this report should be construed as an official position of AHRQ, NIH/NHLBI, or the U.S. Department of Health and Human Services.

None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The National Institutes of Health (NIH) National Heart, Lung, and Blood Institute (NHLBI) requested and provided funding for the report.

The reports and assessments provide organizations with comprehensive, evidence-based information on common medical conditions and new health care technologies and strategies. They also identify research gaps in the selected scientific area, identify methodological and scientific weaknesses, suggest research needs, and move the field forward through an unbiased, evidence-based assessment of the available literature. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review and public comment prior to their release as a final report.

AHRQ expects that the EPC evidence reports and technology assessments, when appropriate, will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

If you have comments on this evidence report, they may be sent by mail to the Task Order Officers named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

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Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report do not necessarily represent the views of individual reviewers.

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Intermittent Inhaled Corticosteroids and Long-Acting Muscarinic Antagonists for Asthma

Structured Abstract

Objective. To assess efficacy of intermittent inhaled corticosteroid (ICS) therapy in different populations (0 to 4 years old with recurrent wheezing, 5 years and older with persistent asthma, with or without long-acting beta agonist [LABA]), and to assess efficacy of added long-acting muscarinic antagonist (LAMA) in patients 12 years and older with uncontrolled, persistent asthma.

Data sources. MEDLINE®, Embase®, Cochrane Central, and Cochrane Database of Systematic Reviews bibliographic databases from earliest date through March 23, 2017; hand searches of references of relevant studies; www.clinicaltrials.gov and the International Controlled Trials Registry Platform.

Review methods. Two investigators screened abstracts of identified references for eligibility and subsequently reviewed full-text files. We abstracted data, performed meta-analyses when appropriate, assessed the risk of bias of each individual study, and graded the strength of evidence for each comparison and outcome. Outcomes for which data were extracted included exacerbations, mortality, asthma control composite scores, spirometry, asthma-specific quality of life, and rescue medication use.

Results. We included 56 unique studies (54 randomized controlled trials, 2 observational studies) in this review. Compared to rescue short-acting beta-agonist (SABA) use, adding intermittent ICS reduces the risk of exacerbation requiring oral steroids and improves caregiver quality of life in children less than 5 years old with recurrent wheezing in the setting of a respiratory tract infection (RTI). In patients 12 years and older with persistent asthma, differences in intermittent ICS versus controller use of ICS were not detected, although few studies provided evidence, leading to primarily low strength of evidence ratings. Using ICS and LABA as both a controller and quick relief therapy reduced the risk of exacerbations and improved symptom control in patients 12 years and older compared to ICS controller (with or without LABA). Data in patients 4 to 11 years old suggest lower risk of exacerbations with ICS and LABA controller and quick relief use, but with a lower strength of evidence than in the older population. In patients 12 years and older with uncontrolled, persistent asthma, LAMA versus placebo as add-on to ICS reduces the risk of exacerbations requiring systemic corticosteroids and improves lung function measure through spirometry. Current evidence does not suggest that a difference exists in the efficacy of LAMA versus LABA as add-on to ICS. Triple therapy of ICS, LAMA, and LABA improves lung function measured through spirometry, although the risk of exacerbation was not different versus ICS and LABA.

Conclusions. Intermittent ICS added to SABA during an RTI provides benefit to patients less than 5 years of age with recurrent wheezing. In patients 12 years and older with persistent asthma, differences in intermittent ICS versus controller use of ICS were not detected, although few studies provided evidence for this question. In patients 12 years and older with persistent asthma, using ICS and LABA as both a controller and quick relief therapy may be more effective

at preventing exacerbations than ICS controller (with or without LABA). LAMA is effective in the management of uncontrolled, persistent asthma in patients 12 years of age and older, and current evidence does not suggest a difference between LAMA and LABA as add-on to ICS.

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Evidence Summary

Objectives and Rationale for the Review

This report summarizes a systematic review of intermittent inhaled corticosteroids and long-acting muscarinic antagonists for asthma, and identifies needs for future research. This was one of the six high priority topics within asthma identified by a National Heart, Lung, and Blood Institute Advisory Council Asthma Expert Working group.[1]

The objectives of the systematic review are:

- To assess efficacy of ***intermittent inhaled corticosteroid (ICS) therapy*** in different populations:
  - Patients 0 to 4 years old with recurrent wheezing
  - Patients 5 years and older with persistent asthma (with or without long-acting beta agonist (LABA)
- To assess efficacy of ***adding long-acting muscarinic antagonist*** (LAMA) to ICS with or without LABA in:
  - Patients 12 years and older with uncontrolled, persistent asthma.

Background

Scheduled, daily dosing of ICS is the preferred pharmacologic controller therapy for persistent asthma in patients of all ages.[1]

"Controller therapy" describes medications taken daily on a long-term basis to achieve and maintain control of persistent asthma.[2] Rather than being taken for immediate symptom relief, controller therapy is intended to reduce future exacerbations and the need for immediate symptom relief. In this report, controller medications are defined by the timing and indication for use rather than by mechanism of action.

"Quick relief" therapy describes medications used as needed upon onset of symptoms for acute symptom relief. Likewise, for this report, quick relief therapy is defined by the timing and indication for use rather than by mechanism of action.

Worsening control of asthma or other criteria may prompt changes in prescription therapy, such as intermittent dosing.

"Intermittent" dosing describes the use of medication that may vary in the dose, frequency, or duration of administration. Some examples of intermittent ICS dosing include initiating a temporary course of ICS or temporarily increasing the dose of ICS that is otherwise taken as controller therapy.

An extension of intermittent ICS therapy is the use of ICS and LABA as controller therapy both on a regular basis and on immediate symptom onset for quick relief therapy.[3]

LAMA represents a new pharmacologic class of long-acting bronchodilators that have been studied as a controller therapy for asthma. At least one LAMA has gained Food and Drug

Administration (FDA) approval for the long-term maintenance treatment of asthma in patients 6 years and older.[4]

The review focuses on drugs as a class, as described in Table A.

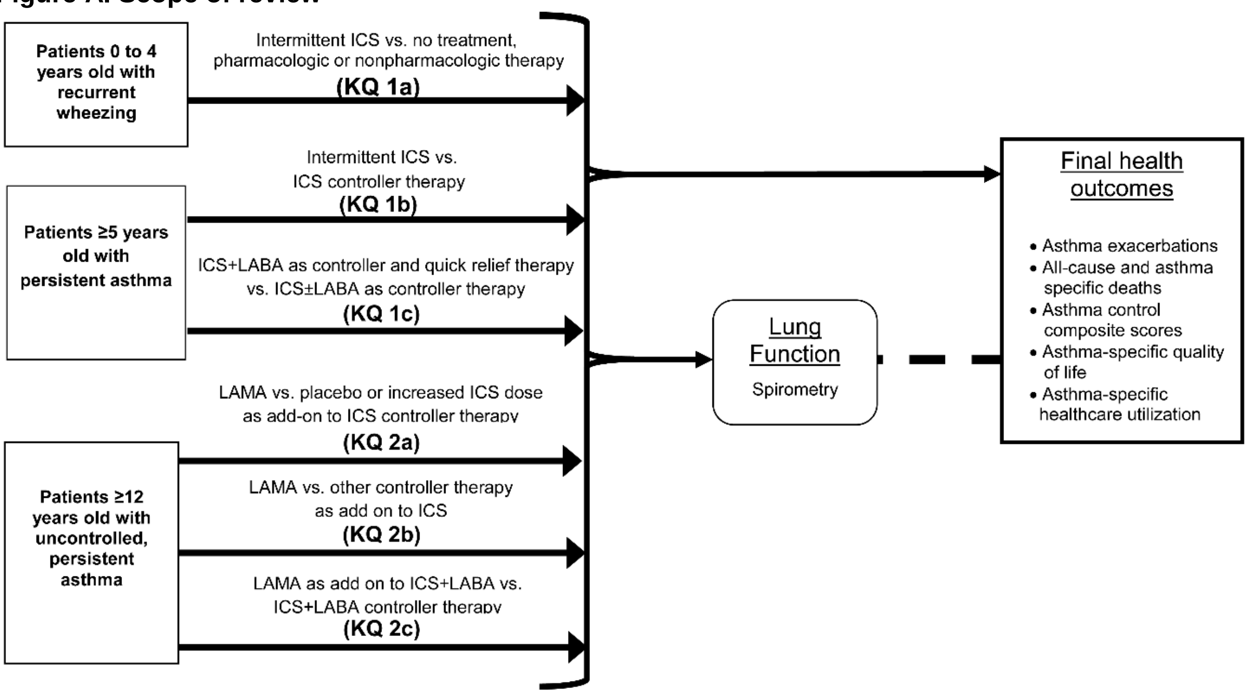
Table A. Drugs included in the review

Class	Drugs
ICS	Beclomethasone,[a] budesonide,[a] ciclesonide,[a] Flunisolide,[a] fluticasone,[a] mometasone,[a] triamcinolone[b]
LABA	Arformoterol, formoterol,[a] olodaterol, salmeterol,[a] vilanterol,[a,c]
LAMA	Aclidinium, glycopyrrolate, tiotropium,[a] umeclidinium

FDA = Food and Drug Administration; ICS = inhaled corticosteroid; LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist

[a] Currently with FDA approval for asthma, either as a single ingredient product or as a component of a multi-ingredient product.
[b] Previously FDA approved, although discontinued in 2010.
[c] Considered an ultra-long-acting β_2-agonist.

Figure A. Scope of review



ICS = inhaled corticosteroid; KQ = Key Question; LABA = long-acting beta agonist; LAMA = long-acting muscarinic antagonist

Data Sources

Data sources were MEDLINE®, Embase®, Cochrane Central, and Cochrane Database of Systematic Reviews bibliographic databases from earliest date through March 23, 2017; hand searches of references of relevant studies; www.clinicaltrials.gov and the International Controlled Trials Registry Platform. The systematic review protocol is available in the full report.

Results

We found 56 unique studies (54 randomized controlled trials, 2 observational studies) in this review. Fifteen randomized controlled trials were specific to LAMA therapy in patients 12 years and older with persistent uncontrolled asthma. An overview of the results is presented in Tables B through E.

Table B. Results for patients 0 to 4 years of age with recurrent wheezing

Intervention	Effect

Intermittent ICS with SABA prn vs. SABA prn at the onset of a URI	• Reduces the risk of exacerbation requiring oral corticosteroids (moderate SOE)
	• Improves QOL (low SOE)
	• Does not affect:
	  o Other measures of exacerbation (low or high SOE)
	  o Rescue medication use (low SOE)

Intermittent ICS vs. ICS controller	• Does affect:
	  o The risk of exacerbations requiring oral corticosteroids (low SOE)
	  o Hospitalization (low SOE)
	  o Rescue medication use (low SOE)

Intermittent ICS vs. no therapy	• No conclusion possible (insufficient SOE)
Intermittent ICS vs. nonpharmacologic therapy	• No conclusion possible (insufficient SOE)

ICS = inhaled corticosteroid; QOL = quality of life; SABA = short-acting beta agonist; SOE = strength of evidence; URI = upper respiratory infection

Table C. Results for patients 5 to 11 years of age with persistent asthma

Intervention	Effect

Intermittent ICS vs. ICS controller	• Does not affect:
	  o QOL (low SOE)
	  o Rescue medication use (low SOE)
	• No conclusion possible for other outcomes (insufficient SOE)

ICS combined with LABA as controller and quick relief vs. a higher ICS controller dose	• Reduces the risk of exacerbations measured as a composite outcome (low SOE)
ICS combined with LABA as controller and quick relief vs. ICS and LABA as controller at the same ICS dose	• Reduces the risk of exacerbations measured as a composite outcome (low SOE)

ICS = inhaled corticosteroid; LABA = long-acting beta agonist; QOL = quality of life; SOE = strength of evidence

Table D. Results for patients 12 years of age and older with persistent asthma

Intervention	Effect
Intermittent ICS and ICS controller vs. ICS controller	• Does not affect the risk of exacerbations, regardless of definition (low SOE) • Decreases asthma-related outpatient visits (low SOE).

Intermittent ICS vs. ICS controller	• Does not affect:
	  o The risk of exacerbation regardless of definition (low SOE)
	  o Asthma control scores (low SOE)
	  o Spirometry (low to high SOE)
	  o QOL (moderate SOE)
	  o Rescue medication use (moderate SOE)

ICS combined with LABA as controller and quick relief vs. the same ICS controller dose	• Reduces:
	  o The risk of exacerbations defined as a composite outcome (moderate SOE)
	  o Rescue medication use (low SOE)
	• Improves spirometry (moderate SOE)

ICS combined with LABA as controller and quick relief vs. a higher ICS controller dose	• Reduces the risk of exacerbations defined as a composite outcome (low SOE)

Intervention	Effect
ICS combined with LABA as controller and quick relief vs. ICS and LABA as controller at the same ICS dose	• Reduces: o The risk of exacerbations defined as a composite outcome (high SOE) o Rescue medication use (low SOE) • Improves asthma control scores (moderate SOE)
ICS combined with LABA as controller and quick relief vs. ICS and LABA as controller at a higher ICS dose	• Reduces the risk of exacerbations defined as a composite outcome (high SOE)
ICS combined with LABA as controller and quick relief vs. conventional best practice of ICS with or without LABA as controller	• Reduces: o The risk of exacerbations defined as a composite outcome (moderate SOE) o Rescue medication use (moderate SOE) • Improves asthma control scores (moderate SOE)

ICS = inhaled corticosteroid; LABA = long-acting beta agonist; QOL = quality of life; SOE = strength of evidence

Table E. Results for patients 12 years of age and older with uncontrolled, persistent asthma

Intervention	Effect
Adding LAMA to ICS vs. adding placebo	• Reduces the risk of exacerbations requiring systemic corticosteroids (high SOE) • Improves spirometry (high SOE) • Does not affect: o Asthma control scores (moderate SOE) o QOL (low to high SOE) o Rescue medication use (moderate SOE)
Adding LAMA to ICS vs. doubling ICS dose	• Does not affect: o The risk of exacerbations requiring systemic corticosteroids (low SOE) o Asthma control scores (low SOE) o Spirometry (low SOE) o QOL (low SOE)
Adding LAMA to ICS vs. adding LABA	• Does not affect: o The risk of exacerbations requiring systemic corticosteroids (low SOE) o Death (low SOE) o Asthma control scores (low to high SOE) o Spirometry (low to high SOE) o QOL (low to high SOE) o Rescue medication use (low SOE)
Adding LAMA to ICS and LABA vs. ICS and LABA	• Does not affect o The risk of exacerbations requiring systemic corticosteroids (moderate SOE) o Hospitalization (low SOE) • Improves o Asthma control scores (low to moderate SOE) o Spirometry (high SOE)

ICS = inhaled corticosteroid; LABA = long-acting beta agonist; LAMA = long-acting muscarinic antagonist; QOL = quality of life; SOE = strength of evidence

Discussion

This review evaluated different ICS dosing strategies and LAMA therapy in people of various ages with persistent asthma. Comparisons were class-based and thus this review does not inform the impact of specific doses on outcomes; rather, it more globally addresses classes and broad dosing strategies (i.e. intermittent dosing of ICS). Although effectiveness is an important part of decision-making, this report did not include harms associated with drug therapies, which should also be taken into consideration.

There is a relatively smaller amount of published evidence on intermittent ICS dosing as compared to the amount of evidence on combined ICS and LABA as quick relief and controller therapy or LAMA therapy. This lack of evidence should not be equated to lack of benefit necessarily. Given most outcomes were rated with low strength of evidence, future research could change the direction or magnitude of effect or the strength of evidence as the consistency and precision in effect estimates improve.

Conclusions

Compared to rescue SABA use, adding intermittent ICS use appears to benefit children less than 5 years old with recurrent wheezing in the setting of an RTI. In patients 12 years and older with persistent asthma, differences in intermittent ICS versus controller use of ICS were not detected, although few studies provided evidence leading to primarily low strength of evidence ratings. Using ICS and LABA combined as both a controller and quick relief therapy showed benefits over use as a controller medication alone (ICS or ICS and LABA controller). In patients 12 years and older with uncontrolled, persistent asthma, adding LAMA to ICS controller or ICS plus LABA controller compared to ICS or ICS plus LABA alone improves some outcomes. However, adding LAMA to ICS controller compared to adding LABA to ICS controller or increasing dosage of ICS controller did not improve outcomes.

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Introduction

Background

Asthma is a chronic inflammatory disorder of the airways, characterized by varying degrees of airflow obstruction. Bronchoconstriction, inflammatory cell infiltration, and airway edema reduce airflow intermittently, often in response to specific exposures, resulting in respiratory symptoms.[1] In the United States, the prevalence of asthma has increased over the past decade, from an estimated 22.2 million Americans in 2005 to 24.6 million Americans in 2015.[2] Asthma can significantly impact patients' and families' quality of life and ability to pursue activities such as school, work, and exercise. Globally, asthma ranks 14th based on the burden of disease, as measured by disability adjusted life years.[3] In the US, asthma contributes significantly to health care resource utilization and associated costs. For example, in 2012, asthma was one of the top twenty leading diagnosis groups for primary care visits and was the main reason for 1.8 million emergency department visits and 439,000 hospitalizations. While the severity of disease varies between patients and over time in the same patient, asthma can be fatal, accounting for approximately 1 death per 100,000 Americans.[4] In 2015, 3,651 Americans died from asthma.[4]

Rationale

In 1989, the National Heart, Lung and Blood Institute (NHLBI) initiated the National Asthma Education and Prevention Program (NAEPP) to address growing concern about asthma in the US. One of the first accomplishments of the NAEPP was to convene a panel of experts who summarized their recommendations in a document, National Asthma Education and Prevention Program Expert Panel Report (EPR): Guidelines for the Diagnosis and Management of Asthma, in 1991. The guidelines address the diagnosis, evaluation, and treatment of asthma. The most recent report, EPR-3, was published in 2007.[1] NHLBI assessed the need for an update by requesting information from the public, NAEPP Coordinating Committee Members and its affiliates, and members of the 2007 Expert Panel. Collected information was provided to the NHLBI Advisory Council Asthma Expert Working Group, which produced a report to summarize the process and recommendations from their needs assessment.[5] The Working Group identified six high priority topics that should be updated. For each topic, Key Questions meriting a systematic literature review were formulated. NHLBI engaged the Agency for Healthcare Research and Quality (AHRQ) to perform the systematic reviews through its Evidence-based Practice Centers (EPC). This report summarizes the systematic review of "Intermittent inhaled corticosteroids and of long-acting muscarinic antagonists for asthma" and highlights areas of controversy and identifies needs for future research on these priority areas.

Intermittent Inhaled Corticosteroid (ICS) Dosing

ICS are highly effective for improving asthma control and reducing exacerbation frequency, yet adherence is often reported to be less than 49 percent to 73 percent in young children and pre-adolescents and less than 50 percent in adolescents and adults.[6-10] Published data suggest that an increase in ICS adherence to between 60 percent and 80 percent results in reduced emergency department visits for asthma.[6,7,11,12] As suggested by the World Health Organization, ‘increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments’.[13] Despite known barriers to the clinical management of asthma, like nonadherence, continued investigation to alternate dosing strategies for ICS or in the development of novel adjunctive therapies as discussed below continues.

Scheduled, daily dosing of ICS is the preferred pharmacologic controller therapy for persistent asthma in patients of all ages.[1] “Controller therapy” will be used in this document to describe medications to be taken daily on a long-term basis to achieve and maintain control of persistent asthma.[1] “Intermittent” ICS dosing will be used in this document to describe the prescribed use of ICS that is not the same on a daily basis. As prescribed, intermittent ICS dosing may specify variations in the dose, frequency, or duration of administration of ICS. The determinant of ICS use with intermittent ICS dosing may be a patient decision (based on need), an index of worsening asthma or some other predefined criteria. Some examples of intermittent ICS dosing include initiating a temporary course of ICS in a patient not regularly taking ICS controller therapy or temporarily increasing the dose of ICS that is otherwise taken as controller therapy, either strategy in response to a measure of worsening asthma.[1,14,15] An extension of the use of intermittent ICS therapy is the combined use of ICS plus long-acting β_2-agonist (LABA) as both a controller and quick relief therapy, particularly when the LABA is considered fast-acting.[16] “Quick relief” therapy will be used in this document to describe inhaled medication to be used as-needed for acute symptom relief.

EPR-3 suggests that intermittent ICS dosing schedules may be useful in some settings though the evidence at that time was insufficient to support the recommendation beyond experts’ consensus.[1] Since the EPR-3, it was determined by the NHLBI Needs Assessment Workgroup that a sufficient number of studies have been published on intermittent ICS dosing to warrant a systematic literature review.

Long-Acting Muscarinic Antagonist (LAMA) Added to ICS or to ICS Plus LABA

LAMAs were not included in the EPR-3 although since then, they have been studied as controller therapy for asthma and at least one LAMA has gained Food and Drug Administration (FDA) approval for the long-term maintenance treatment of asthma in patients 6 years of age and older.[17] This represents a new pharmacologic class of long-acting bronchodilators for consideration in the stepwise approach to asthma management and the NHLBI Needs Assessment Workgroup determined this topic to be of importance for a potential EPR-3 update.

Key Questions (KQs)

KQ1a: What is the comparative effectiveness of intermittent ICS compared to no treatment, pharmacologic, or nonpharmacologic therapy in children 0 to 4 years old with recurrent wheezing?

KQ1b: What is the comparative effectiveness of intermittent ICS compared to ICS controller therapy in patients 5 years of age and older with persistent asthma?

KQ1c: What is the comparative effectiveness of ICS with LABA used as both controller and quick relief therapy compared to ICS with or without LABA used as controller therapy in patients 5 years of age and older with persistent asthma?

KQ2a: What is the comparative effectiveness of LAMA as add-on to ICS controller therapy compared to placebo or increased ICS dose in patients 12 years of age and older with uncontrolled, persistent asthma?

KQ2b: What is the comparative effectiveness of LAMA compared to other controller therapy as add-on to ICS in patients 12 years of age and older with uncontrolled, persistent asthma?

KQ2c: What is the comparative effectiveness of LAMA as add-on to ICS plus LABA compared to ICS plus LABA as controller therapy in patients 12 years of age and older with uncontrolled, persistent asthma?

Population, Intervention, Comparator, Outcomes

Populations: We included all patients that meet the KQ specific criteria regardless of gender, race and ethnicity. Age thresholds per KQ were selected to be consistent with the EPR-3 guidelines.

- KQ1a: Patients 0 to 4 years old with recurrent wheezing
- KQ1b-c: Patients 5 years old and older with persistent asthma
- KQ2a-c: Patients 12 years old and older with uncontrolled, persistent asthma

Interventions: This review focuses on pharmacologic interventions at the class level and includes ICS and inhaled LABA and LAMA, regardless of FDA approval (Table 1).

Table 1. Drugs included in this review

Class	Drugs
ICS	Beclomethasone,[a] budesonide,[a] ciclesonide,[a] flunisolide,[a] fluticasone,[a] mometasone,[a] triamcinolone[b]
LABA	Arformoterol, formoterol,[a] olodaterol, salmeterol,[a] vilanterol[a,c]
LAMA	Aclidinium, glycopyrrolate, tiotropium,[a] umeclidinium

ICS = inhaled corticosteroid; LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist
[a] Currently with FDA approval for asthma, either as a single ingredient product or as a component of a multi-ingredient product.
[b] Previously FDA approved although discontinued in 2010
[c] Considered an ultra-long-acting β_2-agonist

The interventions for each of the KQs is as follows (Table 2):

- KQ1a-b: Intermittent ICS dosing
- KQ1c: ICS and LABA used as controller and quick relief therapy
- KQ2a-b: ICS and LAMA as controller therapy
- KQ2c: ICS and LABA and LAMA as controller therapy

Table 2. Intervention and comparator per Key Question

	Comparator: No treatment, pharmacologic or nonpharmacologic therapy[a]	Comparator: ICS controller therapy	Comparator: ICS and LABA controller therapy	Comparator: ICS and other controller therapy[b]
Intervention: Intermittent ICS	KQ 1a	KQ 1a, 1b	---	---
Intervention: ICS and LABA used as controller and quick relief therapy	---	KQ 1c	KQ 1c	---
Intervention: ICS and LAMA controller therapy	---	KQ 2a[c]	KQ 2b	KQ 2b
Intervention: ICS and LAMA and LABA controller therapy	---	---	KQ 2c	---

Note: The first column represents interventions and the first row represents comparators of interest in this review. The key questions for each intervention are listed below the relevant comparator(s).

ICS = inhaled corticosteroid; KQ = Key Question; LAMA = long-acting muscarinic antagonist; --- = not applicable

[a]Nonpharmacologic treatment is as per EPR-3 (e.g., avoiding environmental triggers)
[b]Other controllers include cromolyn, leukotriene modifiers, immunomodulators, methylxanthines, and systemic corticosteroids
[c]Same or increased ICS dose in the comparator arm relative to intervention dose

Comparators: We are interested in direct comparisons of therapies as described per KQ. Table 2 demonstrates the intervention and comparator for each KQ in a tabular format. The definition of “controller therapy” is provided in the Glossary.

- KQ1a: No treatment (placebo or control) **OR** pharmacologic therapy which includes controller therapy or as-needed short-acting β_2-agonist (SABA) **OR** nonpharmacologic therapy. Controller therapies include ICS, inhaled LABA, leukotriene modifiers, cromolyn, methylxanthines, immunomodulators, and systemic corticosteroids. Nonpharmacologic treatment is as per EPR-3 (e.g., avoiding environmental triggers).
- KQ1b: ICS controller therapy
- KQ1c: ICS controller therapy **OR** ICS and LABA controller therapy
- KQ2a: ICS controller therapy, with or without placebo, where the ICS dose is the same or increased relative to the intervention arm dose
- KQ2b: ICS and another controller therapy, including LABA, leukotriene modifiers, cromolyn, methylxanthines, immunomodulators and systemic corticosteroids
- KQ2c: ICS and LABA controller therapy

Outcomes: We included outcomes that fell into the categories below, using definitions provided by the study.

- Asthma exacerbations
  - Requiring systemic (oral and/or parenteral) corticosteroids, requiring hospitalization, requiring emergency room (ER) visit, requiring intensive care unit or intubation, or as defined by the study

    - Asthma-related hospitalizations, ER visits, urgent care and outpatient visits
- Death
    - All-cause, asthma-specific
- Asthma control
    - Composite Measures: Asthma Control Test (ACT), Asthma Control Questionnaire (ACQ), various versions
    - Spirometry: forced expiratory volume in 1 second (FEV1) forced vital capacity (FVC), FEV1/FVC
- Asthma-specific quality of life:
    - Asthma Quality of Life Questionnaire (AQLQ), Pediatric Asthma Quality of Life Questionnaire (PAQLQ), Pediatric Asthma Caregiver's Asthma Quality of Life Questionnaire (PACQLQ)
- Health care utilization:
    - Additional asthma-medication use/need
    - Additional resource use related to intervention (e.g. personnel time, equipment)

Timing/Setting: There were no requirements based on time or setting.

Methods

The protocol for this review is registered as PROSPERO 2016:CRD42016047985. We developed an analytic framework a priori to guide the systematic review process (Figure 1). We searched Ovid MEDLINE, Ovid MEDLINE In-Process & Other Nonindexed Citations, EMBASE via www.embase.com, Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews via OVID using subject headings and natural language terms reflecting asthma and the drugs of interest (Appendix A). We supplemented the bibliographic database searches with backwards citation tracking of relevant publications. We searched cliniclatrials.gov and the World Health Organization International Controlled Trials Registry Platform (ICTRP) for ongoing studies and those completed with reported results. We reviewed scientific information packets. Searches were updated March 23, 2017 while the draft report was under public/peer review.

We screened titles and abstracts using two independent investigators to determine if the citation met inclusion/exclusion criteria (Table 3). Citations that both reviewers agreed met inclusion criteria were reviewed at the full text level for inclusion into the review. Disagreements were resolved through consensus in consultation with a third reviewer. Corresponding authors were contacted for clarification when needed to assess the inclusion criteria. All authors were given a minimum of 2 weeks to acknowledge queries. Abstracts and meeting presentations were matched to their corresponding full text publication and reviewed for supplemental data.

Data were extracted into standardized collection forms, evidence and outcomes tables by one investigator and verified by a second investigator. Data for crossover trials were extracted from treatment period 1 when available, otherwise authors were contacted for period 1 outcomes. Risk of bias was assessed by two independent reviewers using the Cochrane Collaboration's Risk of Bias Tool[18] for randomized controlled trials (RCTs) and Newcastle Ottawa Scale[19] for observational studies. Overall risk of bias for each study was classified as low, moderate or high, according to the collective risk of bias per evaluated domain and the investigator's confidence in the study results given the identified limitations.[20] Risk of bias was considered unclear if the majority of domains evaluated were unclear.

We assessed clinical and methodologic heterogeneity to determine appropriateness of meta-analysis. We based data synthesis on pharmacologic class (e.g., long-acting muscarinic antagonists [LAMA], long-acting β_2-agonists [LABA], inhaled corticosteroids [ICS]). When a trial included more than one intervention arm for the same drug but with different doses (e.g., tiotropium 2.5μg and 5μg) we combined the arms into a single intervention group using recommended formulae.[21] Synthesis was also based on age categories consistent with the Expert Panel Report-3 of 0 to 4y old, 5 to 11y old and 12y of age and older. When there were 3 or more trials of similar pharmacologic comparisons and outcomes, we pooled data using a Hartung-Knapp[22,23] method random effects model using the 'meta' package in R version 3.1.3 (The R Project for Statistical Computing). Relative risks (RR) with corresponding 95 percent confidence intervals (CI) were estimated for binary outcomes and mean differences (MD) with corresponding 95 percent CI were estimated for continuous outcomes. Peto's odds ratio (OR) and 95 percent confidence intervals were estimated for binary outcomes with rare events (<5%) in place of a RR.[24] We pooled hazard ratios and corresponding 95 percent CI reported by studies for time to first exacerbation and rate ratios for studies reporting number of exacerbations over follow-up. We assessed presence of statistical heterogeneity using the Cochrane p-value ($p<0.10$ significant) and the degree of heterogeneity using the I^2 statistic with a value >50 percent considered substantial.[25] Publication bias was assessed using funnel plot inspection and Egger's weighted regression test when 10 or more trials were pooled.[21,26] A priori determined subgroups of interest included asthma severity, asthma control, age, ICS dose, onset of asthma, obesity, atopy, smoking history, race, pulmonary function, LAMA dose/delivery device, the determinant of ICS use with intermittent ICS dosing and concomitant asthma medications. Subgroup analysis was performed when 3 or more trials per subgroup were available for a given outcome. Studies that fit into more than one predefined age category were not included in the main analysis, unless they were the only source of data, but 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 one age category but reported results separately for the different age subgroups, those subgroups were considered for the main analyses. Included studies that were not amenable to pooling were qualitatively summarized. Interpretation of results was made in the context of established thresholds that indicate clinical significance where available (Table 4). Data from the crossover trial by Peters et al.,[27] were provided by the National Heart, Lung and Blood Institute (NHLBI) Biologic Specimen and Data Repository Information Coordinating Center and independently analyzed by the Evidence-based Practice Center to generate outcomes for period 1 since this data was not reported in the primary manuscript. These results do not necessarily reflect the opinions or views of the BASALT-TALC investigators or the NHLBI.

Strength of evidence (SOE) for each outcome within each comparison was evaluated independently by two senior investigators and then discussed to arrive at the final grading using established guidance.[28] We graded the SOE for asthma exacerbations, mortality, asthma control composite scores, spirometry, asthma-specific quality of life and health care utilization. Five required domains included study risk of bias, consistency, directness, precision and publication bias. Based on these elements we assessed the SOE for each comparison and outcome as:

- High: We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not change the conclusions.
- Moderate: We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe the findings are likely to be stable, but some doubt remains.
- Low: We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
- Insufficient: We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of the effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

We assessed applicability of studies using the population, intervention, comparator, outcomes, timing, setting (PICOTS) framework.[29] Characteristics that may influence applicability include but are not limited to age, gender, race, ethnicity, severity and control of asthma and co-interventions.

Table 3. Inclusion and exclusion criteria

Category	Inclusion criteria	Exclusion criteria
Population	KQ1a: Patients 0 to 4y old[a] with recurrent wheezing KQ1b-c: Patients ≥5y old[a] with persistent asthma KQ2a-c: Patients ≥12y old[a] with uncontrolled, persistent asthma	KQ1a: Patients ≥5y old KQ1b-c: Patients ≤4y old; Patients with intermittent asthma KQ2a-c: Patients ≤11y old; Patients with controlled, persistent asthma or with intermittent asthma
Intervention	KQ1a-b: Intermittent dosing of an ICS KQ1c: ICS and LABA used as both controller and quick relief therapy KQ2a-b: ICS and LAMA controller therapy KQ2c: ICS and LABA and LAMA controller therapy	KQ1c: ICS and LABA used as controller therapy but not quick relief therapy All KQs: All other interventions outside of pharmacologic therapies listed in PICOTS; Combinations of interventions other than those listed in the PICOTS
Comparator	KQ1a: No treatment **OR** pharmacologic therapy **OR** nonpharmacologic therapy (see PICOTS) KQ1b: ICS controller therapy KQ1c: ICS and LABA controller therapy KQ2a: ICS controller therapy, with or without placebo, where the ICS dose is the same or higher than in the intervention arm KQ2b: ICS and another controller therapy as defined in PICOTS KQ2c: ICS and LABA controller therapy	KQ1c: ICS and LABA used as both controller and quick relief therapy All KQs: All other comparators outside of those specified in PICOTS; Combinations of comparators other than those listed in the PICOTS
Outcomes	All KQ: Asthma exacerbations (systemic corticosteroid, hospitalization, ER visit, ICS or intubation or as defined by the study) or asthma-related hospitalizations, ER visits, urgent care and outpatient visits; death (all-cause and asthma-specific); spirometry (FEV1, FVC and FEV1/FVC); asthma symptom control composite measures (ACT, ACQ); asthma-specific quality of life (AQLQ, PAQLQ, PACQLQ); health care utilization (additional asthma medication use, resource use)	Studies that do not include at least one of the outcomes listed in the PICOTS
Timing, Setting	All settings, study durations and follow-up lengths will be included	None
Study design	Randomized-controlled trials, cross-over trials,[b] prospective or retrospective observational cohort studies, case-controlled studies	Case series, case reports, nonsystematic reviews, systematic reviews with or without meta-analysis[c]
Publication language and dates	No restriction in publication language or date of publication	Publications in a non-English language without an English language abstract[d]

ACT = asthma control test; ACQ = Asthma Control Questionnaire; AQLQ = Asthma Quality of Life Questionnaire; ER = emergency room; FDA = Food and Drug Administration; FEV1 = forced expiratory volume over 1 second; FVC = forced vital capacity; ICS = inhaled corticosteroids; KQ = Key Question; LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist; PACQLQ = Pediatric Asthma Caregiver's Quality of Life Questionnaire; PAQLQ = Pediatric Asthma Quality of Life Questionnaire; PICOTS = population, intervention, comparator, outcomes

[a]Studies with age inclusion criteria close to the a prior defined age cut-offs for the given KQ were included in the review if the mean age of the population was within the a priori defined age cut-offs.
[b]Crossover trials were included if the outcomes data can be abstracted after the first period. If data cannot be abstracted after the first period, the trial will be included based on the following criteria, to minimize carry-over effects: for ICS-if the washout period is at least 6 weeks,[30] for LABA or LAMA- if the washout period is at least 4 weeks[31]
[c]Systematic reviews w/meta-analysis were flagged for backwards citation tracking but will not be included in this review.
[d]English language abstracts of non-English language articles were reviewed at the abstract stage and translated when needed to determine eligibility of the full text[32]

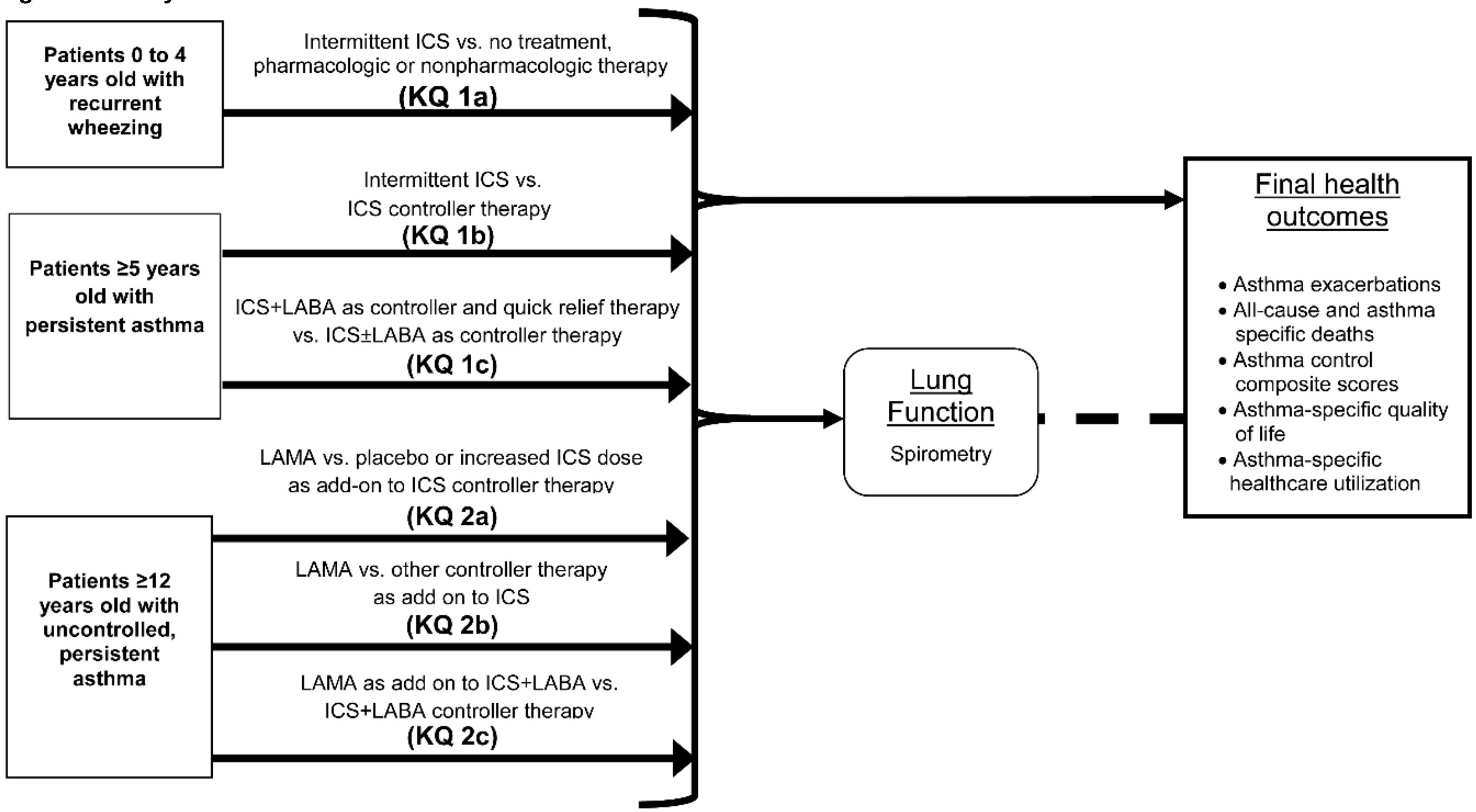
Table 4. Thresholds for clinical significance

Instrument/outcome	Range (points)	Final score	Threshold
ACT	5 to 25	Well controlled: ≥20 Not well controlled: ≤19	≥12y: Δ 3 points[a,33]
ACQ5, ACQ6	0 to 6	Uncontrolled: ≥1.5 Well-controlled: <0.75	≥18y: Δ 0.5 points[a,34]
ACQ7	0 to 6	Uncontrolled: ≥1.5 Well-controlled: <0.75	≥6y: Δ 0.5 points[a,34,35]
AQLQ, AQLQ(S), AQLQ-mini	1 to 7	Severe impairment = 1 No impairment = 7	≥18y: Δ 0.5 points[a,36-38]
AQLQ12+	1 to 7	Severe impairment = 1 No impairment = 7	≥12y: Δ 0.5 points[a,39,40]
PAQLQ, PACQLQ	1 to 7	Severe impairment = 1 No impairment = 7	7-17y: Δ 0.5 points[a,41,42]
FEV1	Continuous measure, L	NA	≥18y: -0.2 L[b,43]
Rescue medication use	Continuous measure, puffs per unit of time	NA	≥18y: -0.81 puffs/day[b,43]

ACT = asthma control test; ACQ = Asthma Control Questionnaire; AQLQ: Asthma Quality of Life Questionnaire; FEV1 = forced expiratory volume in 1 second; L = liter; PACQLQ = Pediatric Asthma Caregiver's Quality of Life Questionnaire; PAQLQ = Pediatric Asthma Quality of Life Questionnaire; y = year

[a]Minimal important difference.
[b]Average minimal patient perceived improvement

Figure 1. Analytic framework



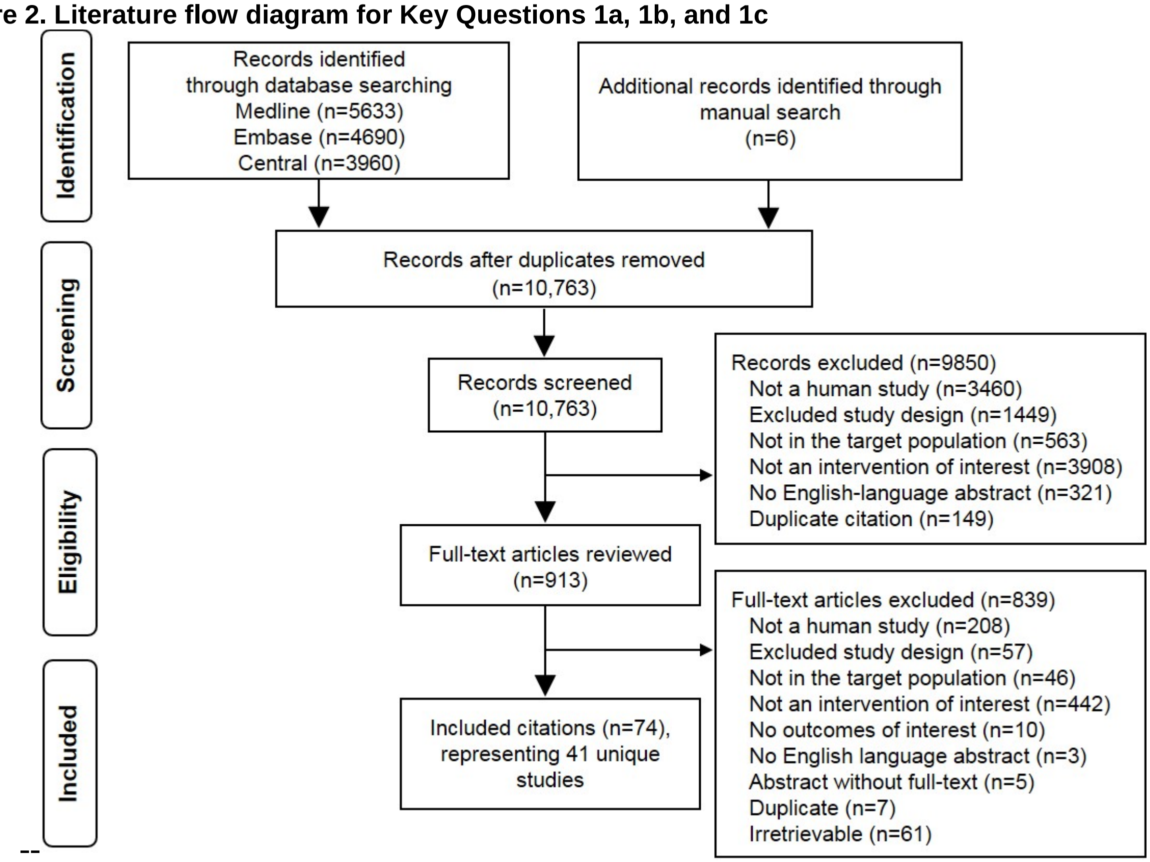
ICS = inhaled corticosteroid; KQ = Key Question; LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist; vs = versus

Results

Search Results

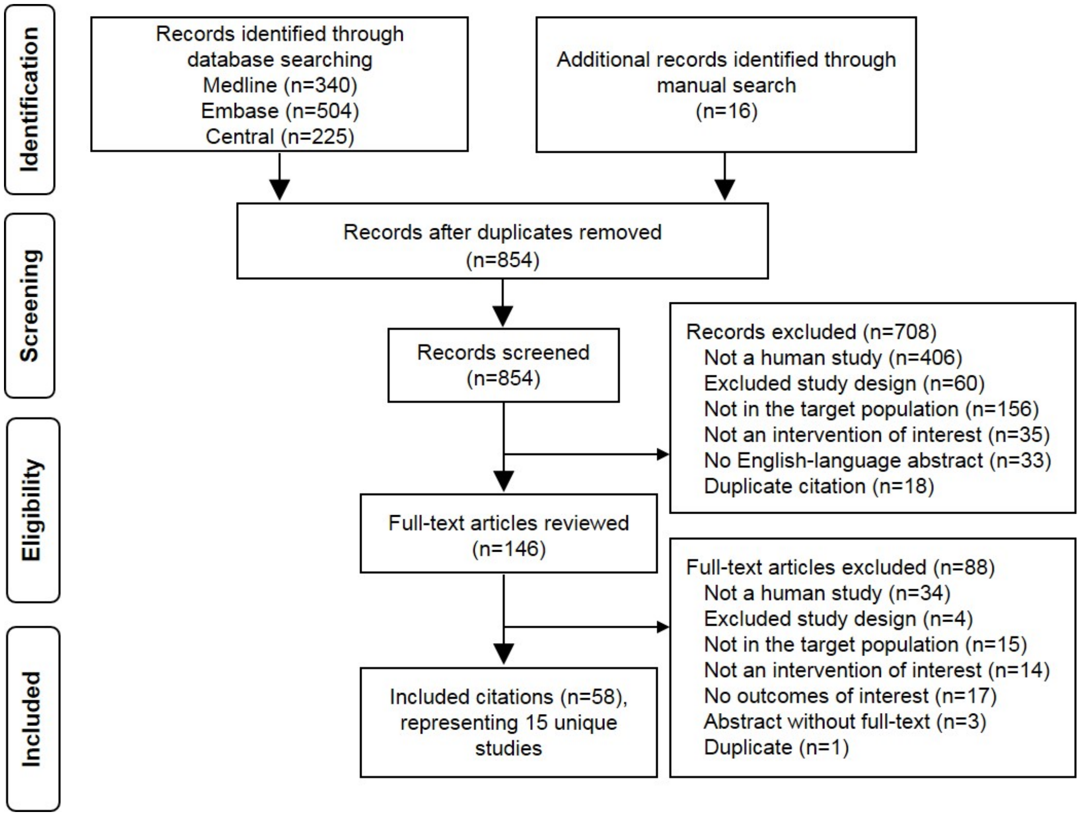
Our search for Key Question (KQ) 1a-c identified 10,763 nonduplicate records, of which 913 required full text review after title and abstract screening, and 74 met eligibility criteria for inclusion in this review (Figure 2). These 74 citations reported results from 41 unique studies, 39 randomized controlled trials (RCTs) and 2 observational studies. Of these 41 studies, 6 met criteria for KQ1a (reported in 7 citations),[44-50] 11 met criteria for KQ1b (reported in 18 citations),[51-68] and 24 met criteria for KQ1c (reported in 49 citations).[69-117] Citations excluded at the full-text review stage are presented in Appendix B.

Figure 2. Literature flow diagram for Key Questions 1a, 1b, and 1c



Our search for KQ2a-c identified 854 nonduplicate records, of which 146 required full text review after title and abstract screening, and 58 met eligibility criteria for inclusion in this review (Figure 3). These 58 citations reported results from 15 unique studies, all of which were RCTs. Of these 15 RCTs, 8 met criteria for KQ2a (reported in 29 citations),[27,118-145] 8 met criteria for KQ2b (reported in 21 citations),[27,118-120,124-126,130-137,144-149] and 4 met criteria for KQ2c (reported in 26 citations).[145,150-174] Citations excluded at the full-text review stage are presented in Appendix B.

Figure 3. Literature flow diagram for Key Questions 2a, 2b, and 2c



In total, 56 unique studies were included, 54 RCTs and 2 observational studies. The distribution of studies by study design and age category are presented in Table 5.

Table 5. Number of studies included per KQ, study design, and age group

	Characteristic	KQ1a	KQ1b	KQ1c (RCT/NonRCT)	KQ2a	KQ2b	KQ2c
Study Design	**RCTs**	6	11	22	8	8	4
	Non RCTs	0	0	2	0	0	0
Age Group	**≥12y**	NA	9	22 (20/2)	8	8	4
	5-11y	NA	0	0	NA	NA	NA
	0-4y	5	0	0	NA	NA	NA
	Mixed	1	2	2 (2/0)	0	0	0
TOTAL		6	11	24	8	8	4

KQ = Key Question; NA = not applicable; RCT = randomized controlled trial; y = years

Organization of This Report

The results are presented in order of KQ and furthermore by intervention/comparator combinations. The same outcomes were sought from all studies regardless of the KQ and are reported when data were available. Supporting tables and figures relevant to the results appear in Tables 6 through 27 and in Appendices C-F, including study and population characteristics, study level outcomes data, study risk of bias assessments and details regarding the strength of evidence grading of each outcome.

KQ1a: What is the comparative effectiveness of intermittent inhaled corticosteroid (ICS) compared to no treatment, pharmacologic, or nonpharmacologic therapy in children 0 to 4 years old with recurrent wheezing?

Results of this KQ are reported separately based on whether the comparator was pharmacologic or nonpharmacologic therapy. There were two distinct pharmacologic comparators: as-needed short-acting β_2-agonist (SABA) and ICS controller, and data were analyzed separately. We found no studies in which the comparator was nonpharmacologic therapy. While this KQ focuses on the age category of 0 to 4y, one included trial[45] allowed enrollment of patients up to the age of 6y but because the mean age was 2y we determined the population was considered to represent that of interest.

Key Points

- Intermittent ICS with as-needed SABA versus as-needed SABA, initiated with onset of a respiratory tract infection (RTI), reduces the risk of exacerbation requiring oral corticosteroids (moderate strength of evidence [SOE]) and improves Pediatric Asthma Caregiver's Quality of Life Questionnaire (PACQLQ) scores (low SOE).
- Intermittent ICS with as-needed SABA versus ICS controller with as-needed SABA did not significantly differ in effect on the risk of exacerbation requiring oral corticosteroid, the risk of exacerbation requiring hospitalization or daytime or nighttime rescue medication use (all low SOE).
- There is insufficient evidence to determine the impact of intermittent ICS versus no therapy on outcomes.

Intermittent ICS With As-Needed SABA Versus As-Needed SABA

Table 6. Evidence overview for KQ1a, intermittent ICS with as-needed SABA vs. as-needed SABA

Outcome category	Outcome	Quantity and type of evidence (n)	Conclusion Effect estimate (95% CI)	Strength of evidence (rationale)
Exacerbations	Requiring oral corticosteroid therapy	3 RCTs[44,45,48] (324)	Favors intermittent ICS RR 0.67 (0.46 to 0.98)	Moderate (imprecise)
	Asthma-related acute care visits	3 RCTs[44,45,48] (324)	No difference RR 0.90 (0.77 to 1.05)	High
	Asthma-related hospital admissions	3 RCT[44,45,48] (324)	No difference RR 0.77 (0.06 to 9.68)	Low (inconsistent, imprecise)
Quality of life	PACQLQ score	2 RCTs[44,48] (270)	Favors intermittent ICS[a] Bacharier, 2008[44] MD -0.10 (-0.36 to 0.34) Ducharme, 2009[48] MD 0.49 (0.10 to 0.86)	Low (inconsistent, imprecise)
Health care utilization	Daytime rescue medication use, number of inhalations/day	1 RCT[47] (166)	No difference Papi, 2009[47] MD -0.08 (-0.21 to 0.05)	Low (unknown consistency)[b]
	Nighttime rescue medication use, number of inhalations/night	1 RCT[47] (166)	No difference Papi, 2009[47] MD -0.04 (-0.11 to 0.03)	Low (unknown consistency)[b]

CI = confidence interval; ICS = inhaled corticosteroid; MD = mean difference; n = patient sample size; PACQLQ = Pediatric Asthma Caregiver's Quality of Life Questionnaire; PRN = pro re nata (i.e., as-needed); RCT = randomized controlled trial; RR = relative risk; SABA = short-acting β_2-agonist

[a]A positive mean difference in PACQLQ suggest improvement in quality of life
[b]Strength of evidence was low even with only one domain downgraded due to the small sample size and lack of confidence in the true effect estimate

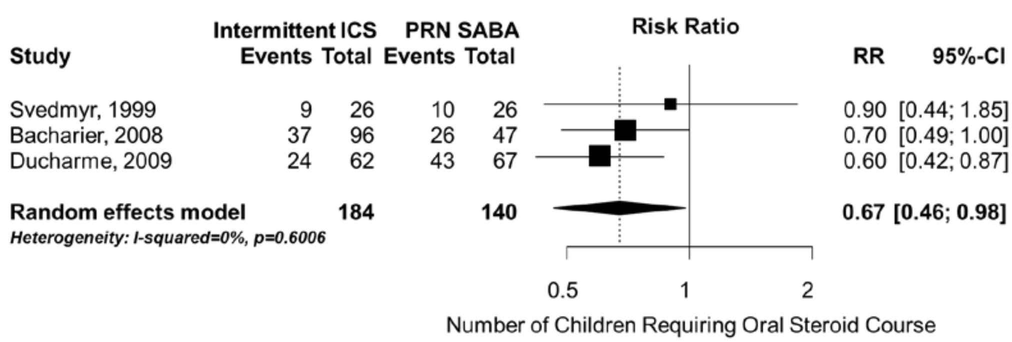
Overview of Studies

Four trials (n=493) were included in the analysis of intermittent ICS with as-needed SABA versus as-needed SABA.[44,45,47,48] Three trials[44,45,48] required a history of recurrent wheezing in the context of RTI and randomized patients to ICS treatment every day for a defined length of time (ranging from 7 to 10d or until symptom free for 48 hours) in addition to SABA as-needed versus placebo with SABA as-needed. Svedmyr et al.,[48] also required patients to be diagnosed with wheezy bronchitis or asthma and allowed continued use of theophylline or cromoglycate during the trial. Bacharier et al., reported that 61 percent of enrolled patients were modified Asthma Prediction Index (mAPI) positive and 64 percent were diagnosed with asthma by a physician.[44] The fourth trial[47] did not specify a requirement of RTI co-occurrence although did require that patients were referred to a specialist due to recurrent wheezing. In this trial, patients were randomized to beclomethasone/salbutamol as-needed for symptom relief versus salbutamol as-needed for symptom relief. Race was reported as 78 percent Caucasian in one trial[45] and as 25 percent minority in a second trial[44]. All trials were multicenter and were conducted in single countries including United States (US), Italy, Sweden and Canada. Two trials[45,47] were industry sponsored, one[44] was nonindustry sponsored, and one trial[48] did not report funding. Studies were 12m in duration except one[47] which was 12 weeks. Risk of bias was low with the exception of Svedmyer et al.,[48] which was determined to be unclear.

Results

In patients 0 to 4 years old with recurrent wheezing, intermittent ICS with as-needed SABA, initiated with and continued during RTI, reduces the risk of exacerbation requiring oral corticosteroids by 33 percent compared to as-needed SABA (moderate SOE) (Figure 4). The risk of asthma-related acute care visits or asthma-related hospitalizations was no different between groups. Mean difference (MD) in PACQLQ score improved in the group receiving intermittent ICS versus as-needed SABA (MD = 0.49, low SOE) in one trial but was not different in a second trial. Change in either daytime or nighttime rescue medication inhalations was no different between groups (low SOE).

Figure 4. Risk of requiring a course of oral steroids: intermittent ICS with as-needed SABA versus as-needed SABA



CI = confidence interval; ICS = inhaled corticosteroids; PRN = as needed; RR = relative risk; SABA = short-acting beta-agonist

Intermittent ICS With As-Needed SABA Versus ICS Controller With As-Needed SABA

Table 7. Evidence overview for KQ1a, intermittent ICS with as-needed SABA versus ICS controller with as-needed SABA

Outcome category	Outcome	Quantity and type of evidence (n)	Conclusion Effect estimate (95% CI)	Strength of evidence (rationale)
Exacerbations	Requiring oral corticosteroid	1 RCT[49] (278)	No difference Zeiger, 2011[49] RR 0.99 (0.80 to 1.22)	Low (unknown consistency)[a]
	Requiring hospitalization	1 RCT[49] (278)	No difference Zeiger, 2011[49] RR 1.25 (0.34 to 4.56)	Low (unknown consistency, imprecise)
Health care utilization	Daytime rescue medication use, number of inhalations/day	1 RCT[47] (220)	No difference Papi, 2009[47] MD 0.07 (-0.4 to 1.8)	Low (unknown consistency, imprecise)
	Nighttime rescue medication use, number of inhalations/night	1 RCT[47] (220)	No difference Papi, 2009[47] MD -0.02 (-0.7 to 0.3)	Low (unknown consistency, imprecise)

CI = confidence interval; ICS = inhaled corticosteroid; MD = mean difference; n = patient sample size; RCT = randomized controlled trial; RR = relative risk

[a]Strength of evidence was low even with only one domain downgraded due to the small sample size and lack of confidence in the true effect estimate

Overview of Studies

Two trials (n=498) were included in the analysis of intermittent ICS with as-needed SABA versus ICS controller with as-needed SABA.[47,49] Papi et al.,[47] was a multicenter trial in Italy of 12 weeks duration, with industry sponsorship and low risk of bias. Patients were required to be referred to a specialist due to recurrent wheezing. They were randomized to the use of beclomethasone/salbutamol on an as-needed basis for symptom relief versus beclomethasone twice daily plus as-needed salbutamol for symptom relief. Race was not reported. Zeiger et al.,[49] was a multicenter trial conducted in the US with 52 weeks duration, nonindustry sponsorship, and low risk of bias. Patients were required to have a history of frequent wheezing and to be positive on the mAPI. They were randomized to budesonide for 7d with onset of RTI versus budesonide controller, both groups received albuterol four times daily for the first 48h of RTI then as-needed. Most patients were Caucasian (62 percent).

Results

The risk of exacerbation requiring oral corticosteroid and the risk of exacerbation requiring hospitalization was no different between intermittent ICS and ICS controller in a single trial (low SOE).[49] Daytime and nighttime rescue medication use was no different between intermittent ICS and ICS controller in a single trial (low SOE).[49] Mean cumulative salbutamol (mg) was similar between intermittent ICS and ICS controller [30.1 (43.0) versus 34.2 (42.3)].[47]

Intermittent ICS Versus No Therapy

Table 8. Evidence overview for KQ1a, intermittent ICS versus no therapy

Outcome category	Outcome	Quantity and type of evidence (n)	Conclusion Effect estimate (95% CI)	Strength of evidence (rationale)
Exacerbations	Requiring systemic corticosteroid	1 RCT[46] (26)	Inconclusive Ghirga, 2002[46] RR 0.54 (0.12 to 2.44)	Insufficient (unknown consistency, imprecise)
	Asthma-related ER visit	1 RCT[46] (26)	Inconclusive Ghirga, 2002[46] RR 0.27 (0.04 to 2.10)	Insufficient (unknown consistency, imprecise)
	Asthma-related hospitalization	1 RCT[46] (26)	Inconclusive Ghirga, 2002[46] No events occurred	Insufficient (no events occurred)

CI = confidence interval; ER = emergency room; ICS = inhaled corticosteroid; n = patient sample size; RCT = randomized controlled trial; RR = relative risk

Overview of Studies

One trial[46] (n=26) was included in the analysis of intermittent ICS versus no therapy. Patients were 7 to 12m in age, presented with a history of recurrent wheezing during RTI and were randomized to beclomethasone 400µg three times daily for 5d at the first sign of RTI versus no preventative treatment. Ethnicity and sponsorship were not reported and the risk of bias was medium because it was open-label.

Results

Although the outcomes of exacerbation requiring oral steroid and the risk of asthma-related emergency room (ER) visits were reported, the evidence is insufficient to draw a conclusion. No asthma-related hospitalizations occurred.

KQ1b: What is the comparative effectiveness of intermittent ICS compared to ICS controller therapy in patients 5 years of age and older with persistent asthma?

Results of this KQ are reported separately based on the comparators. The first group of studies reported below under the subheading of “Intermittent ICS and ICS controller versus ICS controller” compared the addition of intermittent ICS to ICS controller therapy versus ICS controller therapy. The second group of studies reported below under the subheading “Intermittent ICS versus ICS controller” compared intermittent ICS where the patient was not otherwise on ICS controller versus ICS controller therapy. One study was included in both groups because three arms were reported.[60] Although this KQ focuses on 2 of the 3 EPR-3 age categories (5 to 11y, 12y or older), all but two studies[54,60] were specific to the age category of 12y or older. One trial[54] allowed enrollment of patients as young as 4y old although this study was included in the analysis for 5 to 11y because the mean age was 7y and the populations was determined to represent that of interest. One trial[60] enrolled 6 to 18y olds and represents a mixed population based on age and the mean was 10 to 11y, thus this trial was considered under the age category of 5 to 11y. We report results separately per age group when possible.

Key Points

- In patients 12y of age or older, intermittent ICS and ICS controller versus ICS controller does not significantly differ in effect on the risk of exacerbations (low SOE) with exception of asthma-related outpatient visits (low SOE) which favors intermittent ICS with ICS controller versus ICS controller. Evidence is insufficient to draw conclusions in patients 5 to 11y old.
- In patients 12y of age or older, intermittent ICS versus ICS controller therapy does not significantly differ in the risk of exacerbations (low SOE), Asthma Control Questionnaire (ACQ)-7 or ACQ-5 score (low SOE), spirometry (low to high SOE), Asthma Quality of Life Questionnaire (AQLQ)-(S) score (moderate SOE), albuterol rescue use (moderate SOE). Evidence is insufficient to draw conclusions in patients 5 to 11y old aside from Pediatric Asthma Quality of Life Questionnaire (PAQLQ) score and rescue inhaler use which was no different between groups (low SOE).

Intermittent ICS and ICS Controller Versus ICS Controller

Table 9. Evidence overview for KQ1b, intermittent ICS with ICS controller versus ICS controller in patients 12 years of age and older

Outcome category	Outcome	Quantity and type of evidence (n)	Conclusion Effect estimate (95% CI)	Strength of evidence (rationale)
Exacerbations	Requiring oral corticosteroid (full population)[a]	3 RCTs[59,62,67] (908)	No difference RR 0.68 (0.31 to 1.49)	Low (inconsistent, imprecise)
	Requiring oral corticosteroid (of those starting study inhaler)[a]	3 RCTs[55,59,62] (399)	No difference RR 0.64 (0.26 to 1.57)	Low (inconsistent, imprecise)
	Requiring oral corticosteroid, unscheduled doctor visit, ER, or having unstable asthma[b]	1 RCT[55] (98)	No difference Fitzgerald, 2004[55] RR 1.03 (0.63 to 1.65)	Low (unknown consistency, imprecise)
	Asthma-related hospitalization	1 RCT[67] (115)	Inconclusive Lahdensuo, 1996[67] RR 0.70 (0.12 to 4.05)	Insufficient (medium ROB, unknown consistency, imprecise)
	Asthma-related outpatient visit	2 RCTs[59,67] (505)	Favors intermittent ICS and ICS controller Lahdensuo, 1996[67] RR 0.53 (0.29 to 0.96) Harrison, 2004[59] RR 1.14 (0.71 to 1.83)	Low (inconsistent, imprecise)
	Unstable asthma[b]	1 RCT[55] (98)	No difference Fitzgerald, 2004[55] RR 0.57 (0.23 to 1.38)	Low (unknown consistency, imprecise)
	2 or 3 exacerbations requiring oral corticosteroid (full population)[a]	1 RCT[62] (403)	No difference Oborne, 2009[62] RR 0.63 (0.15 to 2.59)	Low (unknown consistency, imprecise)
	2 or 3 exacerbations requiring oral corticosteroid (of those starting study inhaler)[a]	1 RCT[62] (403)	No difference Oborne, 2009[62] RR 0.34 (0.07 to 1.76)	Low (unknown consistency, imprecise)

Outcome category	Outcome	Quantity and type of evidence (n)	Conclusion Effect estimate (95% CI)	Strength of evidence (rationale)
	Fall in PEF <70% from baseline	1 RCT[56] (134)	No difference Foresi, 2000[56] RR 1.09 (0.52 to 2.30)	Low (unknown consistency, imprecise)

CI = confidence interval; ICS = inhaled corticosteroid; MD = mean difference; n = patient sample size; OR = odds ratio; RCT = randomized controlled trial; ROB = risk of bias; RR = relative risk; y=year

[a]The full population reflects all patients randomized in that trial, regardless if they ever initiated the study inhaler which would have provided the intermittent ICS dose. The population which started the study inhaler reflects the patients randomized who actually initiated the study inhaler and thus received the intermittent ICs dose they were randomized too.
[b]Defined as lack of stability, where stability was defined as morning peak expiratory flow 90 percent or more of mean baseline value on either of the two previous days, <4 inhalations of inhaled corticosteroid per day over the past 2 days, no nocturnal awakenings in the prior 2 nights, and a total symptom score not exceeding mean baseline value more than 2 ordinal values over the previous 2 days

Table 10. Evidence overview for KQ1b, intermittent ICS with ICS controller versus ICS controller in patients 4 to 11 years of age

Outcome category	Outcome	Quantity and type of evidence (n)	Conclusion Effect estimate (95% CI)	Strength of evidence (rationale)
Exacerbation	Requiring oral corticosteroids	1 RCT[60] (143)	Inconclusive Martinez, 2011[60] RR 1.12 (0.67 to 1.86)	Insufficient (unknown consistency, imprecise, indirect)[a]
	Requiring hospitalization	1 RCT[54] (29)	Inconclusive Colland, 2004[54] OR 0.14 (0.003 to 7.31)	Insufficient (unclear ROB, unknown consistency, imprecise)
	Treatment failure[b]	1 RCT[60] (143)	Inconclusive Martinez, 2011[60] RR 2.03 (0.39 to 10.72)	Insufficient (unknown consistency, imprecise, indirect)[a]
Spirometry	FEV1 % predicted	1 RCT[54] (29)	Inconclusive Colland, 2004[54] MD 5 (-6.01 to 16.01)	Insufficient (unclear ROB, unknown consistency, imprecise)
Quality of life	PAQLQ score	1 RCT[60] (143)	No difference Martinez, 2011[60] MD -0.003 (-0.25 to 0.25)	Low (unknown consistency, Indirect)[a]
Health care utilization	Albuterol puffs/day	1 RCT[60] (143)	Inconclusive Martinez, 2011[60] MD 0.04 (-0.33 to 0.40)	Insufficient (unknown consistency, imprecise, indirect)[a]

CI = confidence interval; ER = emergency room; FEV1 = forced expiratory volume in one second; ICS = inhaled corticosteroid; MD = mean difference; n = patient sample size; OR = odds ratio; PAQLQ = Pediatric Asthma Quality of Life Questionnaire; RCT = randomized controlled trial; ROB = risk of bias; RR = relative risk; y = year

[a] Martinez et al. enrolled patients 6 to 18 years of age, with mean of 10 and 11y per arm although since this is the only trial that provides data for the EPR-3 age group of 5-11y old, we used the data but downgraded strength of evidence for indirectness
[b]Defined as any of following: (1) Hospitalization due to asthma; (2) Hypoxic seizure due to asthma; (3) Intubation due to asthma; (4) Requirement for a second burst of prednisone within any 6m period; (5) Significant adverse event related to the use of a study medication. The only criterion for assignment of treatment failure during the trial was the requirement for a second burst of prednisone within any six-month period

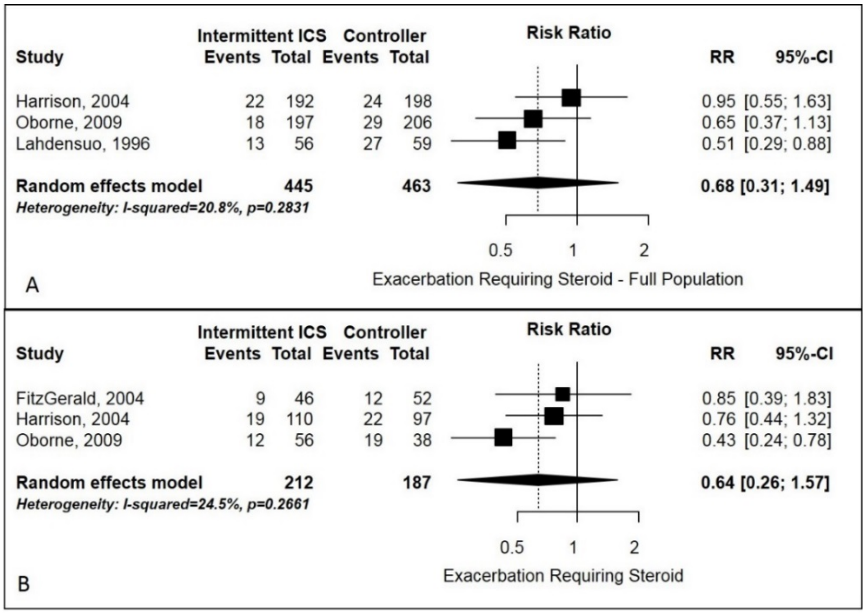
Overview of Studies

Seven RCTs54-56,59,60,62,67 (n=1312) were included in the analysis of intermittent ICS plus ICS controller versus ICS controller. Five RCTs55,56,59,62,67 enrolled patients 12 years of age and older (mean 31 to 55 years). One trial54 enrolled patients 4 to 11y old and 1 trial60 enrolled a mixed population of 6 to 18y olds (mean 10 to 11y); thus, results of these trials are presented separately from results of patients 12y of age or older. The trial60 that enrolled patients 6 to 18 years of age was the only source of data for the population of 4 to 11y old for some of the outcomes evaluated thus we used this data and downgraded the SOE for indirectness. Of the 7 trials, one further specified persistent asthma to be mild,60 one67 specified mild to moderate, and two54,56 specified moderate severity. One trial60 required patients to be well controlled, one59 described patients as stable, two trials54,56 considered patients symptomatic, and the others did not specify asthma control. Race was reported in one trial60 and was mostly Caucasian (71%). In all trials, patients were taking ICS controller therapy and in the intervention arm peak expiratory flow (PEF),55,56,59,62,67 prodromal symptoms,54 or real-life scenarios where the patient would normally use albuterol or treat a reduced PEF60 triggered a temporary increase in the ICS dose. Of the trials that used PEF to trigger additional ICS, trigger values ranged from <70 percent to <85 percent. The duration of increased ICS dose was either 7 or 14d except in a single trial60 instructing patients to use the inhaler whenever albuterol would be normally used. The increase in ICS dose was equivalent to doubling, 54,55,59,67 quadrupling,56,62 or patient driven60. In 5 trials55,56,59,62,67 PEF (either <60% or <70%) also triggered oral corticosteroid initiation for a duration ranging from 3 to 10d. The control arm was randomized to a set ICS dose in all trials except one67 where physicians modified therapy according to their judgement. All trials were multicenter, of either 6 or 12m duration, and conducted in a single country (Canada, US, United Kingdom [UK], Netherlands, Finland, Italy). Three trials were industry sponsored55,56,67 and 4 were nonindustry sponsored.54,59,60,62 Risk of bias was low in 4 trials,55,59,60,62 medium in 1 trial67 and unclear in 2 trials.54,56

Results

In patients 12y of age or older, intermittent ICS and ICS controller versus ICS controller does not significantly differ in the effect on risk of exacerbation requiring oral corticosteroid, for the full study population (Figure 5, Panel A) or in those patients who actually initiated the study inhaler (Figure 5, Panel B) (low SOE), or other measures of asthma exacerbation (low SOE) with exception of asthma-related outpatient visits which decreased with intermittent ICS and ICS controller versus ICS controller (low SOE). In patients 5 to 11y old, there is insufficient evidence to draw conclusions on the impact of intermittent ICS and ICS controller versus ICS controller. The exception is PAQLQ, where there is a low SOE that there is no difference in effect between groups.

Figure 5. Risk of exacerbations requiring oral corticosteroid: Intermittent ICS and ICS controller versus ICS controller



Panel A represents the comparison of intermittent ICS and ICS controller vs. ICS controller on the outcome of exacerbations requiring steroid in the full population, which is all patients regardless if they initiated their intermittent ICS therapy. Panel B represents the same comparison and outcome but only in patients who actually initiated their intermittent ICS therapy.

Subgroup Data

ICS dose: Harrison et al., analyzed a subgroup of patients on ICS doses up to 1000µg of beclomethasone equivalents (considered low to moderate ICS dose) and the risk of starting oral corticosteroids was similar to the main analysis.[59] Fitzgerald et al., compared patients on ICS doses less than or equal to 400µg/d vs. greater than 400µg/d and found the subgroup receiving less that or equal to 400µg/d were less likely to experience treatment failure during the trial.[55] In this study, treatment failure was defined as any one of the following: hospitalization due to asthma, hypoxic seizure due to asthma, intubation due to asthma, requirement for a second burst of prednisone within any 6m period, or significant adverse event related to the use of a study medication.

Age: Fitzgerald et al., also compared adolescents versus adults and found no effect on the outcome of treatment failure (as defined above).[55]

Intermittent ICS Versus ICS Controller

Table 11. Evidence overview for KQ1b, intermittent ICS versus ICS controller in patients 12 years of age and older

Outcome category	Outcome	Quantity and type of evidence (n)	Conclusion Effect estimate (95% CI)	Strength of evidence (rationale)
Exacerbations	Requiring oral corticosteroid	1 RCT[51] (149)	No difference Boushey, 2005[51] RR 0.70 (0.30 to 1.64)	Low (unknown consistency, imprecise)
	Requiring hospitalization	1 RCT[51] (149)	Boushey, 2005[51] No events occurred	Insufficient (no events occurred)
	Asthma-related urgent care visit	1 RCT[52] (227)	No difference Calhoun, 2012[52] RR 0.25 (0.05 to 1.16)	Low (unknown consistency, imprecise)

Outcome category	Outcome	Quantity and type of evidence (n)	Conclusion Effect estimate (95% CI)	Strength of evidence (rationale)
	Mild[a] or severe[b] exacerbation	1 RCT[63] (228)	No difference Papi, 2007[63] RR 0.87 (0.29 to 2.61)	Low (unknown consistency, imprecise)
	Severe exacerbation[b]	1 RCT[63] (228)	No difference Papi, 2007[63] OR 0.11 (0.01 to 1.11)	Low (unknown consistency, imprecise)
Asthma control composite scores	ACQ-7 score	1 RCT[51] (149)	No difference Boushey, 2005[51] MD 0.1 (-0.12 to 0.32)	Low (unknown consistency)[c]
	ACQ-5 score	1 RCT[52] (227)	No difference Calhoun, 2012[52] MD -0.01 (-0.17 to 0.15)[d]	Low (unknown consistency)[c]
Spirometry	FEV1, trough	2 RCTs[52,63] (564)	No difference Papi, 2007[63] MD 0.09 (-0.01 to 0.18) Calhoun, 2012[52] MD 0.01 (-0.13 to 0.15)[d]	High
	FEV1 % predicted	2 RCTs[52,63] (564)	No difference Papi, 2007[63] MD 2.04 (-0.71 to 4.79) Calhoun, 2012[52] MD 0.01 (-1.89 to 1.91)[d]	Moderate (imprecise)
	FVC, trough	1 RCT[63] (228)	No difference Papi, 2007[63] MD 0.07 (-0.03 to 0.18)[d]	Low (unknown consistency)
	FVC % predicted	1 RCT[63] (228)	No difference Papi, 2007[63] MD 1.72 (-1.04 to 4.48)	Low (Unknown consistency, imprecise)
Quality of life	AQLQ(S) score	2 RCT[51,52] (376)	No difference Boushey, 2005[51] MD -0.2 (-0.48 to 0.08) Calhoun, 2012[52] MD 0.01 (-0.19 to 0.21)[d]	Moderate (inconsistent)
Health care utilization	Rescue albuterol puffs/day	2 RCT[52,63] (564)	No difference Papi, 2007[63] MD 0.07 (-0.13 to 0.26) Calhoun, 2012[52] MD -0.04 (-0.11 to 0.03)[d]	Moderate (imprecise)

ACQ = Asthma Control Questionnaire; AQLQ(S) = Standardized Asthma Quality of Life Questionnaire; CI = confidence interval; FEV1 = forced expiratory volume in one second; FVC = forced vital capacity; ICS = inhaled corticosteroid; MD = mean difference; n = patient sample size; OR = odds ratio; RCT = randomized controlled trial; RR = relative risk; y=year

[a]Defined as awakening at night owing to asthma or as a decrease in the morning peak expiratory flow rate to more than 20 percent below the baseline value, the use of more than three additional puffs per day of rescue medication (either albuterol or beclomethasone and albuterol) as compared with during the baseline for 2 or more consecutive days, or both. Single, isolated day on which mild exacerbation occurred were not counted.
[b]Defined as a decrease in the morning peak expiratory flow rate to more than 30 percent below the baseline value on 2 consecutive days or more than eight puffs per day of rescue medication for 3 consecutive days or the need for treatment with oral corticosteroids, as judged by the investigator.
[c] Strength of evidence was low even with only one domain downgraded due to the small sample size and lack of confidence in the true effect estimate
[d]Study reported 97.5 percent confidence intervals which were converted to 95 percent confidence intervals

Table 12. Evidence overview for KQ1b, intermittent ICS versus ICS controller in patients 4 to 11 years of age

Outcome category	Outcome	Quantity and type of evidence (n)	Conclusion Effect estimate (95% CI)	Strength of evidence (rationale)
Exacerbations	Requiring oral corticosteroids	1 RCT[60] (143)	Inconclusive Martinez, 2011[60] RR 1.27 (0.78 to 2.07)	Insufficient (unknown consistency, imprecise, indirect)
	Treatment failure[e]	1 RCT[60] (143)	Inconclusive Martinez, 2011[60] RR 3.04 (0.64 to 14.57)	Insufficient (unknown consistency, imprecise, indirect)
Spirometry	FEV1 % predicted	1 RCT[60] (143)	Inconclusive Martinez, 2011[60] MD -1.30 (-4.24 to 1.64)	Insufficient (unknown consistency, imprecise, indirect)
Quality of life	PAQLQ score	1 RCT[60] (143)	No difference Martinez, 2011[60] MD 0.04 (-0.25 to 0.33)	Low (unknown consistency, Indirect)
Health care utilization	Rescue albuterol puffs/day	1 RCT[60] (143)	No difference Martinez, 2011[60] MD 0.003 (-0.24 to 0.25)	Low (unknown consistency, indirect)

CI = confidence interval; FEV1 = forced expiratory volume in one second; MD = mean difference; n = patient sample size; PAQLQ = Pediatric Asthma Quality of Life Questionnaire; RCT = randomized controlled trial; RR = relative risk; y = year

[a]Defined as any of following: (1) Hospitalization due to asthma; (2) Hypoxic seizure due to asthma; (3) Intubation due to asthma; (4) Requirement for a second burst of prednisone within any 6m period; (5) Significant adverse event related to the use of a study medication. The only criterion for assignment of treatment failure during the trial was the requirement for a second burst of prednisone within any six-month period.

Overview of Studies

Five RCTs[51,52,60,63,64] (n=972) were included in the analysis of intermittent ICS versus ICS controller. Three trials[51,52,63] enrolled patients 12y of age or older (mean 32 to 39y), all requiring an age of at least 18y to enter the trial. One trial enrolled patients 5 to 10y old and one trial[60] enrolled a mixed population (6 to 18y, mean 10 to 11y); thus, results of these trials are presented separately from results of patients 12y of age or older. Three trials[51,60,63] specified asthma to be mild persistent, two of which[60,63] required asthma to be controlled. One trial evaluated patients with mild to moderate persistent asthma that was well or partially well controlled[52] and the final trial[64] evaluated mostly mild persistent asthmatics, symptomatic at the start of the trial. Race was specified as Caucasian in 3 trials[60,63,64] ranging from 64 to 100 percent of subjects. In all trials, patients in the intervention arm were not on controller therapy. In 3 trials, intermittent ICS was triggered by the need for symptom relief where albuterol would normally be used, and ICS doses were taken with SABA doses as-needed.[52,60,63] ICS use was triggered by action plan specified symptoms consistent with the yellow zone in one trial[51] and upon symptom development that prompted contact with study physician who decided if intermittent ICS should be initiated in another trial[64]. In both of these trials[51,64] intermittent ICS duration was fixed (10 and 14d). In one trial, the control arm received physician-modified therapy according to the step-wise approach[52] while in the others patients were randomized to a fixed ICS dose. Duration of trials ranged from 6 to 18m. All but 1 trial[64] were multicenter, 3 trials[51,52,60] conducted in the US and the others outside of the US. Two trials[63,64] were industry sponsored while the others were nonindustry sponsored. Risk of bias was low in all trials.

Results

In patients 12y of age and older, intermittent ICS versus ICS controller therapy does not significantly differ in effect on the risk of exacerbations (low SOE), ACQ-7 or ACQ-5 score (low SOE), spirometry (low to high SOE), AQLQ(S) score (moderate SOE), or albuterol rescue use (moderate SOE).

In patients 5 to 11y old, there is insufficient evidence to draw conclusions on the impact of intermittent ICS versus ICS controller for all endpoints except for rescue albuterol use where there is a low SOE of no difference between the two strategies.

Subgroup Data

Race/ethnicity, albuterol reversibility, baseline FEV1, peak flow, symptoms, nitric oxide, sputum eosinophils: Calhoun et al., found that race/ethnicity and albuterol reversibility predicted the outcome of treatment failure. The odds of treatment failure were increased in Hispanics [Odds Ratio (OR) 3.6 (1.8 to 7.0)] and in blacks [OR 2.1 (1.2 to 4.0)] compared to non-Hispanic white subjects, p<0.02 for both comparisons. [52] There was also a significant interaction between race and efficacy suggesting a in non-Hispanic whites, intermittent ICS prevented treatment failure better than ICS controller [HR 4.50 (1.42 to 14.30)] whereas in Hispanics the opposite was found [HR 0.30 (0.04 to 1.80), p=0.01 comparing the two groups).[52] In this study, treatment failure was defined as a composite of asthma exacerbations, FEV1 measurement at home or in the office, SABA use, or use of additional asthma medications.[52] The following characteristics were not predictive of treatment failure: baseline forced expiratory volume in 1 second (FEV1), peak flow, symptoms, exhaled nitric oxide, sputum eosinophils.

FEV1 percent predicted: Boushey et al., compared subgroups of patients with FEV1 percent predicted 70 to 79 vs. greater than 80 percent and found no impact on the outcome of post-bronchodilatory FEV1.[51]

KQ1c: What is the comparative effectiveness of ICS with long-acting beta agonist (LABA) used as both controller and quick relief therapy compared to ICS with or without LABA used as controller therapy in patients 5 years of age and older with persistent asthma?

Results for this KQ are reported separately based on the comparator being ICS controller, ICS and LABA controller, or either comparator (conventional best practice [CBP]). CBP describes the comparator arm in a trial when either ICS or ICS and LABA controller was allowed. The estimated comparative daily ICS dose[1] was used to further categorize studies into the following 6 groups:

- ICS and LABA controller and quick relief versus ICS controller at the same comparative ICS dose (same dose)
- ICS and LABA controller and quick relief versus ICS controller at a higher comparative ICS dose (higher dose)
- ICS and LABA controller and quick relief versus ICS and LABA controller at the same comparative ICS dose (same dose)
- ICS and LABA controller and quick relief versus ICS and LABA controller at a higher comparative ICS dose (higher dose)
- ICS and LABA controller and quick relief versus ICS and LABA controller at a lower comparative ICS dose (lower dose)

- ICS and LABA controller and quick relief versus conventional best practice (CBP)

Some studies met criteria for more than one of the above 6 groups when multiple arms were reported. Although this KQ focuses on 2 of the 3 EPR-3 age categories (5 to 11y, 12y of age and older), all but two studies[83,115] were specific to the age category of 12 years of age and older. One trial[115] enrolled patients as young as 6y while the second trial[83] enrolled patients as young as 4y. This latter trial[83] was included because the mean age was 36y and the populations was considered to represent that of interest. We report results separately per age group when possible.

Key Points—ICS and LABA Controller and Quick Relief Versus ICS Controller

- In patients 12 years of age and older, ICS and LABA controller and quick relief versus ICS controller at the same comparative ICS dose reduces the risk of exacerbations as composite outcomes (all moderate SOE), improves FEV1 (moderate SOE) and reduces rescue medication inhalations per day (low SOE).
- In patients 12 years of age and older and in patients 4 to 11y old, ICS and LABA controller and quick relief versus ICS controller at a higher comparative ICS dose reduces the risk of exacerbations as composite outcomes (all low SOE).

Key Points—ICS and LABA Controller and Quick Relief Versus ICS and LABA Controller

- In patients 12 years of age and older, ICS and LABA controller and quick relief versus ICS and LABA controller at the same comparative ICS dose reduces the risk of composite exacerbations including systemic corticosteroid, hospitalization, or ER visits (high SOE) as well as each of the individual components of the composite outcome (moderate to high SOE). The chance of being an ACQ-5 responder (moderate SOE) and the mean inhalations per week of rescue inhaler (low SOE) also favored controller and quick relief therapy. Results of a subgroup of patients 4-11y old favor ICS and LABA controller and quick relief on composite exacerbation outcomes and on mild exacerbation risk (all low SOE).
- In patients 12 years of age and older, ICS and LABA controller and quick relief versus ICS and LABA controller at a higher comparative ICS dose reduces the risk of composite exacerbations including systemic corticosteroid, hospitalization, or ER visits (high SOE) but not individual components of the composite outcome (moderate SOE).
- There is insufficient evidence to determine the impact of ICS and LABA controller and quick relief versus ICS and LABA controller at a lower comparative ICS dose.

Key Points—ICS and LABA Controller and Quick Relief Versus CBP

- In patients 12 years of age and older, ICS and LABA as controller and quick relief versus CBP reduces the risk of composite exacerbations (requiring systemic corticosteroids, hospitalization, ER visit, moderate SOE) but not of the individual components of the composite outcome (low SOE). ACQ-5 scores were improved with ICS and LABA controller and quick relief (moderate SOE) and rescue medication use also favored ICS and LABA controller and quick relief (moderate SOE).

ICS and LABA as Controller and Quick Relief Versus ICS Controller at the Same Comparative ICS Dose

Table 13. Evidence overview for KQ1c, ICS and LABA controller and quick relief versus ICS controller (same dose) in patients 12 years of age and older

Outcome category	Outcome	Quantity and type of evidence (n)	Conclusion Effect estimate (95% CI)	Strength of evidence (rationale)
Exacerbations	Requiring systemic corticosteroids, hospitalization, ER visit, or having a PEF<70%	2 RCTs[94,96] (2586)	Favors controller and quick relief Scicchitano, 2004[96] RR 0.65 (0.55 to 0.78) Rabe, 2006[94] RR 0.49 (0.32 to 0.76)	Moderate (imprecise)
	Requiring systemic corticosteroids, hospitalization, or ER visit	1 RCT[96] (1890)	Favors controller and quick relief Scicchitano, 2004[96] RR 0.64 (0.53 to 0.78)	Moderate (unknown consistency)
Death	All-cause	1 RCT[96] (1890)	Inconclusive Scicchitano, 2004[96] OR 0.51 (0.05 to 4.92)	Insufficient (unknown consistency, imprecise)
	Asthma-specific	1 RCT[96] (1890)	Scicchitano, 2004[96] No events occurred	Insufficient[a] (no events occurred)
Spirometry	FEV1	1 RCT[96] (1890)	Favors controller and quick relief Scicchitano, 2004[96] MD 0.1 (0.07 to 0.13)	Moderate (unknown consistency)
Health care utilization	Rescue mediation use, number of inhalations/day	1 RCT[94] (697)	Favors controller and quick relief Rabe, 2006[94] MD -0.34 (-0.51 to -0.17)	Low (unknown consistency, imprecise)

CI = confidence interval; ER = emergency room; FEV1 = forced expiratory volume in one second; MD = mean difference; n = patient sample size; OR = odds ratio; PEF = peak expiratory flow; RCT = randomized controlled trial; RR = relative risk

[a]Strength of evidence was rated insufficient in the setting of downgrading only one domain because this is a single trial with rare events.

Overview of Studies

Three RCTs[94,96,99] (n=2658) were included in the analysis of ICS and LABA controller and quick relief versus ICS at the same comparative dose, all fitting in the age group of 12 years of age and older (mean 38 to 43y). Two trials[94,96] included patients 12 to 80y old and the third trial[99] included patients 18 to 70 years old. Sovani et al.,[99] enrolled patients with suboptimally controlled persistent asthma but also required patients to have evidence of poor adherence to medications and thus results are separately described from the other two trials. Poor adherence was defined in that trial as having collected less than 70 percent of the expected number of prescriptions for ICS in the year prior to the study.[99] The remaining two trials enrolled symptomatic patients, one[94] with mild to moderate persistent asthma and the other[96] with moderate to severe persistent asthma. Race was not reported. All trials compared budesonide/formoterol controller and quick relief to budesonide controller and short-acting β_2-agonist (SABA) quick relief. Two trials[94,96] were multicenter, multinational while the third[99] was multicenter in the UK. All trials were industry sponsored and were either 6 or 12mo in duration. Risk of bias was low in two trials[94,96] but high in one trial[99] due to the open-label design, high attrition, and lack of intention-to-treat analysis.

Results

In patients 12 years of age and older, a single trial[96] found the risk of exacerbation requiring systemic corticosteroid, hospitalization or ER visit was reduced by 36 percent with ICS and LABA controller and quick relief versus ICS at the same comparative dose (moderate SOE). Time to first exacerbation [hazard ratio (HR) 0.61 (0.49 to 0.75)] and exacerbation rate [incident rate ratio (IRR) 0.55 (0.46 to 0.66)] favored ICS and LABA controller and quick relief.[96] Addition of PEF<70 percent to that composite outcome also found a reduction in exacerbation risk favoring ICS and LABA controller and quick relief (moderate SOE). Time to first exacerbation including the PEF component [HR 0.61 (0.50 to 0.74)] and time to first mild exacerbation [HR 0.68 (0.61 to 0.75)] also favored ICS and LABA controller and quick relief versus ICS at the same comparative ICS dose.[96] One trial[96] reported death as an outcome but few events occurred (1 versus 2 deaths, in ICS and LABA controller and quick relief versus ICS controller), none of which were asthma-specific, thus data were insufficient to draw conclusions. Mean change in FEV1 improved (MD = 0.10 L) with ICS and LABA controller and quick relief in a single trial[96] (moderate SOE) as did rescue medication use inhalations/day (MD -0.34, low SOE).[94] Two trials[94,96] reported the total number of oral corticosteroid days which were numerically lower in the ICS and LABA controller and quick relief group (114 versus 498, 1176 versus 3177).

Sovani et al., found no difference in the mean change in ACQ-7 score, FEV1, or AQLQ-mini score.[99] The total number of oral corticosteroid courses was 6 per group.

ICS and LABA as Controller and Quick Relief Versus ICS Controller at a Higher Comparative ICS Dose

Table 14. Evidence overview for KQ1c, ICS and LABA controller and quick relief versus ICS controller (higher dose) in patients 12 years of age and older

Outcome category	Outcome	Quantity and type of evidence (n)	Conclusion Effect estimate (95% CI)	Strength of evidence (rationale)
Exacerbations	Requiring systemic corticosteroid, hospitalization, ER visit, or having a PEF<70%	1 RCT[83] (1851)	Favors controller and quick relief O'Byrne, 2005[a,83] RR 0.57 (0.48 to 0.69)	Low (unknown consistency, indirect)
	Requiring systemic corticosteroid, hospitalization, or ER visit	1 RCT[83] (1847)	Favors controller and quick relief O'Byrne, 2005[a,83] RR 0.58 (0.46 to 0.72)	Low (unknown consistency, indirect)

CI = confidence interval; ER = emergency room;; n = patient sample size; PEF = peak expiratory flow; RCT = randomized controlled trial; RR = relative risk; y = year

[a]O'Byrne enrolled patients 4 to 80y old although given this is the only trial that provides data for the EPR-3 age group of 12 years of age and older, we used the data but downgraded strength of evidence for indirectness

Table 15. Evidence overview for KQ1c, ICS and LABA controller and quick relief versus ICS controller (higher dose) in patients 4 to 11 years of age

Outcome category	Outcome	Quantity and type of evidence (n)	Conclusion Effect estimate (95% CI)	Strength of evidence (rationale)
Exacerbations	Requiring systemic corticosteroid, hospitalization, ER visit, increase in ICS or other medication or having a PEF<70%	1 RCT[75] (224)	Favors controller and quick relief Bisgaard, 2006[75] RR 0.55 (0.32 to 0.94)	Low[a] (unknown consistency, indirect, imprecise)
	Requiring systemic corticosteroid, hospitalization, ER visit or increase in ICS or other medication	1 RCT[75] (224)	Favors controller and quick relief Bisgaard, 2006[75] RR 0.43 (0.21 to 0.87)	Low[a] (unknown consistency, indirect, imprecise)
	Mild exacerbations[b]	1 RCT[75] (224)	No difference Bisgaard, 2006[75] RR 0.86 (0.72 to 1.04)	Low[a] (unknown consistency, indirect)

CI = confidence interval; EPR = Expert Panel Review (Guidelines for the Diagnosis and Management of Asthma); ER = emergency room; ICS = inhaled corticosteroid; n = patient sample size; PEF = peak expiratory flow; RCT = randomized controlled trial; RR = relative risk; y = year

[a] Strength of evidence was downgraded for indirectness due to the dose used in this study, which is lower than that approved in the package insert as well as what the EPR-3 considers "low dose" for this age group.
[b]Defined as 2 consecutive days with one of the following: morning PEF greater than or equal to 20 percent below the average run-in value, as-needed medication use two or more inhalations a day above baseline, or awakenings due to asthma

Overview of Studies

One multicenter, multinational trial[83] (n=1851) of 12m duration was included. The patients represented a mixed age (4 to 80y, mean 36y, 12% of patients <12y) although given this is the only source of data for patients 12 years of age and older, we utilized the data but downgraded SOE for being indirect. Patients had persistent, symptomatic asthma and race was not reported. Patients were randomized to ICS and LABA (budesonide/formoterol) controller and quick relief versus ICS (budesonide) controller at a higher comparative dose with SABA quick relief. The trial reported industry sponsorship and had low risk of bias.

Results

Using the full trial population data to suggest effect in patients 12 years of age and older, the risk of exacerbation requiring systemic corticosteroid, hospitalization or ER visit was reduced by 42 percent with ICS and LABA controller and quick relief versus ICS at a higher comparative dose (low SOE).[83] Time to first exacerbation [HR 0.55 (0.43 to 0.70)] and exacerbation rate [IRR 0.54 (0.44 to 0.66)] favored ICS and LABA controller and quick relief. Addition of PEF<70 percent to that composite outcome also found a reduction in exacerbation risk favoring ICS and LABA controller and quick relief (low SOE). Time to first exacerbation including the PEF component [HR 0.53 (0.43 to 0.65)] and exacerbation rate [IRR 0.53 (0.44 to 0.64)] and the rate of mild exacerbation [IRR 0.64 (0.57 to 0.73)] also favored ICS and LABA controller and quick relief. In the pre-planned subgroup analysis of patients 4 to 11y old (mean 8y), the same two composite exacerbation outcomes also favored ICS and LABA (both low SOE) controller and quick relief although risk of mild exacerbations was no different.[75] Time to first composite exacerbation that included the PEF component favored ICS and LABA controller and quick relief [HR 0.49 (0.27 to 0.90)].

ICS and LABA as Controller and Quick Relief Versus ICS and LABA Controller at the Same Comparative ICS Dose

Table 16. Evidence overview for KQ1c, ICS and LABA controller and quick relief versus ICS and LABA controller (same dose) in patients 12 years of age and older

Outcome category	Outcome	Quantity and type of evidence (n)	Conclusion Effect estimate (95% CI)	Strength of evidence (rationale)
Exacerbations	Requiring systemic corticosteroid	2 RCTs[70,84] (3792)	Favors controller and quick relief Atienza, 2013[70] RR 0.77 (0.62 to 0.95) Papi, 2013[84] RR 0.62 (0.49 to 0.79)	High
	Requiring hospitalization	2 RCTs[70,86] (2224)	Favors controller and quick relief Atienza, 2013[70] RR 0.33 (0.17 to 0.65) Patel, 2013[86] RR 1.01 (0.14 to 7.05)	Low (inconsistent, imprecise)
	Requiring ER visit	1 RCT[70] (2091)	Favors controller and quick relief Atienza, 2013[70] RR 0.74 (0.59 to 0.93)	Moderate (unknown consistency)
	Requiring intubation	1 RCT[86] (1701)	Papi, 2013[86] No events occurred	Insufficient (no events occurred)
	Requiring systemic corticosteroid, hospitalization, or ER visit	5 RCTs[70,84,86,93,103] (8483)	Favors controller and quick relief RR 0.68 (0.58 to 0.80)	High
	Requiring hospitalization or ER visit	5 RCTs[70,84,86,93,103] (8313)	Favors controller and quick relief RR 0.69 (0.63 to 0.76)	High
	Requiring systemic corticosteroid, hospitalization, ER, or unscheduled visit	1 RCT[103] (2143)	Favors controller and quick relief Vogelmeier, 2005[103] RR 0.79 (0.65 to 0.95)	Moderate (unknown consistency)
	Mild exacerbation[a]	3 RCTs[70,84,93] (6037)	No difference RR 0.94 (0.81 to 1.09)	Moderate (inconsistent)
Death	All-cause	4 RCTs[70,86,93,103] (6782)	No difference OR 0.43 (0.04 to 4.49)	Moderate (imprecise)
	Asthma-specific	4 RCTs[70,86,93,103] (6782)	No events occurred	Insufficient (no events occurred)
Asthma control composite scores	ACT score	1 RCT[102] (63)	Inconclusive Takeyama, 2014[102] MD 6.3 (5.15 to 7.45)	Insufficient (unclear ROB, unknown consistency)
	ACQ-5 score	3 RCT[70,78,93] (4353)	No difference MD -0.16 (-0.39 to 0.06)	Low (inconsistent, imprecise)
	ACQ-5 responder[b]	1 RCT[70] (2091)	Favors controller and quick relief Atienza, 2013[70] RR 1.14 (1.05 to 1.24)	Moderate (unknown consistency)
Spirometry	FEV1	5 RCTs[70,84,86,93,101] (6343)	No difference MD 0.04 (0.00 to 0.09)	Low (inconsistent, imprecise)

Outcome category	Outcome	Quantity and type of evidence (n)	Conclusion Effect estimate (95% CI)	Strength of evidence (rationale)
	FEV1 % predicted	2 RCTs[78,86] (304)	No difference Patel, 2013[86] MD 1.8 (-2.8 to 6.4) Hozawa, 2014[78] MD 1.9 (-4.27 to 8.07)	Moderate (medium ROB)
	FVC	1 RCT[84] (1701)	No difference Papi, 2013[84] MD -0.01 (-0.07 to 0.04)	Low (unknown consistency, imprecise)
Health care utilization	Rescue medication use, number of inhalations/day	3 RCT[70,84,93] (6006)	No difference MD -0.16 (-0.45 to 0.14)	Low (inconsistent, imprecise)
	Rescue medication use, number of inhalations/week	2 RCTs[78,101] (93)	Favors controller and quick relief Hozawa, 2014[78] MD -0.73 (-1.42 to -0.04) Takeyama, 2014[101] MD -2.2 (-3.92 to -0.48)	Low (medium ROB, imprecise)

ACQ = Asthma Control Questionnaire; ACT = Asthma Control Test; CI = confidence interval; ER = emergency room; FEV1 = forced expiratory volume in one second; FVC = forced vital capacity; MD = mean difference; n = patient sample size; OR = odds ratio; PEF = peak expiratory flow; RCT = randomized controlled trial; ROB = risk of bias; RR = relative risk; y = year

[a]Defined as meeting one of the following: the need for 2 or more as-needed medication inhalations over baseline, nighttime awakening from asthma or PEF decrease by at least 20 percent
[b]Defined as a reduction in score by 0.5 or more

Table 17. Evidence overview for KQ1c, ICS and LABA controller and quick relief versus ICS and LABA controller (same dose) in patients 4 to 11 years of age

Outcome category	Outcome	Quantity and type of evidence (n)	Conclusion Effect estimate (95% CI)	Strength of evidence (rationale)
Exacerbations	Requiring systemic corticosteroids, hospitalization, ER visit, increase in ICS or other medication or having a PEF<70%	1 RCT[75] (341)	Favors controller and quick relief Bisgaard, 2006[75] RR 0.38 (0.23 to 0.63)	Low (unknown consistency, indirect)[a]
	Requiring hospitalization, systemic corticosteroids, ER visit, or increase in ICS or other medications	1 RCT[75] (341)	Favors controller and quick relief Bisgaard, 2006[75] RR 0.28 (0.14 to 0.53)	Low (unknown consistency, indirect)[a]
	Mild exacerbations[b]	1 RCT[75] (341)	Favors controller and quick relief Bisgaard, 2006[75] RR 0.75 (0.64 to 0.88)	Low (unknown consistency, indirect)[a]

CI = confidence interval; ER = emergency room; n = patient sample size; OR = odds ratio; PEF = peak expiratory flow; RCT = randomized controlled trial; RR = relative risk; y = year

[a] Strength of evidence was downgraded for indirectness due to the dose used in this study, which is lower than that approved in the package insert as well as what the EPR-3 considers "low dose" for this age group.[b] Defined as meeting one of the following: the need for 2 or more as-needed medication inhalations over baseline, nighttime awakening from asthma or PEF decrease by at least 20 percent

Overview of Studies

Nine RCTs[70,78,83,84,86,93,100,101,103] (n=12,902) were included in the analysis of ICS and LABA controller and quick relief versus ICS and LABA controller at the same comparative ICS dose, all but one fitting the age group of 12 years of age and older (mean 39 to 49y). O'Byrne et al.,[83] enrolled patients 4 to 80y old thus was not pooled with the base analysis but added in a sensitivity analysis given the mean age was 36y. The trial provided data from a pre-planned subgroup analysis of 4 to 11y olds which are presented separately.[75] Of the trials meeting the age group 12 years of age and older, most required the age of 12y[93,100,104] or 16y[70,86,101] for inclusion. Vogelmeier et al.,[103] although fitting into this group based on ICS comparative doses at the start of the trial, allowed dose titration in the comparator group; and thus we conducted sensitivity analysis excluding this trial. Of the 9 trials, 1 trial[101] further specified persistent asthma severity as moderate to severe. Six trials enrolled patients with symptomatic asthma,[70,78,83,93,101,103] 1 trial[100] enrolled patients regardless of symptom presence, 4 trials[70,78,84,101] specified patients were not controlled, and 1 trial[86] did specify control or symptom presence. Race was reported in one trial[70] and was 31.8 percent Caucasian and 62.3 percent Asian. Six trials used budesonide/formoterol in both arms[70,83,86,93,100,101] and 1 trial[84] compared beclomethasone/formoterol in both arms. Two trials compared budesonide/formoterol controller and quick relief to fluticasone/salmeterol controller.[78,103] The comparator in Stallberg et al.,[100] included both similar and a higher comparative ICS dose thus this trial was excluded from pooled analysis. Seven trials[70,78,83,84,93,100,103] were industry sponsored and 2 trials[86,101] were nonindustry sponsored. Five trials[70,83,84,93,103] were multicenter, multinational while the others were conducted in a single country (Japan, Sweden, New Zealand). Trials were mostly 12m in duration but ranged from 8 weeks to 1 year. Risk of bias was low in all trials except 4[78,86,100,103] considered medium risk of bias due to the open-label design and 1 trial[101] had an unclear risk of bias.

Results

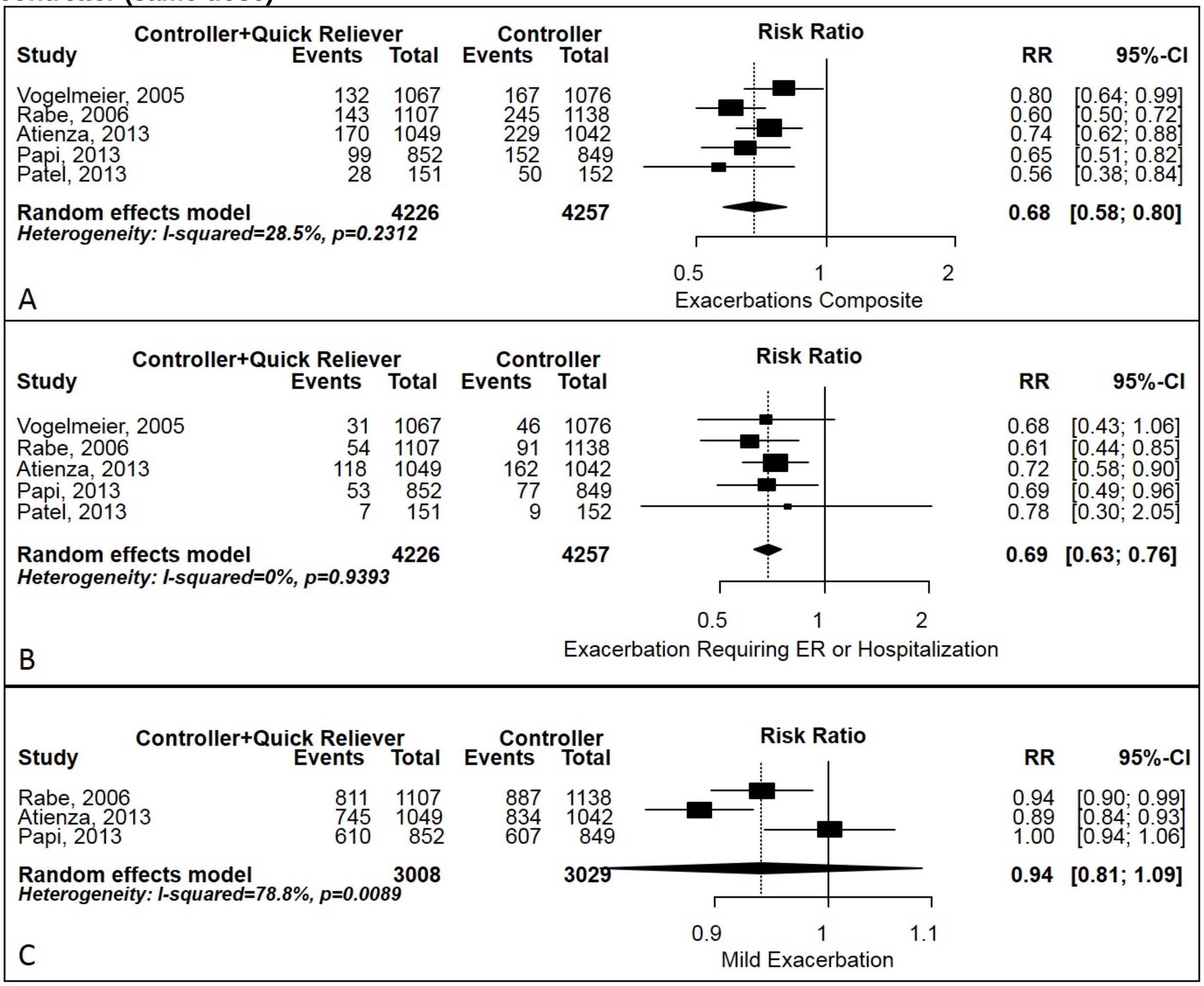
In patients 12y and older, ICS and LABA controller and quick relief versus ICS and LABA controller at the same comparative ICS dose reduces the risk of exacerbation requiring systemic corticosteroids by 23 percent to 38 percent (high SOE), the risk of exacerbation requiring hospitalization by 67 percent (moderate SOE), the risk of exacerbation requiring ER visit by 26 percent (moderate SOE) and the composite outcome of all three exacerbation types by 32 percent (high SOE) (Figure 6, Panel A). Time to first composite exacerbation was reduced in favor of controller and quick relief [HR 0.65 (0.54 to 0.78)] as was rate of composite exacerbations [IRR 0.54 (0.42 to 0.69)]. One trial reported that no patients required intubation from exacerbation.[84] Additional composite outcomes for exacerbation also suggest reduction in risk favoring ICS and LABA as controller and quick relief (moderate to high SOE) (Figure 6, Panel B) although no difference was found for the risk of mild exacerbations (Figure 6, Panel C) or in the time to first mild exacerbation [HR 0.88 (0.71 to 1.10)]. Deaths were infrequent and occurred in 3 of the 4 trials reporting this outcome[70,86,93,103] and no difference was found (moderate SOE). No asthma specific deaths occurred. Sensitivity analysis adding O'Byrne et al.,[83] to the composite of exacerbations requiring systemic steroids, hospitalization or ER visits [relative risk (RR) 0.65 (0.55 to 0.77), HR 0.62 (0.52 to 0.74), IRR 0.52 (0.44 to 0.63)] did not impact the magnitude or direction of effect for any results. Sensitivity analysis removing Vogelmeier et al.,[103] did not impact magnitude or direction of effect for the composite of exacerbations requiring systemic steroids, hospitalization or ER visits [RR 0.66 (0.55 to 0.78), HR 0.62 (0.51 to 0.76)], exacerbation requiring hospitalization or ER visit [RR 0.69 (0.60 to 0.79)] or death [OR 0.68 (0.01 to 34.96)].

Mean difference in ACQ-5 score was no different between groups although 1 trial[86] found the chance of being an ACQ-5 responder to favor ICS and LABA controller and quick relief (moderate SOE). Asthma Control Test (ACT) score was reported by a single trial with unclear risk of bias thus impact of ICS and LABA controller and quick relief is undetermined. Mean change in FEV1, FEV1 percent predicted and FVC were no different between groups although the lower limit of the confidence interval for FEV1 was at zero. Mean inhalations of rescue medication per day was no different between groups but when evaluated as mean inhalations per week, favored ICS and LABA controller and quick relief therapy (low SOE).

Stallberg et al., found no difference in the composite exacerbation outcome of those requiring systemic corticosteroids, hospitalization or ER visit with ICS and LABA controller and quick relief versus ICS and LABA controller and a similar or higher comparative ICS dose, in patients 12y old and older.[100]

In patients 4 to 11 years old ICS and LABA controller and quick relief versus ICS and LABA controller reduces the risk of three exacerbation types (all low SOE): the composite of exacerbations requiring systemic corticosteroids, hospitalization, ER visit, increase in ICS or other medication or having a PEF less than 70 percent; the composite of exacerbations requiring hospitalization, systemic corticosteroids, ER, or increase in ICS or other medications; and finally mild exacerbations.[75]

Figure 6. Risk of exacerbation: ICS and LABA controller and quick relief versus ICS and LABA controller (same dose)



CI = confidence interval; ER = emergency room; RR = relative risk

Subgroup Data

Race/ethnicity: Pilcher et al.,[90] conducted an analysis of a prior trial[86] for ethnicity-treatment interaction with specific interest in Maori versus non-Maori people. Maori are indigenous Polynesians of New Zealand. Maori had a greater improvement in ACQ-7 score than non-Maori [-1.01 (-1.55 to -0.51) versus -0.10 (-0.31 to 0.11), p<0.001] at the end of the trial. Vogelmeier et al., conducted a post-hoc subgroup analysis[104] of patients 16 years of age and older old in Asian countries (China, Taiwan, Korea and Thailand) from a prior international trial that enrolled patients 12 years of age and older .[103] Being Asian vs. the international population did not affect the composite exacerbation outcome. [104]

Baseline ICS dose: Papi et al.,[84] found that regardless if maintenance ICS dose on entry was less than or equal to 500µg or greater than 500µg beclomethasone equivalents, the rate of and time to first exacerbation requiring systemic corticosteroid, hospitalization or ER visit favored ICS and LABA controller and quick relief versus ICS and LABA controller, consistent with the main results study results.

Smoking status: Pilcher et al.,[116] conducted an analysis of a prior trial[86] regarding the effect of smoking status on outcomes. Being a current, former or never smoker did not impact treatment efficacy for the outcomes of exacerbations, hospital or ER attendance, ACQ-7 or FEV1.

FEV1 percent predicted, exacerbation history and gender: Patel et al.,[87] analyzed data from a prior trial[86] and found the following patient characteristics to increase the risk of exacerbation requiring systemic corticosteroids or hospitalization/ER visit for treatment: lower baseline FEV1 percent predicted per 10 percent [rate ratio 1.14 (1.03 to 1.27)], higher number of exacerbations in the prior year per 1 exacerbation [rate ratio 1.15 (1.01 to 1.13)], treatment with ICS and LABA controller as opposed to controller and quick relief [rate ratio 1.62 (1.07 to 2.47)], and female gender [rate ratio 2.18 (1.29 to 3.67)].

ICS and LABA as Controller and Quick Relief Versus ICS and LABA Controller at a Higher Comparative ICS Dose

Table 18. Evidence overview for KQ1c, ICS and LABA controller and quick relief versus ICS and LABA controller (higher dose) in patients 12 years of age and older

Outcome categories	Outcome	Quantity and type of evidence (n)	Conclusion Effect estimate (95% CI)	Strength of evidence (rationale)
Exacerbations	Requiring systemic corticosteroid	1 RCT[76] (2304)	No difference Bousquet, 2007[76] RR 0.82 (0.62 to 1.07)	Moderate (unknown consistency)
	Requiring systemic corticosteroid, hospitalization, or ER visit	3 RCTs[76,81] (6742)	Favors controller and quick relief RR 0.75 (0.59 to 0.96)	High
	Requiring hospitalization or ER visit	3 RCTs[76,81] (6742)	No difference RR 0.76 (0.46 to 1.25)	Moderate (imprecise)
	Mild exacerbation[a]	2 RCTs[81] (3321)	No difference Kuna, 2007a[81] RR 0.97 (0.91 to 1.04) Kuna, 2007b[81] RR 1.04 (0.97 to 1.11)	Moderate (unknown consistency because single trial)
Death	All-cause	4 RCTs[76,81,89] (5757)	No difference OR 2.72 (0.38 to 19.31)	Moderate (imprecise)
	Asthma-specific	4 RCTs[76,81,89] (5757)	No events occurred	Insufficient (no events occurred)
Asthma control composite scores	ACQ-5 score	3 RCTs[76,81] (6559)	No difference Bousquet, 2007[76] MD -0.02 (-0.07 to 0.04) Kuna, 2007a[81] MD -0.02 (-0.08 to 0.05) Kuna, 2007b[81] MD 0.03 (-0.03 to 0.09)	High
Spirometry	FEV1	2 RCTs[81] (4424)	No difference Kuna, 2007a[81] MD 0.01 (-0.03 to 0.04) Kuna, 2007b[81] MD 0.01 (-0.03 to 0.04)	Moderate (unknown consistency)
Quality of life	AQLQ(S) score	2 RCTs[81] (4270)	No difference Kuna, 2007a[81] MD 0.01 (-0.07 to 0.08) Kuna, 2007b[81] MD -0.02 (-0.09 to 0.06)	Moderate (unknown consistency because single trial)

Outcome categories	Outcome	Quantity and type of evidence (n)	Conclusion Effect estimate (95% CI)	Strength of evidence (rationale)
Heath care utilization	Rescue medication use, number of inhalations/day	3 RCTs[76,81] (6559)	No difference Bousquet, 2007[76] MD -0.04 (-0.12 to 0.04) Kuna, 2007a[81] MD -0.03 (-0.12 to 0.06) Kuna, 2007b[81] MD 0.07 (-0.02 to 0.16)	High

ACQ = Asthma Control Questionnaire; AQLQ = Asthma Quality of Life Questionnaire; CI = confidence interval; ER = emergency room; FEV1 = forced expiratory volume in one second; MD = mean difference; n = patient sample size; OR = odds ratio; RCT = randomized controlled trial; RR = relative risk

[a]Defined as meeting one of the following: the need for 2 or more as-needed medication inhalations over baseline, nighttime awakening from asthma or a PEF decrease by at least 20 percent

Overview of Studies

Five RCTs[76,81,89,100,115] (n=7605) were included in the analysis of ICS and LABA as controller and quick relief versus ICS and LABA controller at a higher comparative ICS dose. Kuna et al., contributed two unique comparisons which were considered independently for analysis.[81] All trials fit the age group of 12 years of age and older (mean 38 to 45y) except Lundborg et al.,[115] which studied a mixed age group (≥6y old). However, this trial[115] used formoterol instead of SABA as quick relief in the control arm thus the trial was not pooled with the others. Three trials enrolled patients with symptomatic persistent asthma[76,81,89] and two trials enrolled patients with persistent asthma and mixed control/presence of symptoms.[100,115] Race was not reported. All studies compared budesonide/formoterol as controller and quick relief to either fluticasone/salmeterol controller[76,81] or budesonide/formoterol controller.[81,89,100,115] The comparator in Stallberg et al.,[100] included both similar and a higher comparative ICS dose thus this trial was excluded from pooled analysis. All trials were multicenter and industry sponsored, 3 trials[76,81,89] were multinational and 2[100,115] were conducted in Sweden. Trials ranged from 6 to 12m in duration. Risk of bias was low in 3 trials[76,81,89] and medium in 2 trials[100,115] due to the open-label design and the risk of performance and detection bias.

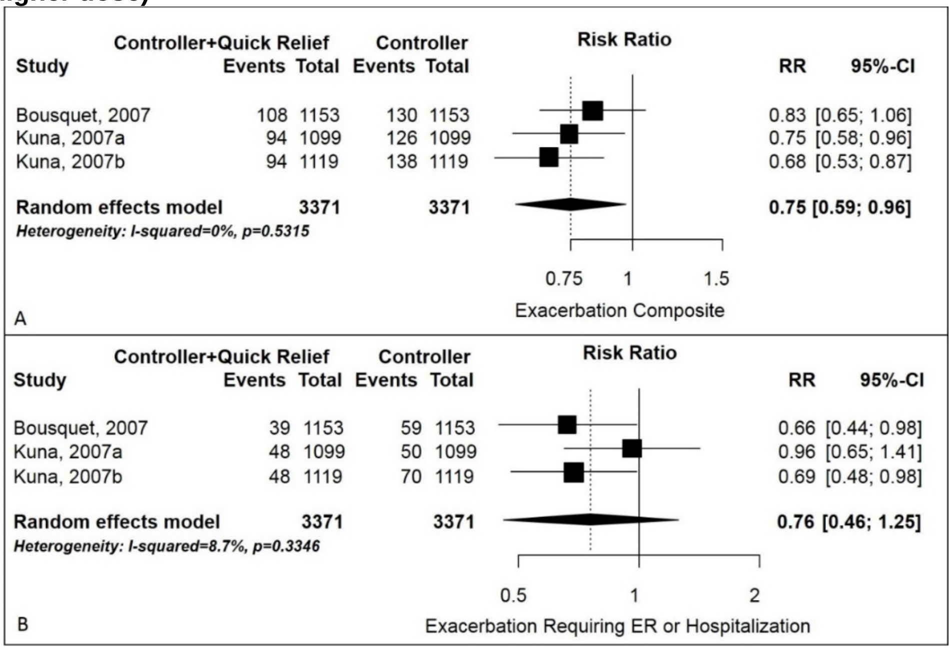
Results

In patients 12 years of age and older, ICS and LABA as controller and quick relief versus ICS and LABA controller at a higher comparative ICS dose did not significantly differ in effect on the risk of exacerbations requiring systemic corticosteroids or requiring hospitalization/ER visit (Figure 7, Panel B) (both moderate SOE) but when evaluated as a composite outcome requiring systemic corticosteroids, hospitalization or ER visit risk was reduced by 25 percent (high SOE) (Figure 7, Panel A). The risk of mild exacerbations was no different (moderate SOE). Deaths occurred in 3 of the 4 trials reporting this outcome[76,81] and no difference was found (moderate SOE). No asthma-specific deaths occurred. There was no difference in ACQ-5 score (high SOE), FEV1 (moderate SOE), AQLQ(S) score (moderate SOE) or rescue medication use (high SOE).

Lundborg et al.,[115] provided data for patients 6y and older and compared two approaches to controller and quick relief therapy, budesonide/formoterol once daily or twice daily, both compared to ICS and LABA controller and formoterol quick relief. ACQ-5 was no different with either controller and quick relief approach compared to ICS and LABA controller. Stallberg et al., found no difference in the composite exacerbation outcome of those requiring systemic corticosteroids, hospitalization or ER visit with ICS and LABA controller and quick relief versus

ICS and LABA controller and a similar or higher comparative ICS dose, in patients 12y old and older.[100]

Figure 7. Risk of exacerbation: ICS and LABA controller and quick relief versus ICS and LABA controller (higher dose)



CI = confidence interval; ER = emergency room; RR = relative risk

Subgroup Data

Race/ethnicity: Lin et al.,[113] conducted a post-hoc subgroup analyses comparing Chinese patients vs. the full international population and found no impact on the outcomes of exacerbation and ACQ-5 score.

Age: Kuna et al.,[80] conducted a post-hoc subgroup analysis of a prior trial[81] in patients 16y of age and older old vs. the original population of 12 years of age and older and found no impact on the outcomes of exacerbations, ACQ-5, AQLQ(S) or rescue medication use inhalations/d.

ICS and LABA as Controller and Quick Relief Versus ICS and LABA Controller at a Lower Comparative ICS Dose

Table 19. Evidence overview for KQ1c, ICS and LABA controller and quick relief versus ICS and LABA controller (lower dose) in patients 12 years of age and older

Outcome category	Outcome	Quantity and type of evidence (n)	Conclusion Effect estimate (95% CI)	Strength of evidence (rationale)
Asthma control composite scores	ACQ-5 score	1 RCT[117] (30)	Inconclusive Hozawa, 2016[117] MD -0.40 (-0.53 to -0.27)	Insufficient (medium ROB, unknown consistency, imprecise)
Spirometry	FEV1 % predicted	1 RCT[117] (30)	Inconclusive Hozawa, 2016[117] MD 3.10 (-1.36 to 7.56)	Insufficient (medium ROB, unknown consistency)

Outcome category	Outcome	Quantity and type of evidence (n)	Conclusion Effect estimate (95% CI)	Strength of evidence (rationale)
Health care utilization	Rescue medication use, number of inhalations/week	1 RCT[117] (30)	Inconclusive Hozawa, 2016[117] MD -0.9 (-1.48 to -0.32)	Insufficient (medium ROB, unknown consistency, imprecise)

ACQ = Asthma Control Questionnaire; CI = confidence interval; FEV1 = forced expiratory volume in one second; MD = mean difference; n = patient sample size; RCT = randomized controlled trial; ROB = risk of bias; RR = relative risk

Overview of Studies

One RCT[117] (n=30) was included in the analysis of ICS and LABA as controller and quick relief versus ICS and LABA controller at a lower comparative ICS dose. Hozawa et al., studied patients 20y of age and older, with a mean age of 41y. Patients were considered to have symptomatic, persistent asthma. Race was not reported. Patient were randomized to budesonide/formoterol as controller and quick relief or fluticasone/vilanterol as controller with procaterol as needed. The trial was single center, industry-sponsored in Japan for 4 weeks. Risk of bias was medium due to the open-label design and the risk of performance and detection bias.

Results

Although the outcomes of ACQ-5 score, FEV1 percent predicted, and rescue medication use were reported, the evidence is insufficient to draw a conclusion.

ICS and LABA as Controller and Quick Relief Versus CBP

Table 20. Evidence overview for KQ1c, ICS and LABA controller and quick relief versus CBP in patients 12 years of age and older

Outcome category	Outcome	Quantity and type of evidence (n)	Conclusion Effect estimate (95% CI)	Strength of evidence (rationale)
Exacerbations	Requiring systemic corticosteroid	4 RCTs[82,91,97,98] (4935)	No difference RR 0.84 (0.61 to 1.17)	Low (medium ROB, imprecise)
	Requiring hospitalization	4 RCTs[82,91,97,98] (4935)	No difference OR 0.89 (0.34 to 2.30)	Low (medium ROB, imprecise)
	Requiring ER visit	4 RCTs[82,91,97,98] (4935)	No difference RR 0.78 (0.50 to 1.21)	Low (medium ROB, imprecise)
	Requiring systemic corticosteroid, hospitalization, or ER visit	6 RCTs[82,91,95,97,98,100] (6354)	Favors controller and quick relief RR 0.78 (0.64 to 0.95)	Moderate (medium ROB)
Death	All-cause	4 RCTs[82,91,97,98] (4935)	No difference OR 2.20 (0.32 to 14.96)	Moderate (imprecise)
	Asthma-specific	4 RCTs[82,91,97,98] (4935)	No events occurred	Insufficient (no events occurred)
Asthma control composite scores	ACQ-5 score	5 RCTs[82,91,95,97,98] (4996)	Favors controller and quick relief MD -0.09 (-0.14 to -0.03)	Moderate (medium ROB)

Outcome category	Outcome	Quantity and type of evidence (n)	Conclusion Effect estimate (95% CI)	Strength of evidence (rationale)
	ACQ-5 responder[a]	2 RCTs[91,97] (2166)	Favors controller and quick relief Sears, 2008[97] RR 1.22 (1.03 to 1.44) Quirce, 2011[91] RR 1.09 (0.92 to 1.30)	Moderate (medium ROB)
Spirometry	FEV1	1 RCT[82] (271)	No difference Louis, 2009[82] MD -0.03 (-0.12 to 0.06)	Low (unknown consistency)[b]
	FEV1 % predicted	1 RCT[95] (102)	No difference Riemersma, 2012[95] MD 0.70 (-1.80 to 3.20)	Low (unknown consistency)[b]
Health care utilization	Rescue medication use, number of inhalations/day	2 RCTs[82,97] (2404)	Favors controller and quick relief Sears, 2008[97] MD -0.16 (-0.26 to -0.05) Louis, 2009[82] MD -0.10 (-0.24 to 0.03)	Moderate (medium ROB)
	≥1 day w/PRN inhalation	2 RCTs[82,91] (1562)	Favors CBP Louis, 2009[82] RR 2.96 (2.42 to 3.61) Quirce, 2011[91] RR 0.96 (0.90 to 1.01)	Low (medium ROB, inconsistent)

Abbreviations: ACQ=Asthma Control Questionnaire; CBP=conventional best practice; CI=confidence interval; ER=emergency room; FEV1=forced expiratory volume in one second; MD=mean difference; n=patient sample size; OR=odds ratio; PRN=pro re nata (as-needed); RCT=randomized controlled trial; ROB=risk of bias; RR=relative risk

[a]Responder was defined as a reduction in score by 0.5 or more
[b]Strength of evidence was rated low even in the setting of one domain downgraded because of the small sample size within a single trial for this outcome and thus lack of confidence in the true effect estimate.

Overview of Studies

Six RCTs[82,91,95,97,98,100] (n=6832) and two observational studies[79,114] (n=536) were included in the analysis of ICS and LABA as controller and quick relief versus CBP, all fitting the age category of 12 years of age and older (mean age 40 to 51y). Two trials enrolled patients with mild to severe asthma,[91,97] 1 enrolled mild to moderate asthma,[95] and the remaining trials did not further classify persistent asthma severity. Two trials enrolled patients considered to have suboptimal asthma control[91,97] and the remaining trials enrolled a mixed population in terms of control and/or symptom presence[82,95,98,100] One trial reported race, which was 94 percent Caucasian.[97] All trials compared budesonide/formoterol as both controller and quick relief to what we refer to as "CBP". All patients in the CBP groups received at a minimum ICS and of the trials reporting further details[82,91,97,98] greater than 80 percent were also on LABA. Changes in medications and doses were determined by the physician throughout the course of the trial. All trials were multicenter industry sponsored. Trials ranged from 6 to 12m in duration. Risk of bias was medium in all trials due to the open-label design and the risk of performance and detection bias.

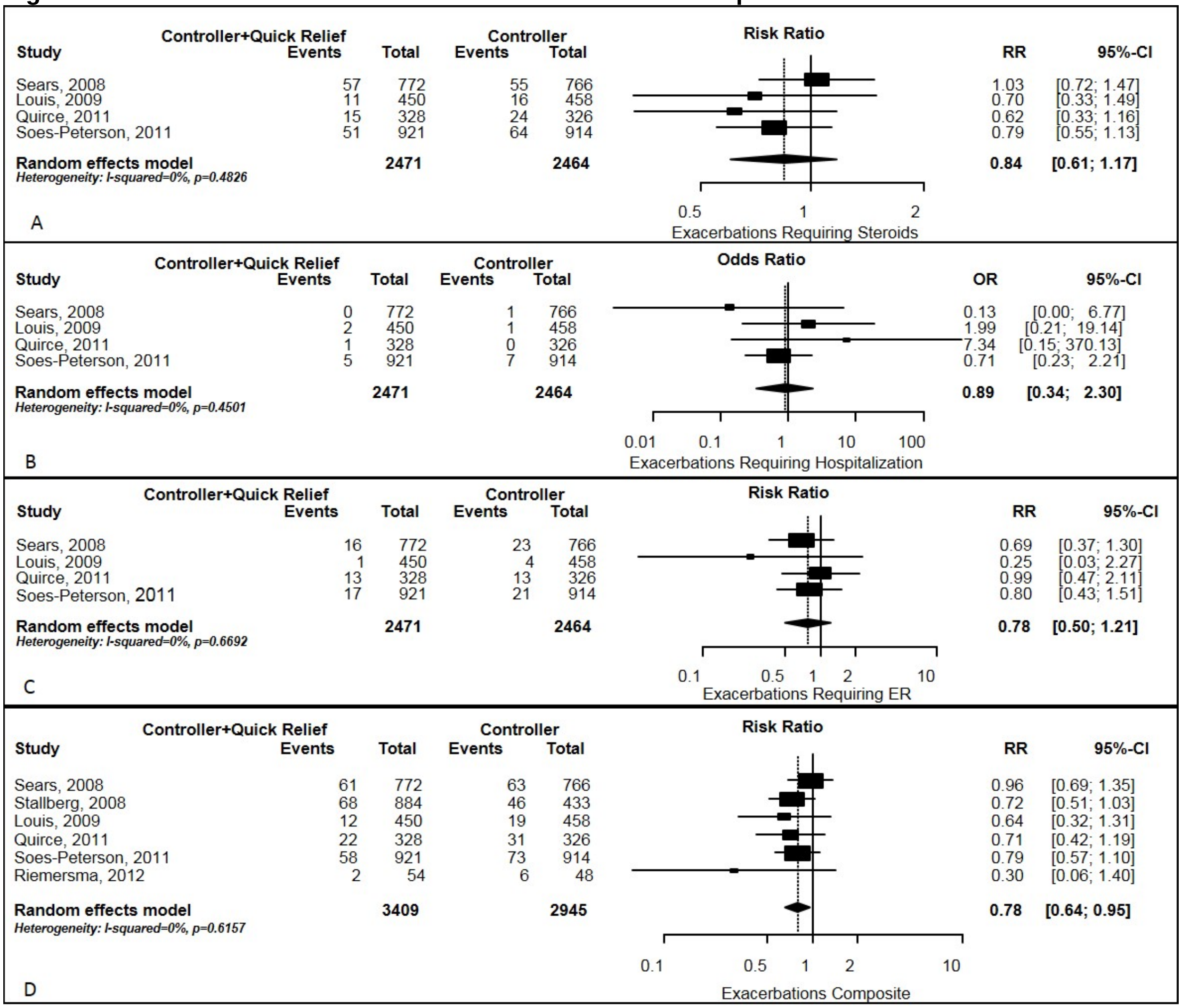
Results

ICS and LABA as controller and quick relief versus CBP did not significantly differ in the effect on the risk of exacerbations requiring systemic corticosteroids, requiring hospitalization, or requiring ER visits (all low SOE) (Figure 8, Panels A-C) but when evaluated as a composite outcome reduces the risk of exacerbations by 22 percent (moderate SOE) (Figure 8, Panel D). Time to first composite exacerbation was not significantly reduced [HR 0.85 (0.58 to 1.23)] while the IRR was in favor of ICS and LABA as controller and quick relief therapy [IRR 0.83 (0.70 to 0.99)]. Deaths were infrequent and occurred in 3 of the 4 trials reporting this outcome[82,97,98] and no difference was detected. No asthma-specific deaths occurred. Spirometry was infrequently reported and in the single trial that measured FEV1 and FEV1 percent predicted, no difference was found (both low SOE). Mean difference in ACQ-5 favored ICS and LABA as controller and quick relief therapy (MD -0.09, moderate SOE) while the chance of being an ACQ-5 responder was increased in 1 trial[97] with ICS and LABA as controller and quick relief by 22 percent (moderate SOE) but a second trial[91] found no difference.

Asthma-specific quality of life was not reported in these trials. The mean difference in rescue medication use favored ICS and LABA controller and quick relief therapy in 1 trial[97] but was no different in a second trial[82] (moderate SOE). The chance of needing at least 1 day with as-needed inhaler use favored CBP in 1 trial[82] but found no difference in a second trial[91]. Three trials[82,91,97] reported the total number of oral corticosteroid days during the trial which was numerically higher with CBP in each trial and one trial provided a p-value indicating statistical significance.

Two observational studies evaluated patients who were treated with ICS and LABA as a controller and quick relief medication versus ICS and LABA as controller with SABA quick relief.[79,114] In both studies, the mean age was 50y, race was not reported, and asthma was described as requiring step 3 treatment according to the Global Initiative for Asthma guidelines. Kardos et al.,[79] was industry sponsored and determined to have low risk of bias while Loh et al.,[114] was nonindustry sponsored but with medium risk of bias due to incomparability of the groups compared. Kardos et al.,[79] found that mean annual exacerbation rate was not significantly different with ICS and LABA controller and quick relief ([0.20 (0.14 to 0.29)] compared to ICS and LABA controller [0.17 (0.10 to 0.29)], p=0.66). Rescue medication use was reduced with ICS and LABA controller and quick relief versus ICS and LABA controller [MD -0.266 (-0.474 to -0.057), p=0.013]. AQLQ(S) change from baseline was greater in the ICS and LABA controller group [mean change 0.42 (0.89)] than in the ICS and LABA controller and quick relief group [mean change 0.25 (0.82)]. FEV1 improved in both groups and the difference was greater in the ICS and LABA controller and quick relief group [mean change 0.13 (0.48) versus 0.07 (0.431)]. Two patients (0.6%) needed ER treatment in the ICS and LABA controller and quick relief group and one (0.6%) needed hospitalization in the ICS and LABA controller group. Loh et al.,[114] found that rescue medication use was reduced significantly in both patients treated with ICS and LABA controller and quick relief and those treated with ICS and LABA controller. In the ICS and LABA controller and quick relief group, FEV1 significantly improved (median difference 90 mL, p=0.013) as did the rate of hospitalizations (p=0.039) compared with ICS and LABA controller, although the rate of ER visits did not differ.

Figure 8. Risk of exacerbation: ICS and LABA controller and quick relief versus CBP



CI = confidence interval; ER = emergency room; RR = relative risk

KQ2a: What is the comparative effectiveness of long-acting muscarinic antagonist (LAMA) as add-on to ICS controller therapy compared to placebo or increased ICS dose in patients 12 years of age and older with uncontrolled, persistent asthma?

Key Points—LAMA Versus Placebo as Add-on to ICS

- LAMA versus placebo as add-on to ICS reduces the risk of exacerbations requiring systemic corticosteroids (high SOE) and the risk of asthma worsening (high SOE), and leads to improved mean differences in peak, trough and area under the curve (AUC) for FEV1 and FVC (all high SOE).
- LAMA versus placebo as add-on to ICS does not significantly differ in effect on asthma control composite scores (moderate SOE), asthma-specific quality of life (low to high SOE) or rescue medication use (moderate SOE).

Key Points—LAMA Add-on to ICS Versus Increasing ICS Dose

- LAMA added on to ICS versus doubling the ICS dose does not significantly differ in effect on the risk of exacerbations requiring systemic corticosteroids or the mean difference in ACQ-6 score, FEV1 trough or AQLQ score (all low SOE).

Table 21. Evidence overview for KQ2a, LAMA as add-on to ICS versus placebo

Outcome category	Outcome	Quantity and type of evidence (n)	Conclusion Effect estimate (95% CI)	Strength of evidence (rationale)
Exacerbations	Requiring systemic corticosteroid	5 RCTs[118-120,122,123] (3036)	Favors LAMA RR 0.67 (0.48 to 0.92)	High
	Asthma worsening[a]	3 RCTs[119,122,123] (2420)	Favors LAMA RR 0.81 (0.68 to 0.97)	High
Death	All-cause	6 RCTs[119-123] (3065)	No deaths occurred	Insufficient (no events occurred)
	Asthma-specific	6 RCTs[119-123] (3065)	No deaths occurred	Insufficient (no events occurred)
Asthma control composite scores	ACQ-7 score	4 RCTs[119,122,123] (2304)	No difference MD -0.10 (-0.28 to 0.07)	Moderate (inconsistent)
	ACQ-7 responder[b]	5 RCTs[119-123] (2680)	No difference RR 1.08 (0.96 to 1.21)	Moderate (inconsistent)
Spirometry	FEV1 peak	4 RCTs[119,122,123] (2310)	Favors LAMA MD 0.18 (0.13 to 0.24)	High
	FEV1 trough	7 RCTs[119-123] (3173)	Favors LAMA MD 0.13 (0.10 to 0.17)	High
	FEV1 AUC	3 RCTs[119,122,123] (2310)	Favors LAMA MD 0.18 (0.13 to 0.23)	High
	FEV1 % predicted	1 RCT[122] (457)	Favors LAMA Paggiaro, 2016[112] MD 3.5 (1.58 to 5.42)	Low (unknown consistency)
	FVC peak	3 RCTs[119,123] (1853)	Favors LAMA MD 0.11 (0.05 to 0.18)	High
	FVC trough	5 RCTs[118,119,121,123] (2390)	Favors LAMA MD 0.08 (0.04 to 0.13)	High
	FVC AUC	3 RCTs[119,123] 1859)	Favors LAMA MD 0.11 (0.05 to 0.17)	High
Quality of life	AQLQ score	2 RCTs[119] (1461)	No difference Kerstjens Trial 1, 2015[119] MD 0.07 (-0.06 to 0.20) Kerstjens Trial 2, 2015[119] MD 0.11 (-0.03 to 0.25)	High
	AQLQ-mini score	1 RCT[118] (253)	No difference Bateman, 2011[118] MD -0.09 (-0.27 to 0.08)	Low (unknown consistency)[c]
Health care utilization	Rescue medication use, number of puffs in 24h	7 RCTs[119-123] (3104)	No difference MD -0.08 (-0.23 to 0.07)	Moderate (inconsistent)

ACQ = Asthma Control Questionnaire; AQLQ = Asthma Quality of Life Questionnaire; AUC = area under the curve; CI = confidence interval; FEV1 = forced expiratory volume in one second; ICS = inhaled corticosteroid; LAMA = long-acting muscarinic antagonist; MD = mean difference; n = patient sample size; PEF = peak expiratory flow; RCT = randomized controlled trial; RR = relative risk

[a] Defined as progressive increase in asthma symptoms compared to day-to-day symptoms or a decrease in morning PEF greater than or equal to 30 percent for 2 or more days
[b] Defined as a decrease in score by 0.5 or more

[c]Strength of evidence was rated low even in the setting of one domain downgraded because of the small sample size within a single trial for this outcome and thus lack of confidence in the true effect estimate.

Table 22. Evidence overview for KQ2a, LAMA as add-on to ICS versus doubling the ICS dose

Outcome category	Outcome	Quantity and type of evidence (n)	Conclusion Effect estimate (95% CI)	Strength of evidence (rationale)
Exacerbations	Requiring systemic corticosteroid	1 RCT[27] (210)	No difference Peters, 2010[27] RR 0.48 (0.12 to 1.84)	Low (unknown consistency, imprecise)
	Requiring oral corticosteroid or increase in ICS or other asthma medication	1 RCT[27] (210)	No difference Peters, 2010[27] RR 0.32 (0.09 to 1.13)	Low (unknown consistency, imprecise)
Asthma control composite scores	ACQ-6 score	1 RCT[27] (127)	No difference Peters, 2010[27] MD -0.15 (-0.45 to 0.15)	Low (unknown consistency)[a]
Spirometry	FEV1 trough	1 RCT[27] (118)	No difference Peters, 2010[27] MD 0.09 (-0.20 to 0.38)	Low (unknown consistency)[a]
Quality of life	AQLQ score	1 RCT[27] (122)	No difference Peters, 2010[27] MD 0.04 (-0.32 to 0.40)	Low (unknown consistency)[a]

ACQ = Asthma Control Questionnaire; AQLQ = Asthma Quality of Life Questionnaire; AUC = area under the curve; CI = confidence interval; FEV1 = forced expiratory volume in one second; ICS = inhaled corticosteroid; LAMA = long-acting muscarinic antagonist; MD = mean difference; n = patient sample size; PEF = peak expiratory flow; RCT = randomized controlled trial; RR = relative risk

[a] Strength of evidence was rated low even in the setting of one domain downgraded because of the small sample size within a single trial for this outcome and thus lack of confidence in the true effect estimate.

LAMA Versus Placebo as Add-on to ICS

Overview of Studies

Seven RCTs[118-123] (n=3321) were included in the analysis of LAMA versus placebo as add-on to ICS, one had a crossover design.[120] Two replicate trials were reported in a single publication and each trial results were considered unique except for the results that were only reported in a combined way.[119] Six trials were multicenter, multinational trials[118-120,122,123] and 1 trial was conducted in Japan.[121] All trials reported industry sponsorship. Trials ranged from 15d to 52 weeks in duration. All trials required an age of at least 18 years for inclusion except (mean age 41 to 47y) one trial[123] which focused on patients 12 to 17y old (mean age 14y). Patients in the trials reporting race[118,120] were mostly Caucasian (87% to 93.3%). One trial[121] allowed the continued use of pretrial LABA while a second trial[123] did so for pretrial leukotriene receptor antagonist (LTRA). One trial[120] studied the LAMA umeclidinium while the others studied tiotropium. Risk of bias was low in 6 trials[118,119,121,-123] and unclear in 1 trial.[120]

Results

As add-on to ICS, LAMA decreases the risk of exacerbation requiring systemic corticosteroid by 33 percent (high SOE) (Figure 9, Panel A) and decreases the risk of asthma worsening by 19 percent (high SOE) (Figure 9, Panel B versus placebo. No deaths occurred in the six trials reporting this outcome.

Most measures of lung function obtained from spirometry were improved with LAMA versus placebo, including peak FEV1 (MD 0.18L), trough FEV1 (MD 0.13L) and FEV1 AUC (MD 0.18L), peak FVC (MD 0.11 L), trough FVC (MD 0.08L) and FVC AUC (MD 0.11L) (all with high SOE). FEV1 percent predicted was reported in one trial[122] and was increased with LAMA versus placebo (MD 3.5%, low SOE). Despite these improvements, the mean difference in ACQ-7 score (moderate SOE) was no different with LAMA versus placebo nor was the chance of being a responder (moderate SOE).

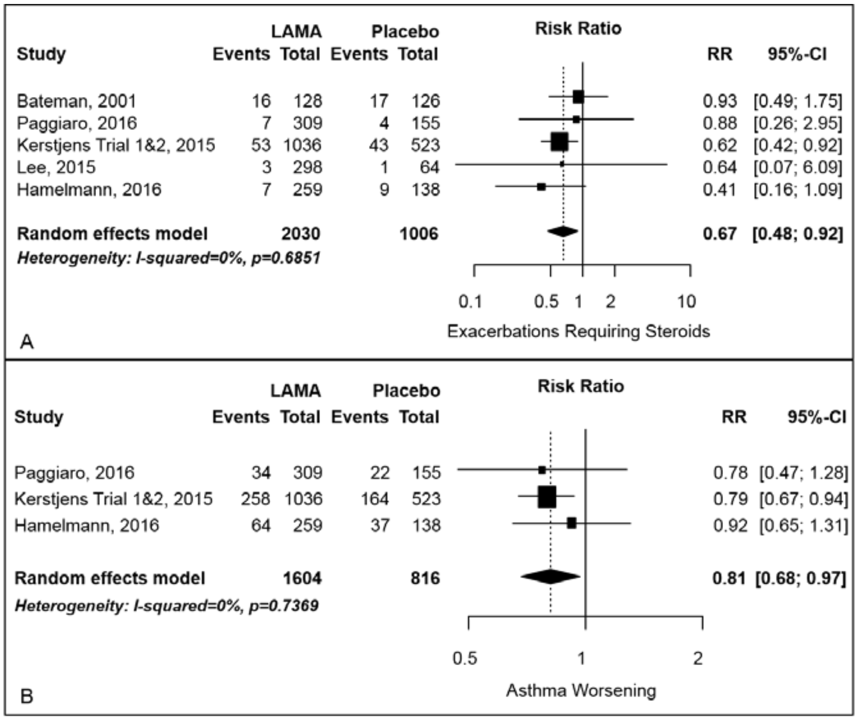
Asthma-specific quality of life was no different with LAMA versus placebo, regardless of AQLQ tool version or when evaluated as a mean difference or as a responder (low to high SOE). The only health care utilization outcome reported was the use of rescue medication defined as the mean number of puffs per 24 hours. The mean difference in rescue medication use was no different with LAMA versus placebo (moderate SOE).

Subgroup Data

Tiotropium dose: We conducted preplanned subgroup analysis based on the dose of tiotropium because the a priori base analysis combined tiotropium doses as one intervention arm. Overall, the data do not suggests any substantial differences in the overall conclusions when tiotropium doses were compared separately versus placebo or against each other (Appendix Table 21).

Disease duration, age, smoking status, FEV1 percent predicted, allergic status, BMI: Four[119,122,123] of the 8 included RCTs conducted subgroup analysis within the original trial. Kertjens et al.,[119] combined data from the two replicate trials and in a pre-planned subgroup analysis found the following did not influence outcomes of FEV1 peak and trough: disease duration, age, smoking history, FEV1 percent predicted at baseline, allergic status and body mass index (BMI). Hamelmann et al.,[123] also found that age did not influence outcomes of FEV1 peak and trough. Paggiaro et al.,[122] also found that age did not influence outcomes of FEV1 peak, trough and percent predicted, neither did smoking history.

Figure 9. Risk of exacerbation and of asthma worsening with LAMA versus placebo as add-on to ICS



CI = confidence interval; LAMA = long-acting muscarinic antagonists; RR = relative risk

LAMA as Add-on to ICS Versus Increasing the ICS Dose

Overview of Studies

One cross-over trial[27] (n=210) compared the addition of tiotropium 18mcg daily to the run-in dose of ICS versus doubling the dose of ICS for a treatment period of 15 weeks. This study was conducted in the US with nonindustry sponsorship and had a low risk of bias. Patients were required to be at least 18y old for enrollment (mean age 42y). Race was Caucasian in 54.8 percent of patients.

Results

There was no difference in the risk of exacerbations requiring oral or intravenous corticosteroids with tiotropium added to ICS versus doubling the ICS dose (low SOE). This trial[27] also reported the number of patients with exacerbations that required oral corticosteroids or increased use of ICS or other asthma medications, which was not different with tiotropium added to ICS versus doubling the ICS dose (low SOE). No other exacerbation outcomes or death were reported. There was no difference with tiotropium added to ICS versus doubling the ICS dose for any other outcome analyzed including mean difference in ACQ-6, FEV1 trough and AQLQ (all low SOE).

KQ2b: What is the comparative effectiveness of LAMA compared to other controller therapy as add-on to ICS in patients 12 years of age and older with uncontrolled, persistent asthma?

Key Points

- LAMA versus LABA as add-on to ICS does not significantly differ in their effect on the risk of exacerbations requiring systemic corticosteroids (low SOE) or risk of asthma worsening (moderate SOE), death (low SOE), asthma control composite scores (low to high SOE), spirometry measures (low to high SOE), asthma-specific quality of life (low to high SOE) or rescue medication use (low SOE).
- Few studies, limited to outcomes of FEV1 percent predicted and rescue medication use, compared LAMA to controllers other than LABA as add-on to ICS.

Table 23. Evidence overview for KQ2b, LAMA versus LABA as add-on to ICS

Outcome category	Outcome	Quantity and type of evidence (n)	Conclusion Effect estimate (95% CI)	Strength of evidence (rationale)
Exacerbations	Requiring systemic corticosteroid	4 RCTs[27,118-120] (2574)	No difference RR 0.87 (0.53 to 1.42)	Low (inconsistent, imprecise)
	Asthma worsening[a]	1 RCT[119] (1577)	No difference Kerstjens Trial 1 & 2, 2015[119] RR 1.00 (0.84 to 1.20)	Moderate (unknown consistency)
	Requiring oral corticosteroid or increase in ICS or other asthma medication	1 RCT[27] (210)	No difference Peters, 2010[27] RR 0.60 (0.15 to 2.42)	Low (unknown consistency imprecise)
Death	All-cause	4 RCTs[119,120,148] (3572)	No difference OR 7.50 (0.78 to 72.27)	Low (inconsistent, imprecise)
	Asthma-specific	4 RCTs[119,120,148] (3572)	No difference OR 7.49 (0.47 to 119.86)	Low (inconsistent, imprecise)
Asthma control composite scores	ACQ-6 score	1 RCT[27] (126)	No difference Peters, 2010[27] MD 0.30 (0.00 to 0.60)	Low (unknown consistency, imprecise)
	ACQ-7 score	2 RCTs[119] (1577)	No difference Kerstjens Trial 1, 2015[119] MD 0.04 (-0.05 to 0.13) Kerstjens Trial 2, 2015[119] MD 0.00 (-0.09 to 0.09)	High
	ACQ-7 responder[b]	2 RCTs[119] (1577)	No difference Kerstjens Trial 1, 2015[119] RR 1.06 (0.96 to 1.18) Kerstjens Trial 2, 2015[119] RR 1.00 (0.90 to 1.12)	High
Spirometry	FEV1 peak	2 RCTs[119] (1483)	No difference Kerstjens Trial 1, 2015[119] MD 0.004 (-0.05 to 0.05) Kerstjens Trial 2, 2015[119] MD 0.014 (-0.03 to 0.06)	High
	FEV1 trough	6 RCTs[27,118-120,148] (3261)	No difference MD 0.02 (-0.03 to 0.06)	High
	FEV1 AUC	2 RCTs[119] (1483)	No difference Kerstjens Trial 1, 2015[119] MD -0.004 (-0.05 to 0.04) Kerstjens Trial 2, 2015[119] MD 0.004 (-0.04 to 0.05)	High

Outcome category	Outcome	Quantity and type of evidence (n)	Conclusion Effect estimate (95% CI)	Strength of evidence (rationale)
	FEV1 % predicted	3 RCTs[146-148] (542)	No difference MD -4.54 (-12.69 to 3.61)	Low (medium ROB, inconsistent)
	FVC peak	2 RCTs[119] (1483)	No difference Kerstjens Trial 1, 2015[119] MD 0.02 (-0.04 to 0.07) Kerstjens Trial 2, 2015[119] MD -0.02 (-0.07 to 0.03)	High
	FVC trough	3 RCTs[118-119] (1745)	No difference MD 0.02 (0.00 to 0.05)	High
	FVC AUC	2 RCTs[119] (1483)	No difference Kerstjens Trial 1, 2015[119] MD 0.005 (-0.05 to 0.06) Kerstjens Trial 2, 2015[119] MD -0.03 (-0.09 to 0.03)	High
Quality of life	AQLQ score	4 RCTs[27,118,119] (1982)	No difference MD -0.06 (-0.15 to 0.03)	High
	AQLQ-mini score	1 RCT[118] (262)	No difference Bateman, 2011[118] MD -0.15 (-0.32 to 0.02)	Low (unknown consistency)[c]
Health care utilization	Rescue medication use, number of puffs in 24h	7 RCT[118-120,146-148] (2450)	No difference MD 0.61 (-0.12 to 1.35)	Low (inconsistent, imprecise)

ACQ = Asthma Control Questionnaire; AQLQ = Asthma Quality of Life Questionnaire; AUC = area under the curve; CI = confidence interval; FEV1 = forced expiratory volume in one second; FVC = forced vital capacity; ICS = inhaled corticosteroid; LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist; MD = mean difference; n = patient sample size; RCT = randomized controlled trial; ROB = risk of bias; RR = relative risk

[a] Defined as progressive worsening of asthma symptoms compared to day-to-day symptoms or a decrease in morning PEF greater than or equal to 30 percent for 2 or more days
[b]Defined as a decrease in score by 0.5 or more
[c]Graded with low strength of evidence in the setting of one domain downgraded due to the small sample size in a single trial and lack of confidence in the true effect estimate.

Table 24. Evidence overview for KQ2b, LAMA versus montelukast as add-on to ICS

Outcome category	Outcome	Quantity and type of evidence (n)	Conclusion Effect estimate (95% CI)	Strength of evidence (rationale)
Spirometry	FEV1 % predicted	2 RCTs[146,147] (214)	Favors montelukast Rajanandh, 2014[146] MD -2.14 (-2.93 to -1.35) Rajanandh, 2015[147] MD -0.87 (-2.77 to 1.03)	Moderate (medium ROB)
Health care utilization	Rescue medication use, number of puffs in 24h	2 RCTs[146,147] (214)	Favors montelukast Rajanandh, 2014[146] MD 0.26 (-0.25 to 0.77) Rajanandh, 2015[147] MD 1.19 (0.88 to 1.50)	Low (medium ROB, inconsistent)

CI = confidence interval; FEV1 = forced expiratory volume in one second; MD = mean difference; n = patient sample size; RCT = randomized controlled trial; ROB = risk of bias; RR = relative risk

Table 25. Evidence overview for KQ2b, LAMA versus doxofylline as add-on to ICS

Outcome category	Outcome	Quantity and type of evidence (n)	Conclusion Effect estimate (95% CI)	Strength of evidence (rationale)
Spirometry	FEV1 % predicted	2 RCTs[146,147] (209)	Favors doxofylline Rajanandh, 2014[146] MD -3.87 (-4.6 to -3.14) Rajanandh, 2015[147] MD -2.69 (-4.79 to -0.59)	Moderate (medium ROB)
Health care utilization	Rescue medication use, number of puffs in 24h	2 RCTs[146,147] (209)	Favors doxofylline Rajanandh, 2014[146] MD 0.30 (-0.21 to 0.81) Rajanandh, 2015[147] MD 1.21 (0.89 to 1.53)	Low (medium ROB, inconsistent)

CI = confidence interval; FEV1 = forced expiratory volume in one second; MD = mean difference; n = patient sample size; RCT = randomized controlled trial; ROB = risk of bias; RR = relative risk

LAMA Versus LABA as Add-on to ICS

Overview of Studies

Eight RCTs[27,118-120,146-148] (n=3679) were included in the analysis of LAMA versus LABA as add-on to ICS, two of which were crossover in design.[27,120] Two replicate trials were reported in a single publication and each trial results were considered unique except for the results that were only reported in a combined way.[119] Four trials were multicenter, multinational trials reporting industry sponsorship.[118-120] Two trials were conducted in India[146,147] and 2 in the US,[122,148] all of which were nonindustry sponsored. Trails ranged from 15d to 18m in duration. All trials required patients to be at least 18y old for enrollment (mean age 36 to 47). One trial[148] enrolled only African Americans while patients in the remaining trials reporting race[27,118,120] were mostly Caucasian (54.8% to 93.3%). All trials randomized patients to LAMA versus LABA in addition to background ICS therapy. Seven trials[27,118,119,146-148] studied tiotropium and one[120] studied umeclidinium. Four trials[27,118,119] studied salmeterol, one studied vilanterol,[120] two studied formoterol,[146,147] and one studied either salmeterol or formoterol based on pre-study use.[148] Two trials allowed concurrent asthma therapy that were similar across arms.[119] Risk of bias was low in 5 trials,[27,118,119,148] medium in 1 trial (open-label),[146] high in 1 trial (open-label and significant attrition),[147] and unclear in 1 trial.[120]

Results

There was no difference in the risk of exacerbation requiring systemic corticosteroids (Figure 10) or in the risk of asthma worsening when LAMA was compared with LABA as add-on to ICS. One trial reported exacerbations requiring oral corticosteroid or an increase in ICS or other asthma medication use and the risk was no different with LAMA versus LABA.[27] Of the four trials that reported death, events occurred in a single trial[148] and the odds of all-cause mortality or of asthma-specific mortality was no different with LAMA versus LABA.

Comparison	Outcome	Quantity and type of evidence (n)	Conclusion Effect estimate (95% CI)	Strength of evidence (rationale)
Spirometry	FEV1 peak	3 RCTs[150,152] (1295)	No difference MD 0.10 (0.00 to 0.22)	Moderate (inconsistent)
	FEV1 trough	3 RCTs[150,152] (1295)	No difference MD 0.07 (0.00 to 0.14)	Moderate (inconsistent)
	FEV1 AUC	3 RCTs[150,152] (1295)	Favors LAMA MD 0.10 (0.01 to 0.19)	High
	FVC peak	3 RCTs[150,152] (1295)	Favors LAMA MD 0.11 (0.05 to 0.17)	High
	FVC trough	3 RCTs[150,152] (1295)	Favors LAMA MD 0.09 (0.03 to 0.15)	High
	FVC AUC	3 RCTs[150,152] (1295)	Favors LAMA MD 0.10 (0.04 to 0.17)	High
Quality of life	AQLQ score	2 RCTs[150] (907)	No difference Kerstjens Trial 1, 2012[150] MD 0.04 (-0.13 to 0.20) Kerstjens Trial 2, 2012[150] MD 0.14 (-0.03 to 0.31)	High
	AQLQ responder[c]	1 RCT[150] (907)	Favors LAMA Kerstjens Trial 1 & 2, 2012[150] RR 1.62 (1.34 to 1.96)	Moderate (imprecise)
Health care utilization	Rescue medication use, number of puffs in 24h	3 RCTs[150,152] (1302)	No difference MD -0.10 (-0.37 to 0.18)	Moderate (inconsistent)

ACQ = Asthma Control Questionnaire; AQLQ = Asthma Quality of Life Questionnaire; AUC = area under the curve; CI = confidence interval; h = hours; FEV1 = forced expiratory volume in one second; FVC = forced vital capacity; LAMA = long-acting muscarinic antagonist; MD = mean difference; n = sample size; OR = odds ratio; PEF = peak expiratory flow; RCT = randomized controlled trial; RR = relative risk

[a]Defined as progressive increase in asthma symptoms compared to usual day-to-day symptoms or decrease in morning PEF greater than or equal to 30 percent for 2 or more days
[b]Defined as a decrease in score by 0.5 or more
[c]Defined as an increase in score of 0.5 or more

Table 27. Evidence overview for KQ2c, LAMA added to ICS plus LABA versus increasing ICS dose plus LABA

Comparison	Outcome	Quantity and type of evidence (n)	Conclusion Effect estimate (95% CI)	Strength of evidence (rationale)
Asthma control composite scores	ACT score	1 RCT[151] (63)	No difference Wang, 2012[151] MD -0.61 (-4.82 to 3.60)	Low (unknown consistency, imprecise)

ACT = Asthma Control Test; CI = confidence interval; h = hours; MD = mean difference; n = sample size; RCT = randomized controlled trial

LAMA as Add-on to ICS Plus LABA Versus ICS Plus LABA

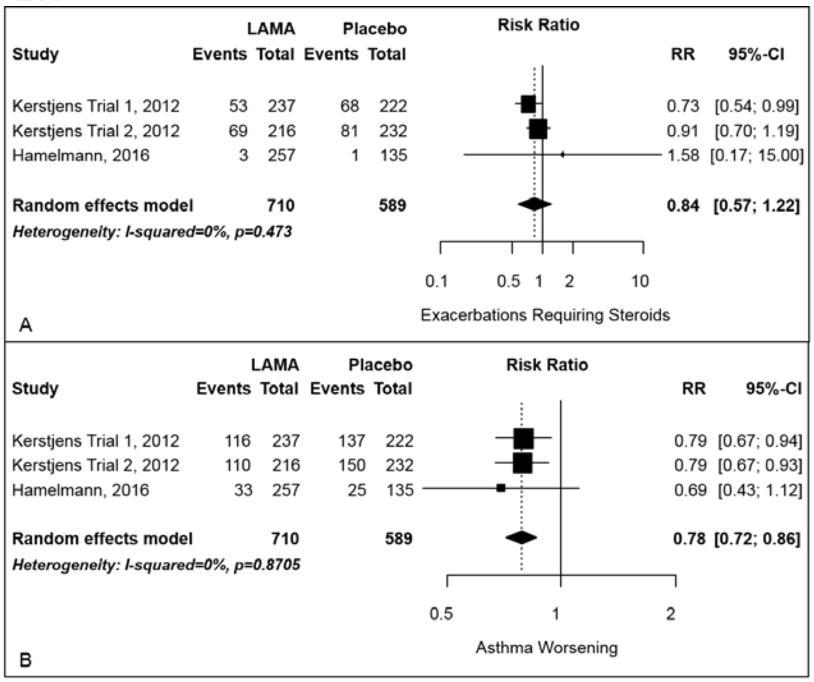
Overview of Studies

Three trials[150,152] (n=1304) were included in the analysis of LAMA as add-on to ICS plus LABA versus ICS plus LABA. All trials were multicenter, multinational trials reporting industry sponsorship and had low risk of bias. Two trials[150] required patients to be at least 18y for enrollment (mean age 51 to 53y) while the third trial[152] focused on patients ages 12 to 17y (mean age 14y). Most patients were Caucasian (82.1% to 94.6%). Two replicate trials randomized patients taking ICS plus LABA to either tiotropium 5µg daily or placebo for 48 weeks.[150] Concurrent asthma therapies were allowed and use was similar in both arms. These two trials were reported in a single publication and each trial was considered unique in the analyses unless the results were only reported in the source documents in a combined fashion.[150] The third trial included patients taking high-dose ICS plus one other controller or medium-dose ICS plus two other controllers and randomized patients to tiotropium 2.5µg daily, 5µg daily or placebo for 12 weeks.[152] LABA was the most common additional controller (83.2%) while use of other controllers was similar in both groups.

Results

There was no difference in the risk of exacerbation requiring systemic corticosteroids (Figure 11, Panel A) or in the risk of exacerbation requiring hospitalization when LAMA added to ICS plus LABA was compared with ICS plus LABA. The risk of asthma worsening was reduced by 22 percent with LAMA added to ICS plus LABA versus ICS plus LABA (high SOE) (Figure 11, Panel B). All three trials reported that no deaths occurred.

Figure 11. Risk of exacerbation and of asthma worsening with LAMA as add-on to ICS and LABA versus ICS and LABA



CI = confidence interval; LAMA = long-acting muscarinic antagonists; RR = relative risk

The MD in ACQ score (whether ACQ-6 or ACQ-7) was no different with LAMA added to ICS plus LABA versus ICS plus LABA. The chance of being an ACQ responder, regardless of the ACQ version, favored LAMA in the combined results of two replicate trials of 48 weeks duration but was no different with LAMA in the single trial of 12 weeks duration.[142] Most measures of lung function obtained from spirometry were improved with LAMA added to ICS plus LABA versus ICS plus LABA including FEV1 AUC (MD 0.10 L), peak FVC (MD 0.11 L), trough FVC (MD 0.09 L) and FVC AUC (MD 0.10 L) (all with high SOE). Data suggest a trend towards improved peak and trough FEV1 with the lower limit of the confidence interval at zero. Mean difference in AQLQ was no different with LAMA added to ICS plus LABA versus ICS plus LABA although the chance of being an AQLQ responder was increased by 62 percent with LAMA added to ICS plus LABA versus ICS plus LABA. The only health care utilization outcome reported was rescue medication use, defined as the mean puffs per 24 hours. The mean change in rescue medication use was no different with LAMA added to ICS plus LABA versus ICS plus LABA.

Subgroup Data

We identified one post-hoc analysis[173] by Kerstjens et al., that combined data from two previous replicate trials[150] and found ACQ-7 responder rate at week 24 was influenced by smoking status and screening FEV1 percent predicted, favoring a response with tiotropium 5mcg versus placebo in ex-smokers and in those with lower FEV1 percent predicted at screening. ACQ-7 responder at 48 weeks was influenced by blood eosinophils favoring a response with tiotropium 5mcg versus placebo with lower blood counts. The following characteristics did not influence outcomes: age, race, ethnicity, disease duration, BMI, screening FEV1 percent predicted, FEV1 percent reversibility, clinician-determined allergic status and serum IgE.

LAMA as Add-on to ICS Plus LABA Versus ICS Plus LABA With a Higher ICS Dose

Overview of Studies

One trial (n=63) randomized participants taking salmeterol/fluticasone 50/250mcg twice daily to either add-on tiotropium 18µg daily or to increasing the salmeterol/fluticasone dose to 50/500mcg twice daily.[151] The trial was conducted in China, funding was not reported, and the risk of bias was unclear. The population was referred to as “adults” and the mean age was 35 to 36.

Results

The only outcome reported was mean difference in ACT score which was no different LAMA added to ICS plus LABA versus increasing the ICS dose and continuing LABA.[151]

Discussion

Overview and Applicability

We conducted a systematic review with meta-analysis to assess the comparative effectiveness of pharmacologic management of asthma, specifically intermittent inhaled corticosteroid (ICS) dosing (with or without long-acting beta agonist (LABA)) and long-acting muscarinic antagonists (LAMA) in comparison to guideline recommended approaches to the treatment of persistent asthma, or recurrent wheezing in the case of patients 4 years (y) old or younger. A total of 54 randomized controlled trials (RCTs) and 2 observational studies comprised the evidence base of this review.

Key Question 1a

In this report, intermittent ICS was defined as the prescribed use of ICS that is not the same on a daily basis. We found several types of intermittent dosing within the evidence base. In patients 0 to 4y old (Key Question [KQ]1a) with recurrent wheezing, intermittent ICS was generally defined as an episode of ICS daily dosing initiated with onset of a respiratory tract infection (RTI) and continued for a defined period, generally 7 to 10 days. Otherwise, the patient was not taking ICS. Data from three trials of 324 patients found this practice, when used with as-needed short-acting β_2-agonist (SABA), reduces the risk of exacerbation requiring oral corticosteroid (moderate strength of evidence [SOE]) in comparison to as-needed SABA. However a difference in exacerbation risk was not detected between intermittent ICS use during RTI compared to ICS controller with as-needed SABA (low SOE), based on a single trial of 278 patients. Thus the strength of evidence was low for the current conclusion. Caregiver quality of life improved (low SOE) versus as-needed SABA although not reaching a minimally important difference and the tool applied has not been validated in this age. Overall, for this KQ the evidence base was limited by the number of trials per comparison and inability to evaluate consistency since several outcomes were based on a single trial, and as such domains of consistency and precision were most impacted for strength of evidence ratings. Evidence was insufficient to draw conclusions for the comparison of intermittent ICS versus no therapy and we found no evidence comparing intermittent ICS to nonpharmacologic therapy.

Key Question 1b

In patients 5y of age or older, intermittent ICS dosing was described in the evidence base in two ways (KQ1b). The first strategy was in patients regularly taking ICS controller therapy who would increase ICS dose temporarily in response to a specific trigger, most often doubling routine ICS dose upon deterioration of peak expiratory flow consistent with the “yellow zone”. However, some studies allowed quadrupling of dose and due to limited studies in this analysis overall, we were unable to discern if a given strategy for providing intermittent ICS (i.e., doubling vs. quadrupling) resulted in differing effects. We found patients resembled a mixture of persistent asthma severity and levels of control as described by the studies. Evidence was limited to exacerbations, of which we found no difference in effect between intermittent ICS and ICS controller in patients 12 years of age and older. The largest analysis was for exacerbations leading to oral corticosteroid use which included three trials with 908 patients. However, the other analyses were mostly limited to a single study and thus imprecision and either inconsistency or lack of the ability to evaluate consistency led to low strength of evidence for all outcomes with this intermittent ICS strategy. The age of patients included in this evidence base reflects middle-aged adults with mean ages in the 30's to 50's. Although data was reported in a single trial for younger patients, evidence was insufficient to draw conclusions in patients 5 to 11y old.

The second strategy of intermittent ICS dosing described by the evidence base was in patients not otherwise on ICS therapy who would temporarily use ICS in comparison to ICS controller therapy. Most studies asked patients to use the ICS study inhaler when they would normally require as-needed SABA, in conjunction with a SABA inhaler. The majority of the population had mild persistent asthma, some of which were required to be at least partially controlled while others were symptomatic at baseline. In the group of studies included in that analysis of 12 years of age and older, the population reflected more of an adult population with the mean age being in the 30's. We did not detect a difference between intermittent ICS and ICS controller in patients 12 years of age and older on exacerbations, asthma control scores, spirometry, quality of life, rescue inhaler use or asthma-related urgent care visits. However, like the other dosing strategy described for KQ1b, the evidence base for this dosing strategy was scarce as well with most outcomes based on a single trial. Thus, strength of evidence was primarily low due to issues of precision and consistency. Evidence is insufficient to draw conclusions in patients 5 to 11y old.

Key Question 1c

Analysis of ICS and long-acting β_2-agonist (LABA) as both controller and quick relief therapy (KQ1c) in patients with persistent asthma was separated based on the comparator being either ICS or ICS and LABA and also in consideration of the comparative daily ICS dose in the intervention and comparator arms, using thresholds set by the Expert Panel Report-3. All but one trial evaluated a single ICS and LABA combination in the intervention arm (budesonide/formoterol) and the majority of control arms were of the same ICS and LABA combination. In the group of studies considered in the evidence base of 12 years of age and older, the age of patients was again more middle-aged with mean ages ranging from the 30's to 50's. The evidence comparing ICS and LABA controller and quick relief therapy to ICS controller was small relative to other groups in this KQ and primarily based on composite outcomes of asthma exacerbations with little to no evidence for asthma control, spirometry, quality of life, or health care utilization. Patients represented a mix of asthma severity (mild to severe) and were mostly symptomatic at baseline. Based on composite exacerbation outcomes, ICS and LABA controller and quick relief versus ICS controller at the same or higher comparative ICS dose reduced exacerbation risk, both in patients 12 years of age and older and in patients 4 to 11y old. Strength of evidence was low or moderate due to imprecision and unknown consistency in the event of single trial. Data for patients 4 to 11y was also downgraded for indirectness given the dosing used in the study was lower than approved doses and what would be considered "low dose" according to the EPR-3.

ICS and LABA controller and quick relief versus ICS and LABA controller at the same comparative ICS dose had the largest literature base in this report and most evidence was focused on asthma exacerbations and forced expiratory volume in 1 second (FEV1). Most patients were described as either symptomatic or not controlled, and not further described in terms of persistent asthma severity. In patients 12 years of age and older, not only was the risk of the composite exacerbation requiring systemic corticosteroids, hospitalization or emergency room (ER) visit reduced with ICS and LABA controller and quick relief therapy (high SOE), so were the individual components of the composite outcome (moderate or high SOE). There was no difference in FEV1 (low SOE) and 3 or fewer trials reported data for other outcomes including asthma control composite scores, spirometry (FEV1 % predicted and forced vital capacity [FVC]), and health care utilization. Thus SOE for these outcomes was low to moderate, mostly suggesting no difference in effect between comparison with exception of asthma control questionnaire (ACQ)-5 responder (moderate SOE) and rescue medication use (low SOE) which both favored ICS and LABA controller and quick relief therapy. Evidence in patients 4 to 11y old was limited to a single subgroup analysis of a larger trial and suggested benefit in reducing composite exacerbation outcomes with ICS and LABA controller and quick relief therapy (low SOE). However, these outcomes were downgraded for indirectness given the dosing used in the study was lower than approved doses and what would be considered “low dose” according to the EPR-3.

ICS and LABA controller and quick relief versus ICS and LABA controller at a higher comparative ICS dose reduces the risk of composite exacerbations (high SOE) in patients 12 years of age and older. This population was primarily either symptomatic or a mixture of patients with and without symptoms at baseline, without further specification of persistent asthma severity. No difference was found for death (moderate SOE), ACQ-5 score (high SOE), FEV1 (moderate SOE), Asthma Quality of Life Questionnaire (AQLQ)-(S) score (moderate SOE), or rescue medication use (high SOE). No evidence was found for patients 5 to 11y old. Finally ICS and LABA controller and quick relief therapy, when compared to physician adjusted asthma therapy reflecting standard of care controller options (at a minimum daily ICS), ICS and LABA controller and quick relief therapy reduces risk of composite exacerbation (moderate SOE) but not the risk of the individual components (low SOE). Patients in the ICS and LABA controller and quick relief group had a greater chance of achieving a minimally important difference in ACQ-5 score (moderate SOE) and used fewer rescue medication inhalations (moderate SOE) while no difference was found in FEV1 (low SOE), or FEV1 percent predicted (low SOE). SOE was reduced in this evidence base due to effect estimates that were imprecise and inconsistent, in addition to evidence with risk of bias given the open-label design being subject to performance and detection bias.

Key Question 2

The role of LAMA therapy in asthma management was addressed in KQ2a-c and specific to a population 12 years of age and older with uncontrolled, persistent asthma. Although the age requirement of included studies could have been as young as 12y old, almost all data were derived from trials requiring participants to be at least 18 years old. The mean ages ranged from the 30’s to 50’s. Most studies defined “uncontrolled” with use of the ACQ, requiring a score of 1.5 or greater for inclusion. Almost the entire evidence base reflects a single LAMA (tiotropium) delivered via a soft mist inhaler as opposed to dry powder inhaler. Many of the trials for KQ2a and KQ2b overlapped as they were three arm trials. We found LAMA to be more effective than placebo as add-on to ICS, supported by the reduction in risk of exacerbation requiring systemic corticosteroids (high SOE) and the peak, trough and area under the curve (AUC) of both FEV1 and FVC (all high SOE). No difference was found for asthma control composite scores, quality of life, or rescue medication use. Add-on LAMA to ICS versus doubling ICS dose did not significantly differ in effect on outcomes of exacerbation, asthma control scores, FEV1 trough, or AQLQ, all with low SOE. LAMA compared to LABA, as add-on to ICS, was no different in any evaluated outcomes including exacerbations, death, asthma control scores, spirometry, quality of life, or rescue medication use. SOE was high for more outcomes than not, and limitations downgrading SOE to low or moderate were due to precision and consistency. Few studies, limited to outcomes of FEV1 and rescue medication use, evaluated other controllers than LABA as a comparator to add-on LAMA. FEV1 and rescue medication use was improved with either montelukast or doxyfylline versus LAMA although SOE was low due to risk of bias and consistency. LAMA added to ICS and LABA in comparison to ICS and LABA did not result in a significant difference on effect of exacerbation risk although most measures of lung function, particularly FEV1 AUC and peak trough and AUC of FVC, were improved. The chance of a patient achieving a minimally important difference in ACQ-7 and AQLQ scores was also increased with LAMA added to ICS and LABA.

Limitations

This review sought to evaluate different ICS dosing strategies and LAMA therapy in persistent asthmatics of various ages, depending on the KQ. Comparisons were class-based and thus this review does not inform the impact of specific doses on outcomes, rather more globally addresses classes and broad dosing strategies (i.e. intermittent dosing of ICS). Although effectiveness is an important part of decision-making, this report did not include harms associated with drug therapies, which should also be taking in to consideration. The majority of patients included in trials, when race was reported, were Caucasian and thus application of data to other races is limited. KQ1 included young pediatric populations, and evidence overall was sparse in those under 5 years old making it difficult to draw conclusions, if at all. Even within the age category of 12 years of age and older, regardless of KQ, data centered around mean ages of 30 to 50y thus extremes of age are underrepresented in the evidence base. Lastly, review of LAMA in patients under 12 years of age was outside of the scope of this review although clinicians should recognize recent approval of tiotropium in the pediatric population as young as 6 years of age. Inclusion criteria of studies rarely provided enough information to determine persistent asthma severity thus we relied on study reported severity, which in the majority of trials was not present. In addition, control of asthma was infrequently reported. In the ICS evidence base, it was more common to find trials describing presence of symptoms during run-in than a clearer measure of asthma control. In the LAMA evidence base, we only included trials evaluating a population with uncontrolled asthma, which most often was defined using the ACQ score. However, this is only one of many criteria of impairment or risk that can be applied to determine asthma control.

Overall, most studies in this review were of low risk of bias. However, particularly in KQ1c, studies were found to have increased risk of bias do to their open-label design and risk of performance and detection bias.

Although we sought to evaluate any LAMA in KQ2a-c, regardless of Food and Drug Administration approval status, the evidence base is driven almost exclusively by tiotropium, administered as a soft mist inhaler. In addition, the evidence base comparing LAMA to other controllers, as add-on to ICS, was limited in number and size of trials and also to very few outcomes, making it challenging to draw conclusions comparing LAMA to other controllers outside of LABA when added to ICS.

Many studies reported exacerbations requiring systemic corticosteroids; however, other exacerbation types, such as those requiring ER visits or hospitalizations, which are important health outcomes, were far less frequently reported. In addition, the evidence base for some KQ relied on composite outcomes that grouped components that likely vary in importance, making results difficult to interpret. Outside of exacerbations and spirometry, measures of asthma control composite scores, quality of life and health care utilization other than rescue inhaler use were infrequently reported.

Little data exists regarding subgroups that are of interest in this field, not limited to but including asthma severity and control. Although we sought to collect and analyze such data when possible, we were only able to perform a subgroup analysis for the dose of tiotropium in in LAMA-related KQs. Additional data reported relevant to subgroups of interest came from analyses of original trials included in this review.

Future Research Needs

Additional research would be valuable in the area of intermittent ICS dosing, particularly that which was evaluated in KQ1a and 1b where currently the evidence base is limited in size, not only overall but also per comparator/outcome evaluated. In addition, there seems to be a relatively lower amount of published evidence related to intermittent ICS dosing in comparison to other KQ addressed in this report such as the use of ICS and LABA as quick relief and controller therapy or the role of LAMA therapy in asthma. This may unfortunately lead to mis-interpretation of evidence suggesting lack of benefit to intermittent therapy when in fact there is a limited data set currently from which to draw conclusions. Given most outcomes were rated with low strength of evidence, future research could change the direction or magnitude of effect or the strength of evidence the consistency and precision in effect estimates improve. For KQ1b, there appears to be several trials evaluating yellow-zone triggered ICS therapy, although evidence of other “intermittent ICS” strategies is limited and may offer different effects. We are aware of at least two ongoing trials (NCT 02066129 and NCT 02298205) registered with www.clinicaltrials.gov that will provide some additional evidence to these research questions in the future.

Since there are several LAMAs other than tiotropium on the US market, it would be valuable to understand their efficacy in asthma management. We are aware of several ongoing clinical trials (NCT 02676089, NCT 02676076, NCT 02433834, NCT 02382510) related to other LAMAs (e.g. glycopyrronium and investigational LAMAs such as TRN-157) in asthma management which may provide future evidence in this area. The same holds true for other combinations of ICS/LABA. Future studies comparing LAMA to controllers other than LABAs would also be of value since currently the evidence base is largest for comparing LAMA to LABA.

Future studies would benefit from consistently defining the severity and control of asthma in the recruited population. There are many potential reasons a patient may be considered to have asthma that is not controlled and this may provide insight into preference for a particular treatment. Future studies should focus on these various causes of having “uncontrolled” asthma as part of investigation for alternative treatments. Knowing more about the severity and control of enrolled participants would also enhance applicability of evidence. Future trials should also consider other subgroups of interest, including racial and ethnic subgroups, and routinely report such results numerically to help decision makers make more individualized treatment decisions. Future studies would also benefit from analyzing and reporting individual components of exacerbation composite outcomes so that various end users can make decisions based on which outcome is most important to them. In addition, studies would benefit from more routine use of validated tools for quality of life and asthma control measurement in addition to incorporation of health resource utilization outcomes so the impact of therapy outside of exacerbation risk can be more thoroughly evaluated.

Conclusions

Compared to rescue SABA use, adding intermittent ICS use appears to benefit children less than 5 years old with recurrent wheezing in the setting of an RTI. In patients 12 years of age and older with persistent asthma, differences in intermittent ICS versus controller use of ICS were not detected, although few studies provided evidence for this KQ leading to primarily low strength of evidence ratings. Using ICS and LABA as both a controller and quick relief therapy showed benefits over use as a controller medication alone (ICS or ICS and LABA controller). In patients 12 years of age and older with uncontrolled, persistent asthma, adding LAMA to ICS controller or adding LAMA to ICS plus LABA controller compared to ICS or ICS plus LABA alone improves some outcomes. However, adding LAMA to ICS controller compared to adding LABA to ICS controller produced no difference in outcomes.

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Glossary

Asthma control: The degree to which the manifestations of asthma (symptoms, functional impairments, exacerbations) are minimized. Asthma control is determined by assessing the domains of impairment (patient self-reported symptoms, nighttime awakenings, rescue SABA use, interference with normal activities; objective measures of lung function) and risk (exacerbations requiring oral systemic corticosteroids).

Asthma severity: The intrinsic intensity of the disease process. Asthma severity is assessed in a patient who is not currently receiving controller therapy using the domains of impairment (patient self-reported symptoms, nighttime awakenings, rescue SABA use, interference with normal activities; objective measures of lung function) and risk (exacerbations requiring oral systemic corticosteroids) or it is inferred from the least amount of treatment required to maintain control. Asthma severity is classified as “intermittent”, “mild persistent”, “moderate persistent”, or “severe persistent”.

Controlled asthma: Minimal manifestations of asthma symptoms and functional impairments, as determined by assessment of the impairment and risk domains.

Controller therapy: Medications recommended to be taken daily on a long-term basis to achieve and maintain control of persistent asthma. Long-term controller medications include inhaled corticosteroids, inhaled long-acting bronchodilators, leukotriene modifiers, cromolyn, theophylline, immunomodulators, and oral systemic corticosteroids.

Intermittent dosing: The prescribed use of ICS that is not the same on a daily basis. As prescribed, intermittent ICS dosing may specify variations in the dose or frequency of administration of ICS. The determinant of ICS use with intermittent ICS dosing may be a patient decision (based on need), an index of worsening asthma, or some other pre-defined criteria.

Persistent asthma: A classification of asthma severity defined either by the assessment of the impairment (patient self-reported symptoms, nighttime awakenings, rescue SABA use, interference with normal activities; objective measures of lung function) and/or risk (exacerbations requiring oral systemic corticosteroids) domains in a patient not taking controller therapy or use of controller therapy to achieve and maintain asthma control. Persistent asthma is further sub-divided as “mild persistent”, “moderate persistent”, and “severe persistent”.

Quick-relief therapy: Medication to be used as-needed for acute symptom relief.

Uncontrolled asthma: A lack of asthma control, as determined by assessment of the impairment and/or risk domains.

Abbreviations

Abbreviation	Definition
ACQ	Asthma Control Questionnaire
ACT	Asthma Control Test
AQLQ	Asthma Quality of Life Questionnaire
AQLQ(S)	Standardized Asthma Quality of Life Questionnaire
AUC	Area Under the Curve
CBP	Conventional Best Practice
CI	Confidence Intervals
EPC	Evidence-based Practice Centers
EPR	Expert Panel Report
ER	Emergency Room
FEV1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
HR	Hazard Ratio
ICS	Inhaled Corticosteroid
ICTRP	International Controlled Trials Registry Platform
KQ	Key Question
LABA	Long-acting $ß_2$ Agonists
LAMA	Long-acting Muscarinic Antagonists
LTRA	Leukotriene Receptor Antagonist
mAPI	modified Asthma Prediction Index
MD	Mean Difference
NAEPP	National Asthma Education and Prevention Program
NHLBI	National Heart, Lung and Blood Institute
OR	Odds Ratio
PACQLQ	Pediatric Asthma Caregivers Asthma Quality of Life Questionnaire
PAQLQ	Pediatric Asthma Quality of Life Questionnaire
PEF	Peak Expiratory Flow
PICOTS	Population, Intervention, Comparison, Outcomes, Timing, Setting
RCT	Randomized Controlled Trial
RR	Relative Risk
RTI	Respiratory Tract Infection
SABA	Short-acting $ß_2$ Agonists
SOE	Strength of Evidence
UK	United Kingdom
US	United States

Appendixes

Contents

Tables

Figures

Appendix A. Search Strategy

Search for KQ 1- Medline, Cochrane Central and Cochrane Database of Systematic Reviews- via Ovid

1. Asthma.mp or Asthma/
2. Wheez$.mp.
3. Bronchial spasm/ or bronchospas$.mp.
4. Bronchoconstriction/ or bronchoconstrict$.mp.
5. Bronchial hyperreactivity/
6. Reactive airway disease.mp.
7. 1 or 2 or 3 or 4 or 5 or 6
8. Inhaled corticosteroid.mp.
9. Inhal$.mp.
10. Ciclesonide.mp.
11. Fluticasone/ or fluticasone.mp.
12. Flunisolide.mp.
13. Beclomethasone/ or beclomethasone.mp.
14. Budesonide/ or budesonide.mp.
15. Mometasone furoate/ or mometasone.mp.
16. Triamcinolone/ or triamcinolone.mp.
17. 9 AND (10 or 11 or 12 or 13 or 14 or 15 or 16)
18. "Single inhaler".mp. OR "single maintenance and reliever therapy".mp. OR SMART
19. 8 or 17 or 18
20. 7 and 19
21. Limit 20 to humans

Search for KQ 1- Embase

1. 'asthma'/de OR asthma
2. 'wheezing'/de OR wheezing
3. 'wheeze'/de OR wheeze
4. 'bronchospasm'/de OR 'bronchospasm'
5. 'bronchoconstriction'/de OR 'bronchoconstriction'
6. 'bronchial hyperreactivity'/de OR
7. 'reactive airway disease'
8. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
9. 'ciclesonide'/exp/dd_ih
10. 'budesonide'/exp/dd_ih
11. 'fluticasone'/exp/dd_ih
12. 'flunisolide'/exp/dd_ih
13. 'beclomethasone'/exp/dd_ih
14. 'mometasone'/exp/dd_ih
15. 'triamcinolone'/exp/dd_ih
16. 'single maintenance and rescue therapy'
17. 'single inhaler therapy'
18. #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17
19. #8 AND #18

Search for KQ 2- Medline, Cochrane Central and Cochrane Database of Systematic Reviews- via Ovid

1. Asthma.mp or Asthma/
2. Wheez$.mp.
3. Bronchial spasm/ or bronchospas$.mp.
4. Bronchoconstriction/ or bronchoconstrict$.mp.
5. Bronchial hyperreactivity/
6. Reactive airway disease.mp.
7. 1 or 2 or 3 or 4 or 5 or 6
8. Long acting muscarinic antagonist.mp.
9. Tiotropium bromide/ or tiotropium.mp.
10. Aclidinium.mp.
11. Glycopyrronium.mp. or glycopyrrolate/ or glycopyrrolate.mp.
12. Umeclidinium.mp.
13. 9 or 10 or 11 or 12
14. 8 or 13
15. 7 and 14
16. Limit 15 to humans

Search for KQ 2- Embase

20. ‘asthma’/de OR asthma
21. ‘wheezing’/de OR wheezing
22. ‘wheeze’/de OR wheeze
23. ‘bronchospasm’/de OR ‘bronchospasm’
24. ‘bronchoconstriction’/de OR ‘bronchoconstriction’
25. ‘bronchial hyperreactivity’/de OR
26. ‘reactive airway disease’
27. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
28. ‘long acting muscarinic antagonist’
29. ‘tiotropium’/exp/dd_ih
30. ‘aclidinium’/exp/dd_ih
31. ‘glycopyrronium’/exp/dd_ih
32. “glycopyrrolaye’/exp/dd_ih
33. ‘umeclidinium’/exp/dd_ih
34. #9 OR #10 OR #11 OR #12 OR #13 OR #14
35. #8 AND #15

Appendix B. List of Excluded Studies

ICS Search

1. 2nd WAO International Scientific Conference, WISC 2012, Abstracts. World Allergy Organ J. 2013;6;Suppl 1:1-67. [Not an intervention of interest]
2. A combination of fluticasone and salmeterol for asthma. Med Lett Drugs Ther. 2001 Apr 16;43(1102):31-3. PMID: 11309534. [Not a human study]
3. Aalbers R, Backer V, Kava TTK, et al. Adjustable maintenance dosing with budesonide/formoterol compared with fixed-dose salmeterol/fluticasone in moderate to severe asthma. Curr Med Res Opin. 2004;20(2):225-40. PMID: 15006018. [Not an intervention of interest]
4. Aalbers R, Mensing M, Boorsma M, et al. Protective effect of budesonide /formoterol in a model of repeated exposure to inhaled adenosine 5'-monophosphate (AMP) in patients with asthma. Eur Respir J. 2007;30;Suppl 51:353s. [Not an intervention of interest]
5. Aalbers R. Fixed or adjustable maintenance-dose budesonide/formoterol compared with fixed maintenance-dose salmeterol/fluticasone propionate in asthma patients aged >or=16 years: Post hoc analysis of a randomized, double-blind/open-label extension, parallel-group study. Clin Drug Invest. 2010;30(7):439-51. PMID: 20528000. [Not an intervention of interest]
6. Aalbers R. Single inhaler as maintenance and reliever therapy--is it SMART? Lancet Respir Med. 2013 Mar;1(1):2-3. PMID: 24321788. [Not a human study]
7. Abramson M, Sim MR. Occupational asthma. Thorax. 2006 Sep;61(9):741-2. [Not a human study]
8. Acun C, Tomac N, Sogut A, et al. A comparison of inhaled budesonide and oral prednisolone for children with acute asthma. 2003 Sep;22;Suppl 45:134s. [Not in the target population]
9. Adachi M, Ishihara K, Inoue H, et al. Safety and efficacy of inhaled ciclesonide in long-term administration to adult patients with bronchial asthma. Ther Res. 2008;29(5):821-32. [Not an intervention of interest]
10. Adelroth E, Thompson S. Advantages of high-dose inhaled budesonide. Lancet. 1988 Feb 27;1(8583):476. PMID: 2893900. [Not an intervention of interest]
11. Adelsberg B. Combined budesonide and formoterol for maintenance and relief provided better asthma control than budesonide for maintenance and terbutaline for relief: commentary. Evid-Based Med. 2006 Oct;11(5):138. [Not a human study]
12. Adler LM, Clarke IC. Efficacy and safety of beclomethasone dipropionate (BDP) delivered via a novel dry powder inhaler (Clickhaler[TM]) in paediatric patients with asthma. Thorax. 1997;52;Suppl 6:A57 P106. [Not an intervention of interest]
13. Adolfsson LE, Lundgren M, Tilling B, et al. Short-term safety and tolerability of double-dose salmeterol/fluticasone propionate in adult asthmatic patients. Clin Drug Invest. 2005;25(4):231-41. DOI: 10.2165/00044011-200525040-00002. [Not an intervention of interest]
14. Aelony Y. Inhaled fluticasone and zafirlukast in persistent asthma. Am J Med. 2002 Mar;112(4):333. PMID: 11893383. [Not a human study]
15. Affrime MB, Banfield C, Nolop K. Systemic bioavailability of inhaled corticosteriods: appropriate and comparable methodology. Eur Respir J. 2001;18(1):246. [Not a human study]

16. Afilalo M, Guttman A, Colacone A, et al. Efficacy of inhaled steroids (beclomethasone dipropionate) for treatment of mild to moderately severe asthma in the emergency department: A randomized clinical trial. Ann Emerg Med. 1999 Mar;33(3):304-9. PMID: 10036345. [Not in the target population]
17. Agarwal SK, Arshad N. Utility of high dose inhaled fluticasone therapy for the early management of acute exacerbations of asthma [Abstract]. European Respiratory Society; 2009 Sep 12-16; Vienna, Austra. E4352. [Not in the target population]
18. Agarwal SK, Sharma S. Effect of fluticasone/formoterol pressurized metered-dose inhaler (pMDI) in early management o facute exacerbations of asthma. Am J Respir Crit Care Med. 2010;181:A5659. [Not in the target population]
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20. Agerroft L, Pedersen S. Comparison of lower leg growth rate in prepubertal children with mild asthma treated with inhaled placebo, ciclesonide, or fluticasone propionate. Allergy. 2007;62:131. [Not an intervention of interest]
21. Agerroft L, Pedersen S. Inhaled ciclesonide does not effect lower leg growth rate or HPA-axis function in children with mild asthma. Eur Respir J. 2004;24;Suppl 48:377s. [Not an intervention of interest]
22. Agerroft L, Pedersen S. Lower-leg growth rate and APA-axis function in children with asthma during treatment with inhaled ciclesonide. J Allergy Clin Immunol. 2004;113;Suppl 2:S119. [Not an intervention of interest]
23. Agertoft L, Pedersen S. Bone mineral density in children with asthma receiving long-term treatment with inhaled budesonide. Am J Respir Crit Care Med. 1998 Jan;157(1):178-83. PMID: 9445297. [Excluded study design]
24. Agertoft L, Pedersen S. Effects of long-term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. Respir Med. 1994 May;88(5):373-81. PMID: 8036306. [Not an intervention of interest]
25. Agertoft L, Pedersen S. Influence of inspiratory flow rate on plasma levels and lung deposition of fluticasone propionate inhaled from diskus dry powder inhaler. European Respiratory Society; 1999 Oct 9-13; Madrid, Spain. 1264p. [Irretrievable]
26. Agertoft L, Pederson S. Long term growth in children with inhaled budesonide or nedocromil. Eur Respir J. 2000;16;Suppl 31:553s. [Irretrievable]
27. Akhtaruzzaman M, Ahmed SU, Hoque MA, et al. Effects of nebulized budesonide as an adjunct to standard treatment of asthma exacerbations: A randomized, double-blind, placebo-controlled trial. Mymensingh Med J. 2014 Jul;23(3):418-25. PMID: 25178590. [Not in the target population]
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29. Alangari AA, Malhis N, Mubasher M, et al. Budesonide nebulization added to systemic prednisolone in the treatment of acute asthma in children: A double-blind, randomized, controlled trial. Chest. 2014 Apr;145(4):772-8. PMID: 24384609. [Not in the target population]

30. Aldridge RE, Hancox RJ, Cowan JO, et al. Eosinophils and eosinophilic cationic protein in induced sputum and blood: Effects of budesonide and terbutaline treatment. Ann Allergy Asthma Immunol. 2002 Nov;89(5):492-7. [Not an intervention of interest]
31. Allen DB, Bronsky EA, LaForce CF, et al. Growth in asthmatic children treated with fluticasone propionate. J Pediatr. 1998 Mar;132(3 Pt 1):472-7. PMID: 9544904. [Not an intervention of interest]
32. Allen DB. Effect of inhaled corticosteroids on growth. Pediatrics. 2001 Nov;108(5):1234-5. PMID: 11694712. [Not a human study]
33. Allen DB. Sense and sensitivity: assessing inhaled corticosteroid effects on the hypothalamic-pituitary-adrenal axis. Ann Allergy Asthma Immunol. 2002 Dec;89(6):537-9. [Not a human study]
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37. Amar NJ, Shekar T, Varnell T, et al. Mometasone furoate (MF) improves lung function in pediatric asthma: a dose-ranging study of MF metered-dose inhaler (MDI). J Allergy Clin Immunol. 2016;137;2 Suppl 1:AB214. Embase 72197450. [Not an intervention of interest]
38. Amirav I, Newhouse MT. Treatment failures in children with asthma due to inappropriate use of turbuhaler. J Pediatr. 2002;140(4):483. [Excluded study design]
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40. Anderson W, McFarlane L, Lipworth B. Prospective follow-up of novel bone turnover markers in asthmatics exposed to low or high doses of inhaled ciclesonide over 1 year. Eur Respir J. 2012 Sep 5;40;Suppl 56:P2100. Embase 71926472. [Not an intervention of interest]
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Appendix C. Study Characteristics

Table C-1. Study and population characteristics for KQ1a

Study, Year, Acronym n, Study design, Duration, Risk of bias	Study population	Intervention Comparisons	Age [mean (SD)]	Males (%)	Parent w/ asthma (%)	Atopy (%)	2nd hand smoke (%)	Systemic corti-costeroid in last 12m (%)	Hospital-ized in last 12m (%)	ICS dose during study (µg/d) [mean (SD)]
Svedmyr, 1999[48] n=55 RCT,12m or 6 treatments	1-3 years of age w/≥3 episodes of wheezing w/URTI, asthma symptoms during last 2 airway infections and no symptoms in-between URTI; physician's diagnosis of wheezy bronchitis or asthma	Budesonide 400µg QID x3d then 400µg BID x7d (MDI), initiated by the parent at first sign of URTI n=28	25m (12 to 47)[b]	60.7	NR	25.0[c]	7.1[d]	NR	1.2 (0 to 4)[b,e]	NR
Unclear	SABA and theophylline use allowed when needed; fixed dose cromoglycate was allowed[a]	Placebo MDI x10d initiated by the parent at first sign of URTI n=27	26m (13 to 47)[b]	77.8	NR	22.2[c]	7.4[d]	NR	1.1 (0 to 3)[b,e]	NR
Ghirga, 2002[46] n=26 RCT, until 4 URTIs[f]	7-12 months old, history of recurrent wheezing during URTI w/at least 2-3 airway infections causing wheezing	Beclomethasone 400µg TID (neb) x5d initiated by parent w/very early phase of URTI before any sign of wheezing[g] n=13	8.2m (1.6)	69.2	NR	NR	NR	NR	NR	NR
Medium		No preventative treatment w/URTI n=13			NR	NR	NR	NR	NR	NR
Bacharier, 2008[44] AIMS n=143 RCT, 12m	12-59 months old w/≥2 episodes of wheezing in context of RTI within past year[h], 1 in the past 6 months and 1 documented by a healthcare provider	Budesonide 1mg BID (neb) x7d initiated by parent at the first sign of RTI n=96	36.7m (13.5)	72.9	41.7	44.8[j]	4.2[k]	1=21.9 2=26.0 3=8.3 4+=3.1	8	NR

Study, Year, Acronym n, Study design, Duration, Risk of bias	Study population	Intervention Comparisons	Age [mean (SD)]	Males (%)	Parent w/ asthma (%)	Atopy (%)	2nd hand smoke (%)	Systemic corti-costeroid in last 12m (%)	Hospital-ized in last 12m (%)	ICS dose during study (µg/d) [mean (SD)]
Low	All patients received albuterol QID while awake + PRN for 48h then PRN; oral corticosteroids were available at home[i]	Placebo x7d initiated at the first sign of RTI n=47	35.7m (13.7)	48.9	53.2	44.7[j]	1.7[k]	1=27.7 2=17.0 3=4.3 4+=4.3		NR
Ducharme, 2009[45] n=129 RCT, 12m	1-6 years old w/≥3 wheezing episodes in lifetime seemingly triggered exclusively by URTI with no symptoms in between, with at least 1 course of rescue systemic corticosteroid in prior 6m or 2 in prior 12m	Fluticasone 750µg BID (MDI) initiated by parent at first sign of URTI until 48h without cough or wheeze n=62	2.60y (1.09)	52	19[l]	10[m]	In utero: 18 In home: 23	2.3 (1.1)[n]	47	50 (39 to 91)[o]
Low	All patients received albuterol 200-400µg q4h PRN for cough, wheeze and dyspnea	Placebo initiated by parent at first sign of URTI until 48h without cough or wheeze n=67	2.86y (1.20)	69	18[l]	12[m]	In utero: 13 In home: 21	2.4 (1.4)[n]	52	NR
Papi, 2009[47] BEST-children n=276 RCT, 12w	1-4 years old with frequent wheeze (≥3 episodes requiring medical attention) referred to specialist centers because of further episode of wheezing in addition to the 3 required	Beclomethasone/ salbutamol 800/1600µg PRN (neb) for symptom relief n=110	2.26y (0.79)	61.8	NR	NR	NR	NR	NR	15.1 (21.5)
Low		Beclomethasone 400µg BID (neb) + salbutamol 2500µg PRN (neb) for symptom relief n=110	2.35y (0.81)	58.2	NR	NR	NR	NR	NR	66.8 (6.8)[p]

Study, Year, Acronym n, Study design, Duration, Risk of bias	Study population	Intervention Comparisons	Age [mean (SD)]	Males (%)	Parent w/ asthma (%)	Atopy (%)	2nd hand smoke (%)	Systemic corti-costeroid in last 12m (%)	Hospital-ized in last 12m (%)	ICS dose during study (µg/d) [mean (SD)]
		Salbutamol 2500µg PRN (neb) for symptom relief n=56	2.29y (0.78)	60.7	NR	NR	NR	NR	NR	NR
Zeiger, 2011[49] MIST n=278 RCT, 52w Low	12-53 months old w/positive mAPI and history of ≥4 wheezing episodes in the prior year with ≥1 physician diagnosed or ≥3 wheezing episodes in the prior year with ≥3 months of asthma controller therapy in the prior year All patients received albuterol QID while awake for the first 48h + PRN	Placebo once daily (neb) + budesonide 1mg BID (neb) x7d at RTI onset n=139	2.9y (0.9)	73.4	64.9	59.9[q]	39.6[r]	79.1	18.7	45.7 (38.9 to 52.8)
		Budesonide 500µg (neb) once daily + placebo neb for RTI n=139	2.9y (0.9)	64.7	63.7	56.8[q]	42.4[r]	71.9	19.4	149.9 (140.1 to 159.6)

Abbreviations: BID=twice daily; CI=confidence interval; d=day; h=hour; ICS=inhaled corticosteroid; m=month; IQR=interquartile range; mAPI=modified Asthma Predictive Index; MDI=metered dose inhaler; mg=milligram; n=patient sample size; neb=nebulized; NR=not reported; PRN=pro re nata (i.e., as needed); Q=every; QID=four times daily; RCT=randomized controlled trial; RTI=respiratory tract infection; SABA=short-acting β_2-agonist; SD=standard deviation; TID=three times daily; URTI=upper respiratory tract infection; µg=microgram; y=year

[a]Treatment with cromoglycate was 17.9% in the budesonide arm and 22.2% in the placebo arm

[b]Data reported as mean (range)

[c]Represents positive skin prick test

[d]Represents parents smoking indoors

[e]Represents number of hospital admissions due to asthma

[f]Patients were not enrolled for a finite time period, but completed the study after 4 URTIs

[g]At least 2 of 3 URTI signs were to be present before starting medication (nasal discharge, coughing and fever). Treatment was stopped if all signs of URTI disappeared within 24h

[h]In an effort to include children with prior moderate-to-severe wheezing episodes, children were required to have experienced either 2 urgent care visits for acute wheezing within the past year, 2 wheezing episodes for which oral corticosteroids were prescribed, or 1 episode requiring urgent care and 1 episode requiring oral corticosteroids

[i]A course of prednisolone was considered if at any point the child had symptoms that did not improve after 3 SABA treatments administered every 15 minutes, if the child needed SABA more than 6 neb treatments or more than 12 puffs/d for >24h, moderate-severe cough or wheeze for at least 5 of the preceding 7 days was present or at physician discretion. The prednisolone course was 2mg/kg/d (maximum 60mg/d) x2d followed by 1mg/kg/d (maximum 30mg/d) x2 d

[j]Represents positive aeroallergen skin test

[k]Represents exposure at home or daycare
[l]Represents maternal asthma
[m]Represents food or drug allergy, allergies to aeroallergens documented by positive skin test or IgE were excluded
[n]Represents courses of systemic corticosteroids in the past year, data reported as mean (SD)
[o]Represents cumulative dose of fluticasone used (mg) per patient-month of observation, data reported as median (IQR)
[p]Beclomethasone dipropionate equivalent dose in mg
[q]Represents sensitivity to any aeroallergen
[r]Represents smoke exposure from birth
[s]Represents cumulative dose (mg) over study course, data reported as mean (95% CI)

Table C-2. Study level outcomes for KQ1a, intermittent ICS with as-needed SABA vs. ICS controller with as-needed SABA

Study, Year, n, Study design, Duration	Population[a]	Exacerbations[b]	Mortality	Asthma Control	Quality of Life	Healthcare Utilization
Svedmyr, 1999[48] n=55 RCT, 12m or 6 treatments	***Age****:* 0-4y ***ICS dose:*** Budesonide 400µg QIDx3d then BIDx7d vs. PRN SABA	Required oral corticosteroid course: RR 0.90 (0.44 to 1.85) Asthma-related ER visit: RR 0.83 (0.44 to 1.58) Hospital admission due to asthma: RR 2.50 (0.53 to 11.74) Number of ER admissions for asthma: 16 vs. 23 Number of hospital admissions for asthma: 6 vs. 2 Total number of oral corticosteroid courses: 14 vs. 17	NR	***Composite measures***: NR ***Spirometry:*** NR	NR	NR

Study, Year, n, Study design, Duration	Population[a]	Exacerbations[b]	Mortality	Asthma Control	Quality of Life	Healthcare Utilization
Bacharier, 2008[44] n=143 RCT, 12m	***Age***: 0-4y ***ICS dose:*** Budesonide 1.0mg BID (high) x7d vs. PRN SABA	Required oral corticosteroid course: RR 0.70 (0.49 to 1.00) Asthma-related urgent/ER visit: RR 0.98 (0.71 to 1.34) Number of urgent care/ER visits per patient: -0.5 (-1.16 to 0.16) Hospital admission due to asthma: RR 0.24 (0.05 to 1.29) Average courses of oral corticosteroid/participant: MD -0.2 (0.6 to 0.26) Days of oral corticosteroid use/participant: MD -0.1 (-1.87 to 1.67)	NR	***Composite measures***: NR ***Spirometry:*** NR	PACQLQ score: MD -0.1 (-0.36 to 0.34)	NR

Study, Year, n, Study design, Duration	Population[a]	Exacerbations[b]	Mortality	Asthma Control	Quality of Life	Healthcare Utilization
Ducharme, 2009[45] n=129 RCT, 12m	***Age***: 0-4y ***ICS dose:*** Fluticasone 750µg BID with URTI vs. PRN SABA	Required a course of oral corticosteroid: RR 0.60 (0.42 to 0.87) URTI w/asthma symptoms: OR 0.64 (0.36 to 1.13) URTI requiring systemic corticosteroid: OR 0.49 (0.3 to 0.83) Asthma-related acute care visit: RR 0.88 (0.72 to 1.07) Hospital admission due to asthma: RR 0.72 (0.35 to 1.48) URTI requiring hospitalization: OR 0.67 (0.29 to 1.38) URTI requiring acute care visit: OR 0.79 (0.53 to 1.19) Number of asthma-related acute care visits: 107 vs. 146 Number of asthma-related hospitalizations: 11 vs. 18	NR	***Composite measures***: NR ***Spirometry:*** NR	PACQLQ score during URTI: MD 0.49 (0.1 to 0.86)	Total number of SABA puffs per URTI [median (IQR)]: 36 (23 to 61) vs. 44 (25 to 78) Total number of days per URTI SABA used [median (IQR)]: 5 (3 to 8) vs. 6 (4 to 10) Duration of SABA use: Rate ratio: 0.85 (0.74 to 0.98) Cumulative number of SABA inhalations: Rate ratio 0.80 (0.68 to 0.94)

Study, Year, n, Study design, Duration	Population[a]	Exacerbations[b]	Mortality	Asthma Control	Quality of Life	Healthcare Utilization
Papi, 2009[47] n=166 RCT, 12w	***Age****:* 0-4y ***ICS dose:*** Beclomethasone 800 µg PRN vs. PRN SABA	Progressive increase in SOB, cough or wheeze: 23 total exacerbations, 14 required oral corticosteroid	NR	***Composite measures***: NR ***Spirometry:*** NR	NR	Cumulative salbutamol dose (mg): 30.1 (43.0) vs. 56.3 (84.2), $p<0.001$ Daytime rescue medication use: MD -0.08 (-0.21 to 0.05) Nighttime rescue medication use: MD -0.04 (-0.11 to 0.03)

Abbreviations: BID=twice daily; EPR=Expert Panel Review (Guidelines for Diagnosis and Management of Asthma); ER=emergency room; HR=hazard ratio; ICS=inhaled corticosteroid; IQR=interquartile range; IRR= incident rate ratio; m=months; MD=mean difference; mg=milligram; n=patient sample size; NR=not reported; OR=odds ratio; PACQLQ=Pediatric Asthma Caregiver's Quality of Life Questionnaire; PRN=pro re nata (i.e., as-needed); RCT=randomized controlled trial; RR=relative risk; SABA=short-acting β_2-agonist; SOB=short of breath; µg=microgram; QID=four times daily; URTI=upper respiratory tract infection; w=weeks

[a]Age is categorized using study inclusion criteria and the age categories used in EPR-3 of 0-4y, 5-11y and 12y+. ICS dose is categorized, when possible, using the study's required ICS dose and the EPR-3 categories of low, medium and high

[b]Relative measures are presented first and include, when reported by the study, RR, HR for time to the event, and IRR for count data allowing multiple events over the period of follow-up. Count data is presented, when reported by the study, for number of hospitalizations, hospital days, and ER visits in association with exacerbations. Number of hospitalizations, hospital days, and ER visits not specified to be due to exacerbation are listed in the healthcare utilization column

Table C-3. Study level outcomes for KQ1a, intermittent ICS with as-needed SABA vs. ICS controller with as-needed SABA

Study, Year, n, Study design, Duration	Population[a]	Exacerbations[b]	Mortality	Asthma Control	Quality of Life	Healthcare Utilization
Papi, 2009[47] n=220 RCT, 12w	***Age****:* 0-4y ***ICS dose:*** Beclomethasone 800 µg PRN vs. 400µg BID	Progressive increase in SOB, cough or wheeze: 23 total exacerbations, 14 required oral corticosteroid	NR	***Composite measures***: NR ***Spirometry:*** NR	NR	Cumulative salbutamol dose (mg): 30.1 (43.0) vs. 34.2 (42.3) Daytime rescue medication use: MD 0.07 (-0.4 to 1.8) Nighttime rescue medication use: MD -0.02 (-0.7 to 0.3)
Zeiger, 2011[49] n=278 RCT, 52w	***Age****:* 0-4y ***ICS dose:*** Budesonide 1.0mg BID (high)x7d vs. 0.5mg (low) daily	Exacerbation requiring prednisolone: HR 0.97 (0.76 to 1.22) IRR 0.99 (0.71 to 1.35) Second exacerbation requiring prednisolone: HR 0.79 (0.49 to 1.32) Exacerbation occurring during RTI: RR 0.99 (0.92 to 1.08) Proportion of RTI in which prednisolone was administered: MD 0.02 (-0.05 to 0.09) Asthma related hospitalization: RR 1.25 (0.34 to 4.56) Asthma related urgent care visit: IRR 0.99 (0.72 to 1.35)	All-cause: No events occurred	***Composite measures***: NR ***Spirometry:*** NR	NR	% days w/albuterol use: MD 0.4 (-1.00 to 2.00)

Abbreviations: BID=twice a day; d=day; EPR=Expert Panel Review (Guidelines for Diagnosis and Management of Asthma); ER=emergency room; HR=hazard ratio; ICS=inhaled corticosteroid; IRR=incident rate ratio; MD=mean difference; mg=milligram; n=patient sample size; NR=not reported; RCT=randomized controlled trial; RR=relative risk; RTI=respiratory tract infection; SOB=short of breath; µg=microgram; w=week; y=year

[a]Age is categorized using study inclusion criteria and the age categories used in EPR-3 of 0-4y, 5-11y and 12y+. ICS dose is categorized, when possible, using the study's required ICS dose and the EPR-3 categories of low, medium and high

[b]Relative measures are presented first and include, when reported by the study, RR, HR for time to the event, and IRR for count data allowing multiple events over the period of follow-up. Count data is presented, when reported by the study, for number of hospitalizations, hospital days, and ER visits in association with exacerbations. Number of hospitalizations, hospital days, and ER visits not specified to be due to exacerbation are listed in the healthcare utilization column

Table C-4. Study level outcomes for KQ1a, intermittent ICS versus no therapy

Study, Year, n, Study design, Duration	Population[a]	Exacerbations[b]	Mortality	Asthma Control	Quality of Life	Healthcare Utilization
Ghirga, 2002[46] N=26 RCT, NR	***Age***: 0-4y ***ICS dose:*** Beclomethasone 400µg TIDx5d vs. no preventative therapy	Received oral corticosteroid: RR 0.54 (0.12 to 2.44) Asthma-related hospitalizations: No events occurred Asthma-related ER visits: RR 0.27 (0.04 to 2.10)	NR	***Composite measures***: NR ***Spirometry:*** NR	NR	NR

Abbreviations: d=day; EPR=Expert Panel Review (Guidelines for Diagnosis and Management of Asthma); ER=emergency room; HR=hazard ratio; ICS=inhaled corticosteroid; IRR=incident rate ratio; n=patient sample size; NR=not reported; RCT=randomized controlled trial; RR=relative risk; TID=three times a day; µg=microgram; y=year

[a]Age is categorized using study inclusion criteria and the age categories used in EPR-3 of 0-4y, 5-11y and 12y+. ICS dose is categorized, when possible, using the study's required ICS dose and the EPR-3 categories of low, medium and high

[b]Relative measures are presented first and include, when reported by the study, RR, HR for time to the event, and IRR for count data allowing multiple events over the period of follow-up. Count data is presented, when reported by the study, for number of hospitalizations, hospital days, and ER visits in association with exacerbations. Number of hospitalizations, hospital days, and ER visits not specified to be due to exacerbation are listed in the healthcare utilization column

Table C-5. Study and population characteristics for KQ1b, intermittent ICS and ICS controller vs. ICS controller

Study, Year, N, Acronym, Study design, Duration, Risk of bias	Study population	Intervention Comparisons	Age (y) [mean (SD)]	Males (%)	Duration of asthma (y) [mean (SD)]	FEV1 (L) [mean (SD)]	FEV1 % predicted (L) [mean (SD)]	Rescue inhaler use (puffs/d) [mean (SD)]	ICS dose during study (μg/d) [mean (SD)]
Lahdensuo, 1996[67] n=115 RCT, 12m Medium	≥18y with mild to moderately severe asthma on budesonide (400-1600μg/d) or beclomethasone (500-2000μg/d) during the prior 6m	Budesonide 200μg/dose (DPI) self-adjusted: PEF <85% double ICS dose x 2w; PEF<70% initiate oral prednisolone 40mg/d x7d; otherwise maintain stable dose n=56	40.6 (14.2)	26.8	8.2 (8.4)	2.84 (0.74)	82.4 (15.8)	NR	979 (375)
	All patients used SABA as rescue PRN. Other concomitant asthma therapies were continued[a]	Budesonide (DPI/MDI) or beclomethasone (MDI) traditional treatment with usual evaluation by physician for adjustments n=59	42.8 (15.2)	47.5	6.8 (7.6)	2.96 (0.89)	81.7 (16.6)	NR	962 (392), 1167 (408)[b]
Foresi, 2000[56] n=134 RCT, 6m Unclear	18-65 years old with moderate perennial asthma, treated with beclomethasone 500-1000μg/d for at least 4w, daily requirement of inhaled β_2-agoniost, wheeze, cough, chest tightness, SOB at rest that interfered with normal activities during 2w pre-study period	Budesonide 100μg BID + 200μg QID x 7d if PEF <70%. If PEF remained <70% after 2 days then prednisolone PO 30mg x3-10d added by investigator n=67	39.0 (13.5)	41.8	<5y=28.4 5-10y= 19.4 >10y=52.2	NR	75.6 (9.9)	NR	NR
	Inhaled β_2-agoniost was allowed PRN and treatment with LABA and theophylline were kept constant[c]	Budesonide 400μg BID+ placebo if PEF <70%. If PEF remained <70% prednisolone initiated as above n=67	36.6 (13.1)	46.3	<5y=25.4 5 to 10y= 28.4 >10y=46.3	NR	73.2 (11.0)	NR	NR

Study, Year, N, Acronym, Study design, Duration, Risk of bias	Study population	Intervention Comparisons	Age (y) [mean (SD)]	Males (%)	Duration of asthma (y) [mean (SD)]	FEV1 (L) [mean (SD)]	FEV1 % predicted (L) [mean (SD)]	Rescue inhaler use (puffs/d) [mean (SD)]	ICS dose during study (µg/d) [mean (SD)]
Colland, 2004[54] n=29 RCT, 1y Unclear	4 to 11 years old with moderate asthma, ICS naïve with an indication to begin ICS maintenance treatment All patients received beclomethasone or budesonide 400µg, or fluticasone 200-250µg divided over 2 doses (spacer/DPI)	Self-initiated doubling of daily ICS dose x1w with occurrence of prodromal signs n=14	6 (4-10)[d]	71.4	NR	NR	100 (13)	NR	NR
		Daily maintenance medications with no adjustments n=15	7 (4–11)[d]	60	NR	NR	105 (17)	NR	NR
FitzGerald, 2004[55] n=98 RCT, 6m Low	≥13 years old with asthma on a stable dose of ≤1200µg beclomethasone or equivalent daily for 1m prior to study, ≥1 exacerbation in prior 12m All patients received budesonide 100-400µg BID depending on their prior maintenance therapy+ terbutaline PRN. Mean budesonide at baseline was 634.7 µg/d. Theophylline was allowed during the study[e]	Add study inhaler which provided doubling of daily ICS dose x14d if prompted by MiniDoc (PEF<80% + additional required symptoms present); PEF<60% prompted by MiniDoc to take oral methylprednisolone 32mg/d x7d[f] n=46	31.6 (14.6)	30	>1y=93	2.9 (0.8)	NR	NR	NR
		Add placebo inhaler x14d if prompted by MiniDoc (PEF<80% + additional required symptoms present); PEF<60% prompted by MiniDoc to take oral methylprednisolone as above n=52	32.7 (11.9)	25	>1yr=90	2.8 (0.6)	NR	NR	NR

Study, Year, N, Acronym, Study design, Duration, Risk of bias	Study population	Intervention Comparisons	Age (y) [mean (SD)]	Males (%)	Duration of asthma (y) [mean (SD)]	FEV1 (L) [mean (SD)]	FEV1 % predicted (L) [mean (SD)]	Rescue inhaler use (puffs/d) [mean (SD)]	ICS dose during study (µg/d) [mean (SD)]
Harrison, 2004[59] n=390 RCT, 12m Low	≥16 years old with asthma taking ICS (100-2000µg/d) regularly, taken oral corticosteroids or temporarily doubled dose in prior 12m due to an exacerbation, stable during run-in based on PEF and symptoms All patients continued usual treatment throughout the study. Mean ICS dose 708-711µg/d, 34.3-37.5% on LABA at baseline	Add study inhaler which provided doubling of daily ICS dose x14d if AM PEF≤85% or daytime symptom score increased by 1 point from run-in value; if PEF≤60% or asthma control deteriorated to point of usual corticosteroid therapy then oral prednisolone 30mg daily x10d was started n=192	50 (13)	36	NR	2.4 (0.8)	79 (19.6)	NR	NR
		Add placebo inhaler x14d for PEF≤85% or symptom score increase. If PEF≤60% or asthma control deteriorated to point of usual corticosteroid therapy then oral prednisolone as above n=198	48 (14)	29	NR	2.4 (0.8)	81 (21.1)	NR	NR
Oborne, 2009[66] n=403 RCT, 12m	≥16y old with asthma, taking 200-1000µg/d beclomethasone or equivalent, have taken oral corticosteroids or doubled ICS dose in prior 12m for exacerbation	Add study inhaler x7-14d which provided a quadrupling of daily ICS dose, otherwise usual ICS dose daily n=197	53 (14)	41	NR	2.4 (0.7)	83.7 (19)	NR	NR

Study, Year, N, Acronym, Study design, Duration, Risk of bias	Study population	Intervention Comparisons	Age (y) [mean (SD)]	Males (%)	Duration of asthma (y) [mean (SD)]	FEV1 (L) [mean (SD)]	FEV1 % predicted (L) [mean (SD)]	Rescue inhaler use (puffs/d) [mean (SD)]	ICS dose during study (µg/d) [mean (SD)]
Low	Patients self-adjusted therapy according to action plan- AM PEF ≤70% for 1 day or ≤85% for two or more days, in presences of symptom worsening or URTI: start study inhaler for 7d in addition to normal asthma treatment[g], continue for another 7d if PEF did not return to baseline AM PEF≤40%, general practitioner advised so, or asthma was at the point of usually starting systemic corticosteroids: start prednisone 30mg PO daily	Add placebo inhaler x7-14d + usual daily ICS dose otherwise n=206	55 (13)	37	NR	2.4 (0.7)	83.2 (18)	NR	NR
Martinez, 2011[60] TREXA n=143 RCT, 44w Low	6-18y of age w/history of mild persistent asthma during prior 2y, qualifying for interruption or discontinuation of controller therapy because illness was well controlled per EPR, asthma remained controlled during run-in on beclomethasone 40µg BID; either naïve to controller therapy with 1-2 exacerbations in prior year, treated in prior 8w on monotherapy other than ICS, or if illness was controlled for prior 8w on low-dose ICS monotherapy (≤160µg/d beclomethasone	Beclomethasone 40µg BID (MDI) with PRN use of beclomethasone 40µg (MDI) + albuterol 90µg (MDI) PRN n=71	11.4 (3.1)	55	NR	NR	101.5 (11.7)	NR	NR

Study, Year, N, Acronym, Study design, Duration, Risk of bias	Study population	Intervention Comparisons	Age (y) [mean (SD)]	Males (%)	Duration of asthma (y) [mean (SD)]	FEV1 (L) [mean (SD)]	FEV1 % predicted (L) [mean (SD)]	Rescue inhaler use (puffs/d) [mean (SD)]	ICS dose during study (µg/d) [mean (SD)]
	equivalent)[h] All patients used PRN inhalers every time they would have used albuterol for symptom relief or to treat decreased in PEF, number of puffs was self-determined. All patients received prednisone x4d for asthma exacerbation	Beclomethasone 40 µg BID (MDI) with PRN use of placebo inhaler + albuterol 90µg (MDI) n=72	10.8 (3.5)	58	NR	NR	100.1 (10.8)	NR	NR

Abbreviations: AM=morning; BID=twice daily; d=day; DPI=dry powder inhaler; EPR=Expert Panel Review (Guidelines for Diagnosis and Management of Asthma); FEV_1=forced expiratory volume in one second; GP=general practitioner; ICS=inhaled corticosteroid; L=liter; LABA=long-acting β_2-agonist; m=month; MDI=metered dose inhaler; n=patient sample size; NR=not reported; PO=by mouth; PRN=pro re nata (i.e., as-needed); PEF=peak expiratory flow; QID=four times daily; RCT=randomized controlled trial; SABA=short-acting β_2-agonist; SD=standard deviation; w=weeks; y=years

[a]Concurrent therapies during the trial in the self-adjusted arm included inhaled anticholinergics (5.4%), methylxanthines (16.1%) and nedocromil (3.6%). Concurrent therapies during the trial in the traditional treatment arm included inhaled anticholinergics (3.6%), methylxanthines (18.6%) and nedocromil (3.4%)

[b]First and second set of values represent budesonide and beclomethasone, respectively

[c]LABA and theophylline use during the trial in the budesonide 100µg BID + additional use arm were 37.3% and 11.9%, respectively. LABA and theophylline use during the trial in the budesonide 100µg BID + placebo arm were 49.3% and 26.9%, respectively, and in the 400µg BID + placebo arm were 41.8% and 13.4%, respectively

[d]Data reported as mean (range)

[e]Theophylline use in the doubled dose and maintenance dose arms were 0% and 3.8%, respectively

[f]MinDoc programmed with alert asthma symptom score (three ordinal values above the mean baseline total symptom score on 2 consecutive days) and alerted the patient in the event of an asthma exacerbation. Patient reported exacerbation to study personnel and given instructions to take additional inhaler

[g]LABA use in the quadrupled dose and maintenance dose arms were 38% and 39%, respectively

[h]Inhaled corticosteroid and leukotriene receptor inhibitor/antagonist use in the previous year in the rescue arm was 72% and 20%, respectively. Previous year use of inhaled ICS and leukotriene receptor inhibitor/antagonist in the combined arm were 76% and 16%, respectively, and in the daily arm were 82% and 10%

Table C-6. Study and population characteristics for KQ1b, intermittent ICS vs. ICS controller

Study, Year, N, Acronym, Study design, Duration Risk of Bias	Study population	Intervention Comparisons	Age (y) [mean, (SD)]	Males (%)	Duration of asthma (y) [mean (SD)]	FEV1 (L) [mean (SD)]	FEV1 % predicted (L) [mean (SD)]	Rescue inhaler use (puffs/d) [mean (SD)]	ICS dose during study (µg/d) [mean (SD)]
Boushey, 2005[51] IMPACT n=149 RCT, 52w Low	18-65 years of age w/mild persistent asthma (self-treatment with β_2-agonist>2d per week, nighttime awakenings related to asthma >2d per month, or variability in the PEF of 20-30%). All patients self-adjusted according to action plan[a]- Green zone: Continue as usual, albuterol PRN Yellow zone: Start budesonide 800µg BID x10d Red zone: Start prednisone 0.5mg/kg PO x5d Extra red zone: albuterol, prednisone and go to ER or call 911	Placebo inhaler BID + placebo tablets BID n=76	32.0 (10.5)	43	19.5 (11.8)	3.2 (0.7)	87.8 (12.7)	NR	NR
		Budesonide 200µg BID (DPI)+ placebo tablets BID n=73	33.2 (9.5)	38	17.1 (11.0)	3.2 (0.8)	90.5 (12.6)	NR	NR
Papi, 2007[63] BEST-adult n=337 RCT, 6m Low	18-65 years old with mild persistent asthma according to EPR2 for at least 6m, adequately controlled at the end of run-in on beclomethasone 250µg BID. No written action plan, orally instructed to use PRN inhaler for symptom relief.	Placebo inhaler BID + Beclomethasone/ albuterol 250/100µg PRN n=122	36.8 (13.1)	41.0	NR	3.0 (0.8)	88.5 (11.3)	0.4 (0.7)	18,480 (25250) [b]
		Beclomethasone/ albuterol 250/100µg BID + albuterol 100µg PRN n=109	39.9 (14.4)	39.4	NR	2.9 (0.7)	87.2 (10.7)	0.5 (0.7)	77,070 (17550) [b]
		Beclomethasone 250µg BID + albuterol 100µg PRN n=106	37.9 (13.5)	42.5	NR	3.0 (0.7)	88.8 (11.1)	0.4 (0.7)	76,970 (17350) [b]

Study, Year, N, Acronym, Study design, Duration Risk of Bias	Study population	Intervention Comparisons	Age (y) [mean, (SD)]	Males (%)	Duration of asthma (y) [mean (SD)]	FEV1 (L) [mean (SD)]	FEV1 % predicted (L) [mean (SD)]	Rescue inhaler use (puffs/d) [mean (SD)]	ICS dose during study (µg/d) [mean (SD)]
Turpeinen, 2007[64] HELSINKI n=116 RCT, 18m Low	5-10 years old with symptoms such as wheezing, prolonged cough or SOB suggesting asthma for at least 1m. According to symptoms and lung function majority of children could be categorized as mild persistent asthma. All patients received terbutaline PRN and physician determined replacement of study medication with budesonide 400µg BID x2w during exacerbations.[c]	Budesonide 400µg BID x1m, 200µg BID x5m, placebo x12m n=58	6.7 (5-10)[d]	66	11.3 (2.0 to 76.4)[d,e]	1.32 (0.72 to 2.36)[d]	82 (52-107)[d]	0.55 (0-3.7)[d]	NR
		Budesonide 400µg BID x1m, 200µg BID x5m, 100µg BID x12m n=58	7.0 (5 to 10)[d]	59	12.8 (1.1 to 70.5)[d,e]	1.43 (0.89 to 2.15)[d]	87 (57-111)[d]	0.47 (0-4.0)[d]	NR
Martinez, 2011[60] TREXA n=143 RCT, 44w Low	6-18y of age w/history of mild persistent asthma during prior 2y, qualifying for interruption or discontinuation of controller therapy because illness was well controlled per EPR, asthma remained controlled during run-in on beclomethasone 40µg BID; either naïve to controller therapy with 1-2 exacerbations in prior year, treated in prior 8w on monotherapy other than ICS, or if illness was controlled for prior 8w on low-dose ICS monotherapy (≤160µg/d beclomethasone	Placebo inhaler BID with PRN use of beclomethasone 40µg (MDI) + albuterol 90µg (MDI) n=71	10.4 (2.8)	52	NR	NR	101.4 (12.1)	NR	NR

Study, Year, N, Acronym, Study design, Duration Risk of Bias	Study population	Intervention Comparisons	Age (y) [mean, (SD)]	Males (%)	Duration of asthma (y) [mean (SD)]	FEV1 (L) [mean (SD)]	FEV1 % predicted (L) [mean (SD)]	Rescue inhaler use (puffs/d) [mean (SD)]	ICS dose during study (µg/d) [mean (SD)]
	equivalent).[f] All patients used PRN inhalers every time they would have used albuterol for symptom relief or to treat decreased in PEF, number of puffs was self-determined. All patients received prednisone x4d for asthma exacerbation	Beclomethasone 40 µg BID (MDI) with PRN use of placebo inhaler + albuterol 90µg (MDI) n=72	10.8 (3.5)	58	NR	NR	100.1 (10.8)	NR	NR
Calhoun, 2012[52] BASALT n=227 RCT, 9m Low	≥18y and older with mild to moderate asthma, need for daily controller therapy based on receiving prescription in prior 12m or symptoms more than twice/w and not on controller, if on ICS ≤1000µg fluticasone or equivalent stable for at least 2w, completely controlled asthma during run-in on beclomethasone 80µg BID, based on asthma evaluation questionnaire and FEV>70% predicted. All patients received unrestricted albuterol (MDI). Investigators were allowed to add open-label budesonide 80µg BID x14d if needed.	Budesonide 40µg (MDI) used on a puff-per-puff basis every time the patient uses albuterol (MDI) n=113	36.0 (12.2)	26.5	21.3 (12.1)	2.90 (0.69)	85.6 (11.0)	0 (0-0.31)[g]	832 (NR)[h]
		Budesonide 80µg BID (MDI) adjusted by physician every 6w based on NHLBI guidelines n=114	34.2 (11.9)	36.8	20.4 (10.4)	3.03 (0.72)	87.7 (12.1)	0.04 (0-0.29)[g]	1610 (NR)[h]

Abbreviations: BID=twice daily; d=day; DPI=dry powder inhaler; EPR=Expert Panel Review (Guidelines for Diagnosis and Management of Asthma); ER=emergency room; FEV_1=forced expiratory volume in one second; ICS=inhaled corticosteroid; L=liter; LABA=long-acting β_2-agonist; m=months; MDI=metered dose inhaler; n=patient sample size; NHLBI=National Heart, Lung and Blood Institute; NR=not reported; PO=by mouth; PRN=pro re nata (i.e., as-needed); PEF=peak expiratory flow; QID=four times daily; RCT=randomized controlled trial; SD=standard deviation; SOB=shortness of breath; w=weeks; y=years

[a]Green zone: symptoms and albuterol use stable; Yellow zone: Awakening from asthma 3+ times in a 2-week period or on 2 consecutive nights, or using albuterol for relief of symptoms 4+ times/day for 2 or more consecutive days, or albuterol has been relieving symptoms for less than 4h each treatment over a 12-hour period, or using albuterol for relief of symptoms daily for 7 days, and this use exceeds 2 times the weekly use of albuterol in the baseline period, or exercise induces unusual breathlessness; Red zone: For the

previous 24 hours, daily life activities cause SOB or breathlessness is present at rest, or albuterol has been relieving symptoms for <2h after each treatment over an 8h period; Extra red zone: Severe SOB at rest, or difficulty talking because of SOB, or albuterol has been relieving symptoms for less than 1h after each treatment over a 4h period, or does not relieve symptoms after 2 treatments repeated within a single hour
[b]Cumulative doses of beclomethasone inhaled during the entire 6-month treatment period
[c]Exacerbations defined as an increase in symptoms not controlled by 6 doses/24h of terbutaline that caused the parent to contact the clinic
[d]Data reported as mean (range)
[e]Data reported in months
[f]Inhaled ICS and leukotriene receptor inhibitor/antagonist use in the previous year in the rescue arm was 72% and 20%, respectively. Previous year use of inhaled corticosteroids and leukotriene receptor inhibitor/antagonist in the combined arm were 76% and 16%, respectively, and in the daily arm were 82% and 10%
[g]Data reported as median (interquartile range)
[h]Represents mean monthly dose

Table C-7. Study level outcomes for KQ1b, intermittent ICS and ICS controller vs. ICS controller

Study, Year, n, Study design, Duration	Population[a]	Exacerbations[b]	Mortality	Asthma control	Quality of life	Healthcare utilization
Lahdensuo, 1996[67] n=115 RCT, 12m	***Age**: 12y+* ***Severity/control**:* Mild to moderately severe asthma ***Intermittent ICS:*** Doubling regular dose	***Relative measures*** Requiring oral corticosteroid: RR 0.51 (0.29 to 0.88) Exacerbation (undefined): RR 0.48 (0.33 to 0.71) Asthma-related hospitalization: RR 0.70 (0.12 to 4.05) Unscheduled outpatient visit: RR 0.53 (0.29 to 0.96) ***Count data*** Number of hospitalizations: 2 vs. 3	NR	***Composite measures***: NR ***Spirometry:*** NR	NR	NR
Foresi, 2000[56] n=134 RCT, 6m	***Age**: 12y+* ***Severity/control**:* Moderate persistent asthma/ symptomatic ***Intermittent ICS:*** Quadrupling regular dose	***Relative measures*** Fall in PEF <70% from baseline: RR 1.09 (0.52 to 2.30) ***Count data*** Total number of oral corticosteroid days: 37 vs. 47	NR	***Composite measures***: NR ***Spirometry:*** NR	NR	NR

Study, Year, n, Study design, Duration	Population[a]	Exacerbations[b]	Mortality	Asthma control	Quality of life	Healthcare utilization
Colland, 2004[54] n=29 RCT, 12m	***Age****:* 5-11y ***Severity/control****:* Moderate persistent asthma/ symptomatic ***Intermittent ICS:*** Doubling regular dose	***Relative measures*** Requiring hospitalization: Peto's OR 0.14 (0.003 to 7.31) ***Count data*** NR	NR	***Composite measures***: NR ***Spirometry:*** FEV1 % predicted: MD 5 (-6.01 to 16.01)	NR	NR
Fitzgerald, 2004[55] n=98 RCT, 6m	***Age****:* 12y+ ***Severity/control****:* Persistent asthma ***Intermittent ICS:*** Doubling regular dose	***Relative measures*** Requiring oral corticosteroid (of those who initiated study inhaler) RR: 0.85 (0.39 to 1.83) Requiring oral corticosteroid, unscheduled doctors visit, ER, or unstable asthma: RR 1.03 (0.63 to 1.65) Unstable asthma[c]: RR 0.57 (0.23 to 1.38) ***Count data*** NR	NR	***Composite measures***: NR ***Spirometry:*** NR	NR	NR
Harrison, 2004[59] n=390 RCT, 12m	***Age****:* 12y+ ***Severity/control****:* Persistent asthma/ stable during run-in ***Intermittent ICS:*** Doubling regular dose	***Relative measures*** Requiring oral corticosteroid (full population): RR 0.95 (0.55 to 1.63) Requiring oral corticosteroid (of those who initiated study inhaler) RR: 0.76 (0.44 to 1.32) ***Count data*** NR	NR	***Composite measures***: NR ***Spirometry:*** NR	NR	Asthma-related general practitioner visits: RR 1.14 (0.71 to 1.83)

Study, Year, n, Study design, Duration	Population[a]	Exacerbations[b]	Mortality	Asthma control	Quality of life	Healthcare utilization
Oborne, 2009[66] n=403 RCT, 12m	***Age****:* 12y+ ***Severity/control****:* Persistent asthma ***Intermittent ICS:*** Quadrupling regular dose	***Relative measures*** Requiring oral corticosteroid (full population): RR 0.64 (0.37 to 1.11) Requiring oral corticosteroid (of those who initiated study inhaler) RR: 0.43 (0.24 to 0.78) 2 to 3 exacerbations requiring oral corticosteroid (full population): RR 0.63 (0.15 to 2.59) 2 to 3 exacerbations requiring oral corticosteroid (of those who initiated study inhaler): RR 0.34 (0.07 to 1.76) ***Count data*** NR	NR	***Composite measures***: NR ***Spirometry:*** NR	NR	NR
Martinez, 2011[60] n=143 RCT, 12m	***Age****:* Mixed, (5-11y and 12y+) ***Severity/control****:* Mild persistent asthma/well controlled ***Intermittent ICS:*** ICS used with albuterol	***Relative measures*** Requiring oral corticosteroid: RR 1.12 (0.67 to 1.86) Treatment failure[d]: RR 2.03 (0.39 to 10.72)	NR	***Composite measures***: NR ***Spirometry:*** FEV1 % predicted: MD 0.57 (-2.24 to 3.38)	PAQLQ score: MD -0.003 (-0.25 to 0.25)	Albuterol puffs/day: MD 0.04 (-0.33 to 0.40)

Abbreviations: d=days; ER=emergency room; EPR-3=Expert Panel Review-3; FEV1=forced expiratory volume in one second; HR=hazard ratio; ICS=inhaled corticosteroid; IRR= incident rate ratio; m=months; MD=mean difference; n=patient sample size; NR=not reported; OR=odds ratio; PAQLQ=Pediatric Asthma Quality of Life Questionnaire; RCT=randomized controlled trial; RR=relative risk; y=year

[a]Categorized using study inclusion criteria and the age categories used in EPR-3 of 0-4y, 5-11y and 12y+. Severity is as reported per the study. Control was usually not specified and rather details about patients being symptomatic or not at entry were given and reported here. Intermittent ICS indicates how the usual ICS dose was altered in the intervention arm

[b]Relative measures are presented first and include, when reported by the study RR, HR for time to the event, and IRR for count data allowing multiple events over the period of follow-up. Count data is presented, when reported by the study, for number of hospitalizations, hospital days, and ER visits in association with exacerbations.

[c]Defined as the absence of stability, where stability is defined as morning peak expiratory flow 90% or more of mean baseline value on either of the two previous days, <4 inhalations of inhaled corticosteroid per day over the past 2 days, no nocturnal awakenings in the prior 2 nights and a total symptom score not exceeding mean baseline value more than 2 ordinal values over the previous 2 days
[d]Defined as any of following: (1) Hospitalization due to asthma; (2) Hypoxic seizure due to asthma; (3) Intubation due to asthma; (4) Requirement for a second burst of prednisone within any 6 months period; (5) Significant adverse event related to the use of a study medication. The only criterion for assignment of treatment failure during the trial was the requirement for a second burst of prednisone within any six-month period

Table C-8. Study level outcomes for KQ1b, intermittent ICS vs. ICS controller

Study, Year, n, Study design, Duration	Population[a]	Exacerbations[b]	Mortality	Asthma Control	Quality of Life	Healthcare Utilization
Boushey, 2005[51] n=149 RCT, 52w	***Age****:* 12y+ ***Severity/control****:* Mild persistent ***Intermittent ICS:*** Yellow zone budesonide 800µg BIDx10d	Requiring oral corticosteroid: RR 0.70 (0.30 to 1.64) Requiring hospitalization: No events occurred	NR	***Composite measures***: ACQ-7 score: MD 0.1 (-0.12 to 0.32) ***Spirometry:*** FEV1 pre-albuterol (% change): MD -3.3 (-6.51 to -0.09) FEV1 post-albuterol (% change): MD -0.7 (-2.1 to 0.7)	AQLQ(S) score: MD -0.2 (-0.48 to 0.08)	NR
Papi, 2007[63] n=337 RCT, 6m	***Age****:* 12y+ ***Severity/control****:* Mild persistent asthma/controlled ***Intermittent ICS:*** Beclomethasone/ albuterol 250/100µg PRN symptom relief	Mild[c] or severe[d] exacerbation: RR 0.87 (0.29 to 2.61) Severe exacerbation: Peto's OR 0.11 (0.01 to 1.11)	NR	***Composite measures***: NR ***Spirometry:*** FEV1, trough MD 0.09 (-0.01 to 0.18) FEV1 % predicted: MD 2.04 (-0.71 to 4.79) FVC, trough MD 0.07 (-0.03 to 0.18) FVC % predicted MD 1.72 (-1.04 to 4.48)	NR	Rescue albuterol use, inhalations/d MD 0.07 (-0.13 to 0.26)

Study, Year, n, Study design, Duration	Population[a]	Exacerbations[b]	Mortality	Asthma Control	Quality of Life	Healthcare Utilization
Turpeinen, 2007[64] n=116 RCT, 18m	***Age**:* 5-11y ***Severity/control**:* Majority mild persistent/ symptomatic ***Intermittent ICS:*** Budesonide 400mg BIDx14d upon symptoms determined by pediatrician to be exacerbation	Exacerbation rate[e]: MD -0.72 (-1.27 to -0.17)	NR	NR	NR	NR
Martinez, 2011[60] n=143 RCT, 44w	***Age**:* Mixed (5-11, 12y+) ***Severity/control**:* Mild persistent/ well controlled ***Intermittent ICS:*** Beclomethasone 40µg+albuterol 90µg PRN symptom relief prompting albuterol use or to treat decrease PEF	Requiring oral corticosteroid: RR 1.27 (0.78 to 2.07) Treatment failure[f]: RR 3.04 (0.64 to 14.57)	NR	***Composite measures***: NR ***Spirometry:*** FEV1 % predicted: MD -1.30 (-4.24 to 1.64)	PAQLQ score: MD 0.04 (-0.25 to 0.33)	Rescue albuterol use, inhalations/d: MD 0.003 (-0.24 to 0.25)

Study, Year, n, Study design, Duration	Population[a]	Exacerbations[b]	Mortality	Asthma Control	Quality of Life	Healthcare Utilization
Calhoun, 2012[52,g] n=227 RCT, 9m	***Age***: 12y+ ***Severity/control***: Mild to moderate persistent/ well or partially well controlled ***Intermittent ICS:*** Beclomethasone 80µg PRN symptom relief prompting albuterol use	Exacerbation[h]: IRR 2.0 (0.87 to 4.61) Urgent care visit for asthma: RR 0.25 (0.05 to 1.16) Treatment failure[i]: HR 1.6 (0.86 to 2.98) IRR 1.7 (0.96 to 3.00)	NR	***Composite measures***: ACQ-5 MD -0.01 (-0.17 to 0.15) ***Spirometry:*** FEV1 trough pre albuterol: MD 0.01 (-0.13 to 0.15) FEV1 trough post albuterol: MD -0.01 (-0.06 to 0.04) FEV1 % predicted pre albuterol: MD 0.01 (-1.89 to 1.91) FEV1 % predicted post albuterol: MD -0.48 (-1.97 to 1.01)	AQLQ(S) score: MD 0.01 (-0.19 to 0.21)	Rescue albuterol use, inhalations/d: MD -0.04 (-0.11 to 0.03)

Abbreviations: ACQ=Asthma Control Questionnaire; AQLQ=Asthma Quality of Life Questionnaire; AQLQ(S)=Standardized Asthma Quality of Life Questionnaire; BID=twice daily; d=days; ER=emergency room; FEV1=forced expiratory volume in one second; FVC=forced vital capacity; HR=hazard ratio; ICS=inhaled corticosteroid; IRR= incident rate ratio; m=months; MD=mean difference; mg=milligrams; n=patient sample size; NR=not reported; OR=odds ratio; PAQLQ=Pediatric Asthma Quality of Life Questionnaire; PEF=peak expiratory flow; PRN=pro re nata (i.e., as-needed); RCT=randomized controlled trial; RR=relative risk; µg=micrograms; w=weeks; y=year

[a]Age is categorized using study inclusion criteria and the age categories used in Expert Panel Review-3 (EPR-3) of 0-4y, 5-11y and 12y+. Severity is as reported per the study. Control was usually not specified and rather details about patients being symptomatic or not at entry were given and reported here. Intermittent ICS indicates how the usual ICS dose was altered in the intervention arm

[b]Relative measures are presented first and include, when reported by the study, relative risk (RR), hazard ratio (HR) for time to the event, and incident rate ratio (IRR) for count data allowing multiple events over the period of follow-up. Count data is presented, when reported by the study, for number of hospitalizations, hospital days, and ER visits in association with exacerbations

[c]Defined as awakening at night owing to asthma or as a decrease in the morning peak expiratory flow rate to more than 20% below the baseline value, the use of more than three additional puffs per day of rescue medication (either albuterol or beclomethasone and albuterol) as compared with during the baseline for 2 or more consecutive days, or both. Single, isolated days on which mild exacerbation occurred were not counted

[d]Defined as a decrease in the morning peak expiratory flow rate to more than 30% below the baseline value on 2 consecutive days or more than eight puffs per day of rescue medication for 3 consecutive days or the need for treatment with oral corticosteroids, as judged by the investigator

[e]Defined as the mean number of exacerbations divided by the number of patients in the group. An asthma exacerbation was defined as an increase in symptoms that were not controlled with six doses of rescue terbutaline per 24 h that caused the parent to contact the clinic. At clinic pediatrician determined if exacerbation occurred and prescribed budesonide inhaler

[f]Defined as any of following: (1) Hospitalization due to asthma; (2) Hypoxic seizure due to asthma; (3) Intubation due to asthma; (4) Requirement for a second burst of prednisone

within any 6 months period; (5) Significant adverse event related to the use of a study medication. The only criterion for assignment of treatment failure during the trial was the requirement for a second burst of prednisone within any six-month period

[g]Study reported 97.5% confidence intervals which were converted to 95% confidence intervals

[h]Defined as unscheduled medical contact for increased asthma symptoms that results in use of oral corticosteroids, increased inhaled corticosteroids, or additional medications for asthma

[i]Defined as any of the following: (1) Asthma exacerbation; (2) An at-home measurement of prebronchodilator AM PEF <65% of baseline on 2 consecutive mornings, postbronchodilator PEF <80% of baseline despite 60 minutes of rescue treatment, or an increase in albuterol use of more than 8 puffs per 24 hours over baseline use for 48 hours or more than 16 puffs per 24 hours for more than 48 hours; (3) In-clinic measurements of prebronchodilator FEV1 on 2 consecutive sets of spirometric determinations measured 24 to 72 hours apart that are less than 80% of baseline, physician judgement for patient safety, patient dissatisfaction with asthma control achieved by study regimen or requirement for open-label ICS or another new asthma medication without the addition of systemic corticosteroids

Table C-9. Study and population characteristics for KQ1c, ICS and LABA controller and quick relief vs. ICS controller (same dose)

Study, Year, n, Acronym, Study design, Duration, Risk of bias	Study population	Intervention Comparisons	Age (y) [mean (SD)]	Males (%)	Duration of asthma (y) [mean (SD)]	FEV1 (L) [mean (SD)]	FEV1 % predict-ed (L) [mean (SD)]	Rescue inhaler use (puffs/d) [mean (SD)]	ICS dose during study (µg/d) [mean (SD)]
Scicchitano, 2004[96] n=1890 RCT, 12m Low	12-80 years of age with moderate to severe (83% with severe according to GINA guidelines), symptomatic asthma on ICS 400-1600µg/d, FEV1 50-90% predicted, history of at least 1 exacerbation in prior year ICS dose at entry: 744-748µg/d Taking LABA at entry: 35%	Budesonide/formoterol 320/9µg in the evening + 160/4.5µg PRN (DPI) n=947	43 (12 to 79)[a]	41	12 (1 to 65)[a]	NR	70 (46 to 102)[a]	1.9 (0 to 15.6)[a]	466 (NR)
		Budesonide 160µg BID (DPI) + terbutaline PRN (DPI) n=943	43 (11 to 80)[a]	43	12 (1 to 71)[a]	NR	70 (37 to 95)[a]	2.0 (0 to 9.2)[a]	640 (NR)
Rabe, 2006[94] n=697 RCT, 6m Low	12-80 years of age with mild to moderate asthma on ICS 200-500µg/d, FEV1 60-100% predicted, symptomatic with ≥7 SABA inhalations during last 10 run-in days ICS dose at entry: 343-353µg/d LABA at entry: 10-13%	Budesonide/formoterol 160/9µg in the evening + 80/4.5mcg PRN (DPI) n=355	38 (12 to 79)[a]	41	10 (1 to 70)[b]	NR	75 (51 to 123)[a]	NR	240 (NR)
		Budesonide 160µg in the evening (DPI) + terbutaline PRN (DPI) n=342	38 (11 to 78)[a]	36	10 (1 to 61)[b]	NR	75 (52 to 109)[a]	NR	320 (NR)
Sovani, 2008[99] n=71 RCT, 6m High	18-70 years of age with asthma on ICS 400-1000µg/d of beclomethasone or equivalent, with evidence of poor asthma control (in prior year ≥2 courses of prednisolone or 10 SABA canisters, and taking ≥4 SABA puffs in ≥4d/week in prior month ICS dose at entry:565-611µg/d	Budesonide/formoterol 160/4.5µg BID + PRN (DPI) n=36	40.3 (12.8)	47.2	23.1 (12)	2.9 (0.84)	88.1 (19.3)	NR	448 (NR)
		Budesonide 160µg BID (DPI) + SABA PRN n=35	40.3 (12.3)	42.9	22.6 (14)	2.65 (0.82)	82.3 (18.7)	NR	252 (NR)

Abbreviations: BID=twice daily; d=day; DPI=dry powder inhaler; FEV_1=forced expiratory volume in one second; GINA= Global Initiative for Asthma; ICS=inhaled corticosteroid; L=liter; LABA=long-acting β_2-agonist; m=months; n=patient sample size; NR=not reported; PRN=pro re nata (i.e., as-needed); RCT=randomized controlled trial; SABA=short-acting β_2-agonist; SD=standard deviation; µg=microgram; w=week; y=year

[a]Data reported as mean (range)

[b]Data reported as median (range)

Table C-10. Study and population characteristics for KQ1c, ICS and LABA controller and quick relief vs. ICS controller (higher dose)

Study, Year, n, Acronym, Study design, Duration, Risk of bias	Study population	Intervention Comparisons	Age (y) [mean (SD)]	Males (%)	Duration of asthma (y) [mean (SD)]	FEV1 (L) [mean (SD)]	FEV1 % predict-ed (L) [mean (SD)]	Rescue inhaler use (puffs/d) [mean (SD)]	ICS dose during study (μg/d) [mean (SD)]
O'Byrne, 2005[83] n=1851 STAY RCT, 12m Low	4-80 years of age with asthma treated with 400-1000μg/d of ICS (200-500μg/d if 4-11 years old), history of 1 or more exacerbation in prior year, FEV1 60-100% predicted, 12+ (8+ if 4-11y) SABA inhalations during last 10d of run-in. ICS dose at entry: 598-620μg/d Taking LABA at entry: 27-29%	Budesonide/formoterol 80/4.5μg BID + PRN (DPI) n=925	35 (4 to 77)[a]	45.5	9 (0 to 63)[b]	2.13 (0.65 to 4.28)[a]	73 (43 to 108)[a]	1.74 (0 to 8.0)[a,c]	235.5 (NR)[d]
		Budesonide 320μg BID (DPI) + terbutaline 0.4mg PRN (DPI) n=926	36 (4 to 79)[a]	44.9	9 (0 to 96)[b]	2.14 (0.64 to 4.02)[a]	73 (49 to 100)[a]	1.69 (0 to 7)[a,c]	641.5 (NR)[d]
	4-11 year old subgroup with asthma treated with 200-500μg/d of ICS, history of 1 or more exacerbation in prior year, FEV1 60-100% predicted, 8+ SABA inhalations during last 10d of run-in. ICS dose at entry:319-321μg/d	Budesonide/formoterol 80/4.5μg QD + PRN (DPI) n=118	8 (4 to 11)[a]	72.0	3 (1 to 10)[b]	1.6 (0.9 to 2.7)[a]	76 (57 to 108)[a]	1.7 (0.7 to 5.9)[a]	125.6 (NR)
		Budesonide 320μg QD (DPI) + terbutaline 0.4mg PRN (DPI) n=106	8 (4 to 11)[a]	66.4	3 (0 to 10)[b]	1.6 (0.7 to 3.1)[a]	76 (60 to 100)[a]	1.6 (0.1 to 4.0)[a]	320.1 (NR)

Abbreviations: BID=twice daily; d=day; DPI=dry powder inhaler; FEV1=forced expiratory volume in one second; ICS=inhaled corticosteroid; L=liter; LABA=long-acting β_2-agonist; m=months; n=patient sample size; NR=not reported; PRN=pro re nata (i.e., as-needed); QD=daily; RCT=randomized controlled trial; SABA=short-acting β_2-agonist; SD=standard deviation; μg=microgram; y=years

[a]Data reported as mean (range)

[b]Data reported as median (range)

[c]Represents inhalations/d (vs. night)

[d]Represents patients 12y+

Table C-11. Study and population characteristics for KQ1c, ICS and LABA controller and quick relief vs. ICS and LABA controller (same dose)

Study, Year, n, Acronym, Study design, Duration, Risk of bias	Study population	Intervention Comparisons	Age (y) [mean (SD)]	Males (%)	Duration of asthma (y) [mean (SD)]	FEV1 (L) [mean (SD)]	FEV1 % predicted (L) [mean (SD)]	Rescue inhaler use (puffs/d) [mean (SD)]	ICS dose during study (µg/d) [mean (SD)]
O'Byrne, 2005[75,83], STAY n=1834 RCT, 12m Low	4-80 years of age with asthma treated with 400-1000µg/d of ICS (200-500µg/d if 4-11 years old), history of 1 or more exacerbation in prior year, FEV1 60-100% predicted, 12+ (8+ if 4-11y) SABA inhalations during last 10d of run-in ICS dose at entry: 598-620µg/d Taking LABA at entry: 27-29%	Budesonide/formoterol 80/4.5µg BID + PRN (DPI) n=925	35 (4 to 77)[a]	45.5	9 (0 to 63)[b]	2.13 (0.65 to 4.28)[a]	73 (43 to 108)[a]	1.74 (0 to 8.0)[a,c]	235.5 (NR)[d]
		Budesonide/formoterol 80/4.5µg BID (DPI) + terbutaline 0.4mg PRN (DPI) n=909	36 (4 to 79)[a]	43.3	9 (0 to 65)[b]	2.10 (0.62 to 4.50)[a]	73 (46 to 108)[a]	1.69 (0 to 9.4)[a,c]	165.5 (NR)[d]
	4-11 year old subgroup with asthma treated with 200-500µg/d of ICS, history of 1 or more exacerbation in prior year, FEV1 60-100% predicted, 8+ SABA inhalations during last 10d of run-in ICS dose at entry: 302-319µg/d	Budesonide/formoterol 80/4.5µg QD + PRN (DPI) n=118	8 (4 to 11)[a]	72.0	3 (1 to 10)[b]	1.6 (0.9 to 2.7)[a]	76 (57 to 108)[a]	1.7 (0.7 to 5.9)[a]	125.6 (NR)
		Budesonide/formoterol 80/4.5µg QD (DPI) + terbutaline 0.4mg PRN (DPI) n=117	8 (4 to 11)[a]	70.1	3 (0 to 11)[b]	1.5 (0.7 to 2.9)[a]	76 (54 to 99)[a]	1.6 (0.3 to 5.6)[a]	81.8 (NR)
Vogelmeier, 2005[104] COSMOS n=2143 RCT, 12m Medium	≥12 years of age with asthma, taking ≥500µg/d of budesonide or fluticasone (or ≥1000µg/d for other ICS), FEV1 40-90% predicted, at least 1 severe exacerbation in prior year, rescue medication use ≥4 of 7 days in run-in	Budesonide/formoterol 320/9µg BID + 160/4.5µg/d PRN (DPI) n=1067	45 (12 to 80)[a]	42.3	13 (1to 75)[a]	NR	73 (39 to 115)[a]	2.6 (0.2 to 10.7)[a]	1019 (NR)[e]

Study, Year, n, Acronym, Study design, Duration, Risk of bias	Study population	Intervention Comparisons	Age (y) [mean (SD)]	Males (%)	Duration of asthma (y) [mean (SD)]	FEV1 (L) [mean (SD)]	FEV1 % predicted (L) [mean (SD)]	Rescue inhaler use (puffs/d) [mean (SD)]	ICS dose during study (µg/d) [mean (SD)]
	ICS dose at entry: 881-888µg/d LABA use at entry: 38% Doses of randomized therapies could be titrated and additional controllers added during trial if needed[f]	Fluticasone/salmeterol 250/50µg BID (DPI) + salbutamol PRN (DPI/MDI) n=1076	45 (12 to 84)[a]	39.9	12 (0 to 74)[a]	NR	73 (28 to 100)[a]	2.7 (0.3 to 33.7)[a]	1166 (NR)[e]
Rabe, 2006[93] n=3394 RCT, 12m Low	≥12 years of age with asthma on ICS, FEV1 50-100% predicted, at least 1 severe asthma exacerbation in prior year, symptomatic during run-in ICs dose at entry: 751-758µg/d LABA use at entry: 59%	Budesonide/formoterol 160/4.5µg BID + PRN (DPI) n=1113	42 (12 to 89)[a]	39	9 (0 to 64)[b]	2.21 (0.61 to 4.68)[a]	72 (30 to 110)[a]	1.8 (0 to 8.9)[a]	NR
		Budesonide/formoterol 160/4.5µg BID (DPI) + formoterol 4.5µg (DPI) PRN n=1140	42 (12 to 81)[a]	40	10 (1 to 77)[b]	2.20 (0.74 to 4.58)[a]	72 (38 to 115)[a]	1.9 (0 to 9.1)[a]	NR
		Budesonide/formoterol 160/4.5µg BID (DPI) + terbutaline 0.4mg n=1141	43 (12 to 83)[a]	39	10 (1 to 69)[b]	2.16 (0.68 to 4.58)[a]	72 (39 to 100)[a]	1.9 (0.3 to 9.7)[a]	NR
Atienza, 2013[70] n=2091 RCT, 12m Low	≥16 years of age with persistent asthma, FEV1≥50% predicted, not adequately controlled despite maintenance ICS, at least 1 exacerbation in prior year, SABA use ≥5 of last 7 run-in days ICs dose at entry:659-662µg/d LABA use at entry: 61-62%	Budesonide/formoterol 160/4.5µg BID + PRN (DPI) n=1049	45.7 (14.5)	31.2	12 (1 to 67)[b]	1.93 (0.64)	70.18 (14.65)	2.41 (1.55)	514 (NR)
		Budesonide/formoterol 160/4.5µg BID (DPI) + terbutaline 0.4mg PRN (DPI) n=1042	45.6 (14.5)	33.6	12 (1 to 74)[b]	1.93 (0.65)	69.64 (13.75)	2.43 (1.58)	320 (NR)

Study, Year, n, Acronym, Study design, Duration, Risk of bias	Study population	Intervention Comparisons	Age (y) [mean (SD)]	Males (%)	Duration of asthma (y) [mean (SD)]	FEV1 (L) [mean (SD)]	FEV1 % predicted (L) [mean (SD)]	Rescue inhaler use (puffs/d) [mean (SD)]	ICS dose during study (µg/d) [mean (SD)]
Papi, 2013[84] n=1701 RCT, 48w Low	≥18 years of age with asthma not fully controlled on ICS alone (≥1000µg/d beclomethasone equivalents) or ICS (≥500µg/d beclomethasone equivalents) +LABA, FEV1 ≥60% predicted, at least 1 severe exacerbation in prior year ICS dose at entry: 1128-1139 beclomethasone equivalents LABA use at entry: 79-83%	Beclomethasone/ formoterol 84.6/5µg BID + PRN (MDI) n=852	49 (18 to 83)[a]	39	9 (0.5 to 62.0)[g]	2.21 (0.88 to 5.04)[a]	74 (29 to 127)	0.98 (0.00 to 8.71)	701 (293)[e]
		Beclomethasone/ formoterol 84.6/5µg BID (MDI) + salbutamol 100µg PRN (MDI) n=849	47 (18 to 77)[a]	38	9 (0.5 to 61.0)[g]	2.27 (1.00-4.74)[a]	75 (50 to 127)	0.97 (0.00 to 9.43)	489 (48)[e]
Patel, 2013[86] SMART n=303 RCT, 24w Medium	16-65 years of age with asthma on ICS, at least 1 exacerbation requiring steroids in prior year ICS dose at entry: 804-812µg/d LABA use at entry: 61-68%	Budesonide/formoterol 320/9µg BID + PRN (MDI) n=151	41.3 (13.7)	32	26.7 (14.5)	2.62 (0.91)[h]	81.6 (18.9)[h]	NR	943.5 (1502.5)
		Budesonide/formoterol 320/9µg BID (MDI) + salbutamol 100-200µg PRN n=152	42.6 (14.5)	30	26.2 (14.6)	2.50 (0.78)[h]	80.4 (20.5)[h]	NR	684.3 (390.5)
Hozawa, 2014[78] n=30 RCT, 8w Medium	≥20 years of age with asthma not well controlled (ACQ>0.75) on medium dose ICS (budesonide 800µg/d, fluticasone or mometasone 400µg/d) without another controller, SABA use 2-6 times/w	Budesonide/formoterol 320/9µg BID + 160/4.5µg PRN (DPI) n=15	41.9 (8.7)	33.3	6.9 (3.6)	NR	NR	NR	NR
		Fluticasone/salmeterol 250/50µg BID (DPI) + procaterol 20µg PRN n=15	41.3 (9.9)	33.3	6.7 (3.1)	NR	NR	NR	NR

Study, Year, n, Acronym, Study design, Duration, Risk of bias	Study population	Intervention Comparisons	Age (y) [mean (SD)]	Males (%)	Duration of asthma (y) [mean (SD)]	FEV1 (L) [mean (SD)]	FEV1 % predicted (L) [mean (SD)]	Rescue inhaler use (puffs/d) [mean (SD)]	ICS dose during study (µg/d) [mean (SD)]
Takeyma, 2014[101] n=63 RCT, 1y Unclear	16-80 years of age with moderate to severe persistent asthma, on ICS (budesonide 320-640µg/d or fluticasone 200-500µg/d) +LABA, at least 1 exacerbation in prior year, ACT score<20, reliever use ≥5 times per week, FEV1 60-100% predicted ICS dose at entry: 574-610µg/d	Budesonide/formoterol 320/9µg BID + 160/4.5µg PRN n=32	41 (NR)	40.6	NR	1.86 (0.33)	68.3 (8.7)	NR	NR
		Budesonide/formoterol 320/9µg BID + salbutamol 100µg PRN n=31	39 (NR)	32.3	NR	1.89 (0.40)	70.4 (10.2)	NR	NR
Stallberg, 2008[100] SHARE n=1343 RCT, 12m Medium	≥12 years of age with persistent asthma on free combination ICS+LABA or symptomatic despite ICS alone, on ICS ≥400µg/d ICS dose at entry: 636-650µg/d LABA use at entry: 51-52% Randomized therapy stratified by baseline ICS dose[i]	Budesonide/formoterol 160/9µg or 320/9µg QD + PRN **OR** 80/4.5µg or 160/4.5µg BID + PRN n=887	43 (NR)	40	NR	NR	NR	NR	291 (NR)
		Budesonide/formoterol 160/9µg or 320/9µg BID + terbutaline PRN n=456	45 (NR)	44	NR	NR	NR	NR	368 (NR)

Abbreviations: ACQ=Asthma Control Questionnaire; ACT=Asthma Control Test; BID=twice daily; CI=confidence interval; d=day; DPI=dry powder inhaler; FEV1=forced expiratory volume in one second; ICS=inhaled corticosteroid; L=liter; LABA=long-acting β_2-agonist; m=month; MDI=metered dose inhaler; n=patient sample size; NR=not reported; PRN=pro re nata (i.e., as-needed); QD=daily; RCT=randomized controlled trial; SABA=short-acting β_2-agonist; SD=standard deviation; µg=microgram; w=week; y=year

[a]Data reported as mean (range)

[b]Data reported as median (range)

[c]Represents inhalations/d (vs. night)

[d]Represents patients 12y+

[e]Beclomethasone dipropionate equivalent dose in µg

[f]In the control group (fluticasone/salmeterol BID + salbutamol PRN), 27% and 14% of patients completed the study on the maximum 1000/100µg/d dose and lowest dose of fluticasone/salmeterol, respectively

[g]Data reported as median (95% CI)

[h]Represents values on treatment

[i]Patients previously treated with ICS 400-500µg/d received budesonide/formoterol 80/4.5µg dose and those previously treated with ICS >500µg/d received budesonide/formoterol 160/4.5µg dose

Table C-12. Study and population characteristics for KQ1c, ICS and LABA controller and quick relief vs. ICS and LABA controller (higher dose)

Study, Year, N, Acronym, Study design, Duration, Risk of bias	Study population	Intervention Comparisons	Age (y) [mean (SD)]	Males (%)	Duration of asthma (y) [mean (SD)]	FEV1 (L) [mean (SD)]	FEV1 % predicted (L) [mean (SD)]	Rescue inhaler use (puffs/d) [mean (SD)]	ICS dose during study (µg/d) [mean (SD)]
Bousquet, 2007[76] AHEAD n=2309 RCT, 6m Low	≥12 years of age with persistent asthma on ICS alone (800-1600µg/d) or ICS (400-1000µg/d) +LABA, symptomatic with use of SABA during run-in ≥5 of 7 days, FEV1≥50% predicted ICs dose at entry: 705-720µg/d LABA use at entry: 54-56%	Budesonide/formoterol 320/9µg BID + PRN (DPI) n=1154	40 (12 to 80)[a]	38	14 (1 to 67)[b]	2.08 (0.60 to 4.65)[a]	70.2 (45 to 114)[a]	NR	792 (NR), 1238 (NR)[c]
		Fluticasone/salmeterol 500/50µg BID (DPI) + terbutaline 0.4mg PRN (DPI) n=1155	39 (12 to 80)[a]	38	13 (1 to 77)[b]	2.10 (0.72 to 4.89)[a]	71.0 (45 to 222)[a]	NR	1000 (NR), 2000 (NR)[c]
Kuna, 2007[81] COMPASS n=3335 RCT, 6m Low	≥12 years of age with asthma on ICS ≥500µg/d fluticasone or budesonide (or ≥1000µg/d of other ICS), FEV1 ≥50% predicted, at least 1 exacerbation in prior year, SABA used ≥5 of last 7 run-in days ICS dose at entry: 740-750µg/d LABA use at entry:46-47%	Budesonide/formoterol 160/4.5µg BID + PRN (DPI) n=1107	38 (17)	43	NR	NR	72 (14)	NR	483 (NR), 755 (NR)[c]
		Budesonide/formoterol 320/9µg BID + terbutaline PRN (DPI) n=1105	38 (17)	41	NR	NR	73 (14)	NR	640 (NR), 1000 (NR)[c]
		Fluticasone/salmeterol 250/50 µg BID (MDI) + terbutaline PRN (DPI) n=1123	38 (17)	43	NR	NR	73 (14)	NR	500 (NR), 1000 (NR)[c]
Pavord, 2009[89] n=127 RCT, 1yr Low	18-65 years of age with asthma on ICS alone 800-1600µg/d or ICS 400-1000µg/d +LABA, FEV1≥60% predicted. SABA or symptoms ≥4 of last 7 run-in days with mean morning PEF 50-85%	Budesonide/formoterol 160/4.5µg BID + PRN (DPI) n=64	39 (19 to 63)[a]	55	20 (1 to 62)[b]	2.9 (1.2 to 4.7)[a]	81.4 (58 to 121)[a]	1.5 (0-6.0)[a]	NR

Study, Year, N, Acronym, Study design, Duration, Risk of bias	Study population	Intervention Comparisons	Age (y) [mean (SD)]	Males (%)	Duration of asthma (y) [mean (SD)]	FEV1 (L) [mean (SD)]	FEV1 % predicted (L) [mean (SD)]	Rescue inhaler use (puffs/d) [mean (SD)]	ICS dose during study (µg/d) [mean (SD)]
	ICS dose at entry: 741-867µg/d LABA use at entry: 81-84%	Budesonide/formoterol 320/9µg BID (MDI) + budesonide 400µg BID (DPI) + terbutaline 0.5mg PRN (DPI) n=63	41 (20-65)[a]	54	21 (1 to 54)[b]	2.8 (1.4 to 4.3)[a]	80.6 (60 to 110)[a]	1.2 (0 to 7.4)[a]	NR
Lundborg, 2006[115] N=491 RCT, 26w Medium	≥6 years of age with asthma not well controlled on ICS alone (25-36%) or well controlled on ICS+LABA (64-75%), treated with ICS 500-1200µg/d (250-600µg/d for 6-11y), FEV1 ≥60% predicted ICS dose at entry: 4-11y 419-435µg/d; 12y+ 708-721µg/d; Allowed to continue disodium cromoglycate and montelukast at stable pre-study dose[e]	Budesonide/formoterol 160/4.5µg QD + PRN (DPI) (80/4.5µg/d used for 4-11y) n=162	39.7 (19.6)	43	NR	3.0 (0.9)[d]	95.7 (13.7)[d]	NR	339.0 (NR)[f], 129.0 (NR)[g]
		Budesonide/formoterol 160/4.5µg BID + PRN (DPI) (80/4.5µg/d used for 4-11y) n=165	38.2 (20.6)	49	NR	3.0 (0.9)	96.2 (14.7)	NR	405.2 (NR)[f], 194.1 (NR)[g]
		Budesonide/formoterol 320/9µg BID + formoterol 4.5µg PRN n=164	40.8 (19.9)	49	NR	3.0 (0.9)	96.5 (15.2)	NR	637.5 (NR)/ 325.8 (NR)
Stallberg, 2008[100] SHARE N=1343 RCT, 12m Medium	≥12 years of age with persistent asthma on free combination ICS+LABA or symptomatic despite ICS alone, on ICS ≥400µg/d ICS dose at entry: 636-650µg/d LABA use at entry: 51-52% Randomized therapy stratified by baseline ICS dose[h]	Budesonide/formoterol 160/9µg or 320/9µg QD + PRN **OR** 80/4.5µg or 160/4.5µg BID + PRN n=887	43 (NR)	40	NR	NR	NR	NR	291 (NR)
		Budesonide/formoterol 160/9µg or 320/9µg BID + terbutaline PRN n=456	45 (NR)	44	NR	NR	NR	NR	368 (NR)

Abbreviations: BID=twice daily; d=day; DPI=dry powder inhaler; FEV1=forced expiratory volume in one second; ICS=inhaled corticosteroid; L=liter; LABA=long-acting β_2-agonist; m=month; MDI-metered dose inhaler; n=patient sample size; NR=not reported; PEF=peak expiratory flow; PRN=pro re nata (i.e., as-needed); QD=daily; RCT=randomized controlled trial; SABA=short-acting β_2-agonist; SD=standard deviation; µg=microgram; w=week; y=year

[a]Data reported as mean (range)

[b]Data reported as median (range)

[c]Beclomethasone dipropionate equivalent dose in µg

[d]Represents values post-bronchodilator

[e]Percentage of patients continued on concurrent disodium cromoglycate and montelukast not reported
[f]Represents values from adults (≥12y)
[g]Represents values from children (6-11y)
[h]Patients previously treated with ICS 400-500µg/d received budesonide/formoterol 80/4.5µg dose and those previously treated with ICS >500µg/d received budesonide/formoterol 160/4.5µg dose

Table C-13. Study and population characteristics for KQ1c, ICS and LABA controller and quick relief vs. ICS and LABA controller (lower dose)

Study, Year, N, Study design, Duration, Risk of bias	Study population	Intervention Comparisons	Age (y) [mean (SD)]	Males (%)	Duration of asthma (y) [mean (SD)]	FEV1 (L) [mean (SD)]	FEV1 % predicted (L) [mean (SD)]	Rescue inhaler use (puffs/d) [mean (SD)]	ICS dose during study (µg/d) [mean (SD)]
Hozawa, 2016[117] n=30 RCT, 4w Medium	≥20 years of age with persistent asthma on ICS alone (BUD 800mcg/d, FP or MF 400mg/d), symptomatic with use of SABA 2 to 6 times/w and ACQ≥1.5 ICS dose at entry: 705-720µg/d	Budesonide/formoterol 320/9µg BID + PRN (DPI) n=15	41.7 (5.9)	46.7	8.7 (3.2)	NR	88.5 (5.6)	NR	688.8mcg (NR)
		Fluticasone/vilanterol 100/25µg QD (DPI) + procaterol 20mcg PRN n=15	40.4 (7.6)	40.0	8.0 (2.7)	NR	90.2 (6.4)	NR	NR

Abbreviations: BID=twice daily; d=day; DPI=dry powder inhaler; FEV1=forced expiratory volume in one second; ICS=inhaled corticosteroid; L=liter; n=patient sample size; NR=not reported; PRN=pro re nata (i.e., as-needed); QD=daily; RCT=randomized controlled trial; SABA=short-acting β_2-agonist; SD=standard deviation; µg=microgram; w=week; y=year

Table C-14. Study and population characteristics for KQ1c, ICS and LABA controller and quick relief vs. CBP

Study, Year, n, Acronym, Study design, Duration, Risk of bias	Study population	Intervention Comparisons	Age (y) [mean (SD)]	Males (%)	Duration of asthma (y) [mean (SD)]	FEV1 (L) [mean (SD)]	FEV1 % predict-ed (L) [mean (SD)]	Rescue inhaler use (puffs/d) [mean (SD)]	ICS dose during study (µg/d) [mean (SD)]
Loh, 2008[114] n=38 Retrospective observational cohort study, 3m Medium	≥14 years of age with moderate to severe asthma and inadequately controlled despite step 3 or 4 (52.6% step 3, 47.4% step 4, per GINA guidelines) treatment ICS dose at entry: 400-1200 µg/d LABA at entry: 100%	Budesonide/formoterol maintenance + PRN (DPI) n=22	49 (36 to 65)[a]	13.6	NR	1.16 (0.71 to 2.35)[a]	41 (21 to 74)[a]	NR	1200 (200-1400)[a]
		Budesonide/formoterol maintenance (DPI) + SABA PRN (MDI/DPI) n=16	50 (14 to 66)[a]	43.8	NR	1.41 (0.52 to 2.79)[a]	48 (20 to 91)[a]	NR	NR
Sears, 2008[97] n=1538 RCT, 6m Medium	≥12 years of age with mild-severe persistent asthma (18% mild, 43% moderate, 39% severe per GINA guidelines) on ICS ≥400µg/d and sub-optimal control or on daily maintenance ICS+LABA ICS dose at entry: 566-572µg/d LABA use at entry:73-75%	Budesonide/formoterol 160/4.5µg BID + PRN (DPI) n=772	42.1 (16.4)	42.2	NR	NR	NR	1.25 (1.67)	748 with (0 to 2710)[b,c]
		Conventional best practice[d] n=766	43.1 (16.0)	37.5	NR	NR	NR	1.22 (1.69)	1015 (30 to 4000)[b,c]
Stallberg, 2008[100] SHARE n=1776 RCT, 12m	≥12 years of age with persistent asthma on free combination ICS+LABA or symptomatic despite ICS alone, on ICS ≥400µg/d	Budesonide/formoterol 160/9µg or 320/9µg QD + PRN **OR** 80/4.5µg or 160/4.5µg BID + PRN n=887	43 (NR)	40	NR	NR	NR	NR	291 (NR)
Medium	ICS dose at entry: 636-650µg/d LABA use at entry: 51-52% Randomized therapy stratified by baseline ICS dose[e]	Budesonide 100-400µg (DPI) + formoterol 4.5 or 9µg (DPI) at a dose judged by investigator + terbutaline PRN[f] n=433	43 (NR)	41	NR	NR	NR	NR	550 (NR)

Study, Year, n, Acronym, Study design, Duration, Risk of bias	Study population	Intervention Comparisons	Age (y) [mean (SD)]	Males (%)	Duration of asthma (y) [mean (SD)]	FEV1 (L) [mean (SD)]	FEV1 % predict-ed (L) [mean (SD)]	Rescue inhaler use (puffs/d) [mean (SD)]	ICS dose during study (μg/d) [mean (SD)]
Louis, 2009[82] SALTO n=908 RCT, 26w Medium	≥12 years of age with persistent asthma, symptomatic on ICS alone ≥500μg/d beclomethasone equivalents or without regard to symptoms on ICS+ another controller therapy ICS dose at entry:570-589μg/d	Budesonide/formoterol 160/4.5μg BID + PRN (DPI) n=450	43.4 (NR)	44.0	21.0 (0 to 86)[a]	NR	NR	1.09 (0-15)[b]	749 (NR)[c]
		Conventional best practice[g] n=458	42.9 (NR)	41.0	20.2 (0 to 78)[a]	NR	NR	1.02 (0-11)[b]	1059 (NR)[c]
Quirce, 2011[91] n=654 RCT, 26w Medium	≥18 years of age with persistent asthma (mild 26%, moderate 32%, severe 42%) on ICS±LABA, ICS ≥400μg/d budesonide or equivalent, history of suboptimal control per investigator, SABA use ≥3 occasion in prior week ICS dose at entry: 1028-1040μg/d beclomethasone equivalents LABA use at entry: 80-81%	Budesonide/formoterol 160/4.5μg BID + PRN (DPI) n=328	43.7 (18-89)[b]	33.5	9.7 (0.3 to 57.4)[a]	NR	NR	1.6 (1.2)	799 (NR)[c]
		Conventional best practice[h] n=326	44.3 (8-82)[b]	38	11.2 (0.3 to 60.6)[a]	NR	NR	1.6 (1.2)	1184 (NR)[c]
Soes-Peterson, 2011[98] MONO n=1854 RCT, 26w Medium	≥12 years of age with persistent asthma on ICS ≥320μg/d ±LABA, including patients on ICS alone with history of suboptimal asthma control indicating need for additional treatment ICS dose at entry: 1018-1051μg/d beclomethasone equivalents LABA use at entry: 74-75%	Budesonide/formoterol 160/4.5μg BID + PRN (DPI) n=921	43.0 (15.9)	39.3	NR	NR	NR	1.1 (1.4)	753 (0 to 2500)[b,c]
		Conventional best standard[i] n=914	42.0 (15.9)	41.4	NR	NR	NR	1.1 (1.5)	1092 (42 to 6000)[b,c]
Riemersma, 2012[95] n=102 RCT, 12m	≥18 years of age with mild to moderate persistent, stable asthma on daily ICS, FEV1≥60% predicted, 36% well-controlled (ACQ≤0.75)	Budesonide/formoterol 80/4.5μg QD + PRN n=54	44.7 (13.2)	41	NR	NR	96.0 (16.0)	0.6 (1.3)	326 (NR)[c]

Study, Year, n, Acronym, Study design, Duration, Risk of bias	Study population	Intervention Comparisons	Age (y) [mean (SD)]	Males (%)	Duration of asthma (y) [mean (SD)]	FEV1 (L) [mean (SD)]	FEV1 % predict-ed (L) [mean (SD)]	Rescue inhaler use (puffs/d) [mean (SD)]	ICS dose during study (μg/d) [mean (SD)]
Medium	ICS dose at entry: 757-851μg/d beclomethasone equivalents	Usual care[j] n=48	40.6 (12.0)	35	NR	NR	101.5 (17.5)	0.4 (0.7)	798 (NR)[c]
Kardos, 2013[79] n=482 Prospective observational cohort study, 6m Low	≥18 years of age requiring step 3 or 4 (78% step 3, 22% step 4, per GINA guidelines) treatment and with history of at least 1 severe exacerbation in prior 24 months (but not in the previous month)	Budesonide/formoterol maintenance + PRN at a dose judged by investigator[k] n=310	49.1 (15.2)	38.4	NR	2.64 (0.87)	NR	NR	615 (318)[l]
	LABA at entry: 100%	ICS + LABA maintenance + SABA PRN at a dose judged by the investigator[m] n=172	51.4 (15.4)	34.3	NR	2.45 (0.73)	NR	NR	678 (380)[l]

Abbreviations: ACQ=Asthma Control Questionnaire; BID=twice daily; d=day; DPI=dry powder inhaler; FEV1=forced expiratory volume in one second; GEMA=Guía Española para el Manejo del Asma; GINA= Global Initiative for Asthma; ICS=inhaled corticosteroid; L=liter; LABA=long-acting β_2-agonist; LAMA=long-acting muscarinic antagonist; LTRA=leukotriene receptor antagonist; m=months; MDI=meter-dose inhaler; n=patient sample size; NR=not reported; PRN=pro re nata (i.e., as-needed); QD=daily; RCT=randomized controlled trial; SABA=short-acting β_2-agonist; SD=standard deviation; w=week; y=year

[a]Data reported as median (range)

[b]Data reported as mean (range)

[c]Beclomethasone dipropionate equivalent dose in μg

[d]Therapy managed by investigator following Canadian Asthma Consensus Guidelines and could involve ICS+LABA combination products but not combination products used as single maintenance and reliever therapy. During the trial, 18% of patients were on ICS alone and 82% of patients were on ICS+LABA

[e]Patients previously treated with ICS 400-500μg/d received budesonide/formoterol 80/4.5μg dose and those previously treated with ICS >500μg/d received budesonide/formoterol 160/4.5μg dose

[f]Therapy used at appropriate dose according to asthma severity as judged by the investigator. Doses could be adjusted up or down within the range but budesonide could not be completely withdrawn

[g]Physician's choice of stepwise maintenance therapy with multiple controller therapies allowed. However, an ICS+LABA combination single maintenance and reliever therapy and oral steroids were not allowed. Investigators were encouraged to use the GINA guidelines. Prescribed maintenance medications included ICS+LABA combination inhaler (86%), LTRA (27%), separate ICS inhaler (7%), separate LABA inhaler (7%), inhaled LAMA (4%), xanthines (3%) and mucolytics (1%)

[h]Active stepped and individualized treatment in accordance with GINA and GEMA guidelines. Patients had to be treated with at least ICS as maintenance treatment and could be treated with any asthma medication except ICS+LABA combination single maintenance and reliever therapy and oral steroids. During the trial, 91% of patients were treated with ICS+LABA either in single or separate inhalers, 27% with LTRAs, 2% with inhaled anticholinergics and 2.5% with mucolytics

[i]Any guideline-defined treatment was allowed, except ICS+LABA combination single maintenance and reliever therapy. During the trial, 81% of patients were treated with LABA in addition to their ICS, 11% used LTRAs and 88% used SABAs for rescue

[j]Continued medication as before randomization and treated as usual by general practitioner

[k]Investigators were provided with the package insert for budesonide/formoterol including dosage and Symbicort maintenance and reliever therapy treatment principles. No other restrictions were applied. No concomitant therapies were disallowed (with the exception of systemic corticosteroids and β-blockers), but investigators were asked to take into account relevant information from the budesonide /formoterol summary of product characteristics
[l]Represents prescribed inhaled corticosteroid dose
[m]Only directions given to investigators regarding the comparator group was that these patients had to be treated with inhaled corticosteroids plus long-acting β_2-agonist and as-needed short-acting β_2-agonist via separate inhalers and should be treated according to the relevant information in the product package inserts

Table C-15. Study level outcomes for KQ1c, ICS and LABA controller and quick relief vs. ICS and LABA controller and quick relief vs. ICS controller (same dose)

Study, Year, n, Study design, Duration	Population[a]	Exacerbations[b]	Mortality	Asthma control	Quality of life	Healthcare utilization
Scicchitano, 2004[86] n=1890 RCT, 12m	***Age***: 12y+ ***Severity/control***: Moderate to severe persistent asthma/ symptomatic ***ICS daily dose:*** Low vs. low	***Relative measures*** Requiring systemic corticosteroids, hospitalization, or ER visit: RR 0.64 (0.53 to 0.78) HR 0.61 (0.49 to 0.75) IRR 0.55 (0.46 to 0.66) Requiring systemic corticosteroids, hospitalization, ER visit, or PEF <70%: RR 0.65 (0.55 to 0.78) HR 0.61 (0.50 to 0.74) Mild exacerbation: HR 0.68 (0.61 to 0.75) ***Count data*** Hospitalization or ER visit: 15 vs. 25 Total number of oral corticosteroid days: 1776 vs. 3177	All-cause: Peto's OR 0.51 (0.05 to 4.92) Asthma-specific: No events occurred	***Composite measures***: NR ***Spirometry:*** FEV1 MD 0.1 (0.07 to 0.13)	NR	Rescue medication, inhalations/d: 0.9 vs. 1.42, p<0.001

Study, Year, n, Study design, Duration	Population[a]	Exacerbations[b]	Mortality	Asthma control	Quality of life	Healthcare utilization
Rabe, 2006[94] n=697 RCT, 6m	***Age***: 12y+ ***Severity/control***: Mild to moderate persistent asthma/ symptomatic ***ICS daily dose:*** Low vs. low	***Relative measures*** Requiring systemic corticosteroids, hospitalization, ER visit, or PEF <70%: RR 0.49 (0.32 to 0.76) ***Count data*** Total number of oral corticosteroid days: 114 vs. 498	NR	***Composite measures***: NR ***Spirometry:*** FEV1, change from baseline 0.21 vs. 0.06, p<0.001	NR	Rescue medication, inhalations/d: MD -0.34 (-0.51 to -0.17)
Sovani, 2008[99] n=71 RCT, 6m	***Age***: 12y+ ***Severity/control***: Persistent asthma/ poor asthma control ***ICS daily dose:*** Low vs. low	***Relative Measures*** NR ***Count data*** Number of oral corticosteroid courses: 6 vs. 6	NR	***Composite measures***: ACQ-7 score: MD 0.15 (-0.5 to 0.7) ***Spirometry:*** FEV1 MD 0.01 (-0.2 to 2.00)	AQLQ-mini score: MD 0.35 (-0.3 to 1.00)	NR

Abbreviations: ACQ=Asthma Control Questionnaire; AQLQ=Asthma Quality of Life Questionnaire; d=day; EPR=Expert Panel Review (Guidelines for the Diagnosis and Management of Asthma); ER=emergency room; FEV1=forced expiratory volume in one second; HR=hazard ratio; ICS=inhaled corticosteroid; IRR= incident rate ratio; m=month; MD=mean difference; n=patient sample size; NR=not reported; OR=odds ratio; PEF=peak expiratory flow; RCT=randomized controlled trial; RR=relative risk; y=year

[a]Age is categorized using study inclusion criteria and the age categories used in EPR-3 of 0-4y, 5-11y and 12y+. Severity is as reported per the study. Control was usually not specified and rather details about patients being symptomatic or not at entry were given and reported here. ICS daily dose is categorized using the study's required ICS dose and the EPR-3 categories of low, medium and high

[b]Relative measures are presented first and include, when reported by the study, RR, HR for time to the event, and IRR for count data allowing multiple events over the period of follow-up. Count data is presented, when reported by the study, for number of hospitalizations, hospital days, and ER visits in association with exacerbations

Table C-16. Study level outcomes for KQ1c, ICS and LABA controller and quick relief vs. ICS controller (higher dose)

Study, Year, n, Study design, Duration	Population[a]	Exacerbations[b]	Mortality	Asthma control	Quality of life	Healthcare utilization
O'Byrne, 2005[75,83] n=1851 RCT, 12m	***Age****:* Mixed (5-11y and 12+y) ***Severity/control****:* Persistent asthma/ symptomatic during run-in[c] ***ICS daily dose:*** Low vs. high	***Full population*** ***Relative measures*** Composite systemic corticosteroids, hospitalization, ER visit, or increase in ICS or other medication for 4-11y: RR 0.58 (0.46 to 0.72) HR 0.55 (0.43 to 0.70) IRR 0.54 (0.44 to 0.66) Composite systemic corticosteroids, hospitalization, ER visit, or increase in ICS or other medication for 4-11y, PEF<70%: RR 0.57 (0.48 to 0.69) HR 0.53 (0.43 to 0.65) IRR 0.53 (0.44 to 0.64) Mild exacerbation: IRR 0.64 (0.57 to 0.73) ***Count data*** Requiring hospitalization or ER visit: 25 vs. 29 Average courses of corticosteroid/y: 0.19 vs. 0.38	NR	***Composite measures***: NR ***Spirometry:*** NR	NR	NR

Study, Year, n, Study design, Duration	Population[a]	Exacerbations[b]	Mortality	Asthma control	Quality of life	Healthcare utilization
		4-11y subgroup (n=224) ***Relative measures*** Composite hospitalization, ER visit, systemic corticosteroid, or increase in ICS or other treatment: RR 0.43 (0.21 to 0.87) Composite systemic corticosteroid, hospitalization, ER visit, increase in ICS or other treatment, or PEF <70%: RR 0.55 (0.32 to 0.94) HR 0.49 (0.27 to 0.90) Mild exacerbation: RR 0.86 (0.72 to 1.04) ***Count data*** Requiring hospitalization or ER: 1 vs. 8 Average courses of corticosteroid/y: 0.05 vs. 0.25 Total number of days requiring oral cortisteroids: 32 vs. 141	NR	***Composite measures***: NR ***Spirometry:*** NR	NR	NR

Abbreviations: EPR=Expert Panel Review (Guidelines for the Diagnosis and Management of Asthma); ER=emergency room; HR=hazard ratio; ICS=inhaled corticosteroid; IRR= incident rate ratio; m=month; n=patient sample size; NR=not reported; PEF=peak expiratory flow; RCT=randomized controlled trial; RR=relative risk; y=year

[a]Age is categorized using study inclusion criteria and the age categories used in EPR-3 of 0-4y, 5-11y and 12y+. Severity is as reported per the study. Control was usually not specified and rather details about patients being symptomatic or not at entry were given and reported here. ICS daily dose is categorized using the study's required ICS dose and the EPR-3 categories of low, medium and high

[b]Relative measures are presented first and include, when reported by the study, RR, HR for time to the event, and IRR for count data allowing multiple events over the period of follow-up. Count data is presented, when reported by the study, for number of hospitalizations, hospital days, and ER visits in association with exacerbations

[c]Defined as 12+ short-acting β_2-agonist inhalations during last 10 days of the run-in or 8+ short-acting β_2-agonist inhalations during last 10 days of the run-in for 4-11y olds

Table C-17. Study level outcomes for KQ1c, ICS and LABA controller and quick relief vs. ICS and LABA controller (same dose)

Study, Year, n, Study design, Duration	Population[a]	Exacerbations[b]	Mortality	Asthma control	Quality of life	Healthcare utilization
O'Byrne, 2005[75,83] n=1834 RCT, 12m	***Age**:* Mixed (5-11y and 12y+) ***Severity/control**:* Persistent asthma/ symptomatic during run-in[c] ***ICS daily dose:*** Low vs. low	***Full population*** ***Relative measures*** Composite systemic corticosteroid, hospitalization, ER visit, or increase in ICS or other medication for 4-11y: RR 0.52 (0.42 to 0.65) HR 0.50 (0.40 to 0.63) IRR 0.47 (0.39 to 0.57) Composite systemic corticosteroid, hospitalization, ER visit, increase in ICS or other medication for 4-11y, PEF <70%: RR 0.59 (0.49 to 0.71) HR 0.55 (0.44 to 0.67) IRR 0.53 (0.44 to 0.65) Mild exacerbation: IRR 0.70 (0.62 to 0.80) ***Count data*** Requiring hospitalization or ER visit: 25 vs. 32 Average courses of corticosteroid/yr: 0.19 vs. 0.42	NR	***Composite measures***: NR ***Spirometry:*** NR	NR	NR

Study, Year, n, Study design, Duration	Population[a]	Exacerbations[b]	Mortality	Asthma control	Quality of life	Healthcare utilization
		4-11y subgroup (n=235) ***Relative measures*** Composite hospitalization, ER visit, systemic corticosteroid, or increase in ICS or other treatment: RR 0.28 (0.14 to 0.53) Composite systemic corticosteroid, hospitalization, ER visit, increase in ICS or other treatment, or PEF <70%: RR 0.38 (0.23 to 0.63) HR 0.34 (0.19 to 0.60) Mild exacerbation: RR 0.75 (0.64 to 0.88) ***Count data*** Requiring hospitalization or ER visit: 1 vs. 8 Average courses of corticosteroid/y: 0.05 vs. 0.30 Total number of days requiring oral corticosteroid: 32 vs. 230	NR	***Composite measures***: NR ***Spirometry:*** NR	NR	NR

Study, Year, n, Study design, Duration	Population[a]	Exacerbations[b]	Mortality	Asthma control	Quality of life	Healthcare utilization
Vogelmeier, 2005[104] n=2143 RCT, 12m	***Age****:* 12y+ ***Severity/control****:* Persistent asthma/ symptomatic during run-in[d] ***ICS daily dose:*** Medium vs. medium	***Relative Measures*** Composite systemic cortisteroid, hospitalization, or ER visit: RR 0.80 (0.64 to 0.99) HR 0.77 (0.61 to 0.97) Composite hospitalization, ER, systemic corticosteroid, or unscheduled visit: RR 0.79 (0.65 to 0.95) HR 0.75 (0.61 to 0.93) IRR 0.88 (0.56 to 0.91) Requiring hospitalization or ER visit: RR 0.68 (0.43 to 1.06) ***Count data:*** Hospitalization or ER visit: 44 vs. 50 Unscheduled visit: 39 vs. 62 Asthma-related hospital day: 59 vs. 94 Asthma-related ER visit: 38 vs. 45 Unscheduled visit: 117 vs. 154 Total number of oral corticosteroid day: 1980 vs. 2978	All-cause: Peto's OR 0.14 (0.01 to 2.18) Asthma-specific: No events occurred	***Composite measures***: NR ***Spirometry:*** NR	NR	NR

Study, Year, n, Study design, Duration	Population[a]	Exacerbations[b]	Mortality	Asthma control	Quality of life	Healthcare utilization
Rabe, 2006[93] n=3394 RCT, 12m	***Age****:* 12y+ ***Severity/control****:* Persistent asthma/ symptomatic during run-in ***ICS daily dose:*** Low vs. low	***Relative Measures*** Composite systemic corticosteroid, hospitalization, or ER visit: RR 0.60 (0.50 to 0.72) HR 0.55 (0.45 to 0.68) IRR 0.52 (0.44 to 0.62) Requiring hospitalization or ER visit: RR 0.61 (0.44 to 0.85) HR 0.57 (0.41 to 0.81) IRR 0.61 (0.45 to 0.82) Mild exacerbation: RR 0.94 (0.90 to 0.99) HR 0.88 (0.80 to 0.97) IRR 0.82 (0.74 to 0.91) ***Count Data*** Hospitalization or ER visit: 70 vs. 115	All-cause: Peto's OR 0.53 (0.05 to 5.08) Asthma-specific: No events occurred	***Composite measures***: ACQ-5 score: MD -0.15 (-0.21 to -0.08) ***Spirometry:*** FEV1: MD 0.08 (0.05 to 0.10)	NR	Rescue medication use, inhalations/d: MD -0.20 (-0.28 to -0.12)

Study, Year, n, Study design, Duration	Population[a]	Exacerbations[b]	Mortality	Asthma control	Quality of life	Healthcare utilization
Atienza, 2013[70] n=2091 RCT, 12m	***Age***: 12y+ ***Severity/control***: Persistent asthma/ not adequately controlled, symptomatic during run-in[e] ***ICS daily dose:*** Low vs. low	***Relative Measures*** Requiring systemic corticosteroids: RR 0.77 (0.62 to 0.95) HR 0.74 (0.59 to 0.93) IRR 0.73 (0.60 to 0.88) Requiring hospitalization: RR 0.33 (0.17 to 0.65) HR 0.33 (0.17 to 0.65) Requiring ER visit: RR 0.74 (0.59 to 0.93) HR 0.69 (0.54 to 0.88) IRR 0.66 (0.54 to 0.80) Composite systemic corticosteroid, hospitalization, or ER visit: RR 0.74 (0.62 to 0.88) HR 0.70 (0.57 to 0.85) IRR 0.47 (0.40 to 0.55) Requiring hospitalization or ER visit: RR 0.72 (0.58 to 0.90) HR 0.68 (0.53 to 0.86) IRR 0.65 (0.54 to 0.79) Mild exacerbation: RR 0.89 (0.84 to 0.93) HR 0.81 (0.73 to 0.89) ***Count data*** Requiring hospitalization: 11 vs. 39 Requiring ER visit : 163 vs. 244 Requiring hospitalization or ER visit: 171 vs. 260 Total number of oral prednisone days: 1215 vs. 1697	All-cause: Peto's OR 0.99 (0.06 to 15.89) Asthma-specific: No events occurred	***Composite measures***: ACQ-5 score: MD -0.124 (-0.179 to -0.069) ACQ-5 responder: RR 1.14 (1.05 to 1.24) ***Spirometry:*** FEV1: MD 0.04 (0.015 to 0.064)	NR	Rescue medication use, inhalations/d: MD -0.25 (-0.35 to -0.15)

Study, Year, n, Study design, Duration	Population[a]	Exacerbations[b]	Mortality	Asthma control	Quality of life	Healthcare utilization
Papi, 2013[84] n=1701 RCT, 48w	***Age****:* 12y+ ***Severity/control****:* Persistent asthma/ not fully controlled ***ICS daily dose:*** Low vs. low	***Relative Measures*** Requiring systemic corticosteroid: RR 0.62 (0.49 to 0.79) IRR 0.65 (0.54 to 0.80) Composite systemic corticosteroid, hospitalization, or ER visit: RR 0.65 (0.51 to 0.82) HR 0.64 (0.49 to 0.83) IRR 0.66 (0.55 to 0.80) Requiring hospitalization or ER visit: RR 0.69 (0.49 to 0.96) IRR 0.67 (0.54 to 0.84) Requiring hospitalization: RR 1.18 (0.2 to 2.2) Mild exacerbation: RR 1.00 (0.94 to 1.06) HR 0.97 (0.87 to 1.09) IRR 0.86 (0.76 to 0.98) ***Count Data*** Requiring hospitalization or ER visit: 67 vs. 99 Hospitalization: 5 vs. 17 Intubation: No events occurred	NR	***Composite measures***: ACQ-7 score: MD -0.06 (-0.13 to 0.02) ***Spirometry:*** FEV1: MD 0.001 (-0.04 to 0.04) FVC: MD -0.01 (-0.07 to 0.04)	NR	Rescue medication use, inhalations/d: MD -0.02 (-0.13 to 0.09)

Study, Year, n, Study design, Duration	Population[a]	Exacerbations[b]	Mortality	Asthma control	Quality of life	Healthcare utilization
Patel, 2013[86] n=303 RCT, 24w	***Age****:* 12y+ ***Severity/control****:* Persistent asthma ***ICS daily dose:*** Medium vs. medium	***Relative Measures*** Composite systemic corticosteroid, hospitalization, or ER visit: RR 0.56 (0.38 to 0.84) HR 0.53 (0.33 to 0.85) IRR 0.54 (0.36 to 0.81) Hospital or ER admission for asthma: RR 0.78 (0.30 to 2.05) HR 0.85 (0.37 to 2.00) Hospital admission for asthma: RR 1.01 (0.14 to 7.05) HR 1.54 (0.26 to 9.09) Oral corticosteroid dose (mg prednisone): MD -49.1 (-121.34 to 23.14) Rate of prednisone courses per year: HR 0.58 (0.41 to 0.84) ***Count data*** NR	All-cause: No events occurred Asthma-specific: No events occurred	***Composite measures***: ACQ-7 score: MD -0.23 (-0.47 to 0.01) ***Spirometry:*** FEV1: MD 0.15 (-0.06 to 0.36) FEV1 % predicted: MD 1.8 (-2.8 to 6.4)	NR	NR
Hozawa, 2014[78] n=30 RCT, 8w	***Age****:* 12y+ ***Severity/control****:* Persistent asthma/ not well controlled and symptomatic ***ICS daily dose:*** Medium vs. medium	NR	NR	***Composite measures***: ACQ-5 score: MD -0.37 (-0.58 to -0.16) ***Spirometry:*** FEV1 % predicted: MD 1.9 (-4.27 to 8.07)	NR	Rescue medication use, inhalations/w: MD -0.73 (-1.42 to -0.04)

Study, Year, n, Study design, Duration	Population[a]	Exacerbations[b]	Mortality	Asthma control	Quality of life	Healthcare utilization
Takeyama, 2014[101,102] n=63 RCT, 1y	***Age****:* 12y+ ***Severity/control****:* Moderate to severe persistent asthma/ not well controlled and symptomatic[g] ***ICS daily dose:*** Low vs. low	***Relative Measures*** Any exacerbation: HR 0.34 (0.11 to 0.92) ***Count data*** NR	NR	***Composite measures***: ACT: MD 6.3 (5.15 to 7.45) ***Spirometry:*** FEV1: MD 0.04 (0.02 to 0.06)	NR	Rescue medication use, inhalations/w: MD -2.2 (-3.92 to -0.48)
Stallberg, 2008[100] n=1343 RCT, 12m	***Age****:* 12y+ ***Severity/control****:* Persistent asthma/ symptomatic or without symptoms ***ICS daily dose:*** Low vs. low to medium	***Relative Measures:*** Composite systemic corticosteroid, hospitalization, or ER visit: RR 0.77 (0.53 to 1.12) IRR 0.81 (0.61 to 1.09) ***Count Data:*** Hospitalizations/pt/y: 0.007 vs. 0.000 Unplanned or ER visits/ pt/y: 0.448 vs. 0.346	NR	***Composite measures***: NR ***Spirometry:***: NR	NR	

Abbreviations: ACQ=Asthma Control Questionnaire; ACT=Asthma Control Test; d=day; EPR=Expert Panel Review (Guidelines for the Diagnosis and Management of Asthma); ER=emergency room; FEV1=forced expiratory volume in one second; FVC=forced vital capacity; HR=hazard ratio; ICS=inhaled corticosteroid; IRR= incident rate ratio; m=month; mg=milligram; MD=mean difference; n=patient sample size; NR=not reported; PEF=peak expiratory flow; pt=patient; RCT=randomized controlled trial; RR=relative risk; w=week; y=year

[a]Age is categorized using study inclusion criteria and the age categories used in EPR-3 of 0-4y, 5-11y and 12y+. Severity is as reported per the study. Control was usually not specified and rather details about patients being symptomatic or not at entry were given and reported here. ICS daily dose is categorized using the study's required ICS dose and the EPR-3 categories of low, medium and high

[b]Relative measures are presented first and include, when reported by the study, RR, HR for time to the event, and IRR for count data allowing multiple events over the period of follow-up. Count data is presented, when reported by the study, for number of hospitalizations, hospital days, and ER visits in association with exacerbations

[c]Defined as 12+ short-acting β_2-agonist inhalations during last 10 days of the run-in or 8+ short-acting β_2-agonist inhalations during last 10 days of the run-in for 4-11y olds

[d]Defined as rescue medication use 4 or more of the last 7 days in the run-in period

[e]Defined as rescue medication use 5 or more of the last 7 days in the run-in period

[f]Defined as Asthma Control Questionnaire >0.75 and short-acting β_2-agonist use 2-6 times per week

[g]Defined as Asthma Control Test <20 and reliever use at least 5 times per week

Table C-18. Study level outcomes for KQ1c, ICS and LABA controller and quick relief vs. ICS and LABA controller (higher dose)

Study, Year, n, Study design, Duration	Population[a]	Exacerbations	Mortality	Asthma control	Quality of life	Healthcare utilization
Bousquet, 2007[76] n=2309 RCT, 6m	***Age****:* 12y+ ***Severity/control****:* Persistent asthma/ symptomatic ***ICS daily dose:*** Medium vs. high	***Relative measures:*** Requiring systemic corticosteroid: RR 0.82 (0.62 to 1.07) Composite systemic corticosteroid, hospitalization, or ER visit: RR 0.83 (0.65 to 1.06) HR 0.82 (0.63 to 1.05) IRR: 0.79 (0.63 to 0.99) Requiring hospitalization or ER visit: RR 0.66 (0.44 to 0.98) HR 0.64 (0.43 to 0.96) IRR: 0.69 (0.49 to 0.99) ***Count data:*** Total number of oral corticosteroid days: 764 vs. 990	All-cause: OR 7.39 (0.15 to 372.38) Asthma-specific: No events occurred	***Composite measures***: ACQ-5: MD -0.02 (-0.07 to 0.04) ***Spirometry:***: NR	NR	PRN inhalations/d: MD -0.04 (-0.12 to 0.04)

Study, Year, n, Study design, Duration	Population[a]	Exacerbations	Mortality	Asthma control	Quality of life	Healthcare utilization
Kuna, 2007[81] n=3335 RCT, 6m	***Age***: 12y+ ***Severity/control***: Persistent asthma/ symptomatic during run-in[c] ***ICS daily dose:*** Low vs. medium	***Relative Measures vs. budesonide/formoterol:*** Composite systemic corticosteroid, hospitalization, or ER visit: RR 0.75 (0.58 to 0.96) HR 0.74 (0.56 to 0.96) IRR 0.72 (0.57 to 0.90) Requiring hospitalization or ER visit: RR 0.96 (0.65 to 1.41) HR 0.97 (0.65 to 1.44) IRR 0.88 (0.63 to 1.24) Mild exacerbation: RR 0.97 (0.91 to 1.04) ***Count data:*** Total number of oral corticosteroid days: 619d vs. 1044d	All-cause: OR 7.39 (0.15 to 372.38) Asthma-specific: No events occurred	***Composite measures***: ACQ-5: MD -0.02 (-0.08 to 0.05) ***Spirometry:***: FEV1 MD 0.01 (-0.03 to 0.04)	AQLQ(S): MD 0.01 (-0.07 to 0.08)	PRN inhalations/d: MD -0.03 (-0.12 to 0.06)
		Relative Measures vs. salmeterol/fluticasone: Composite systemic corticosteroid, hospitalization or ER visit: RR 0.68 (0.53 to 0.87) HR 0.67 (0.52 to 0.87) IRR 0.61 (0.49 to 0.76) Requiring hospitalization or ER visit: RR 0.69 (0.48 to 0.98) HR 0.69 (0.48 to 0.99) IRR 0.61 (0.44 to 0.83) Mild exacerbation: RR 1.04 (0.97 to 1.11) ***Count data:*** Total number of oral corticosteroid days: 619d vs. 1132d	All-cause: OR 1.00 (0.06 to 16.00) Asthma-specific: No events occurred	***Composite measures***: ACQ-5: MD 0.03 (-0.03 to 0.09) ***Spirometry:***: FEV1 MD 0.01 (-0.03 to 0.04)	AQLQ(S): MD -0.02 (-0.09 to 0.06)	PRN inhalations/d: 0.07 (-0.02 to 0.16) Total number of oral corticosteroid days: 619d vs. 1132d

Study, Year, n, Study design, Duration	Population[a]	Exacerbations	Mortality	Asthma control	Quality of life	Healthcare utilization
Pavord, 2009[89] n=127 RCT, 1yr	***Age****:* 12y+ ***Severity/control****:* Persistent asthma/ symptomatic ***ICS daily dose:*** Low vs. medium	***Relative Measures*** Rate of composite systemic steroids, hospitalization, ER visit: IRR 1.02 (0.52 to 2.02) ***Count data:*** NR	All-cause: No events occurred Asthma-specific: No events occurred	***Composite measures***: NR ***Spirometry:***: NR	NR	NR
Lundborg, 2006[115] n=491 RCT, 26w	***Age****:* Mixed (5-11y and 12+) ***Severity/control****:* Persistent asthma/ well controlled and not well controlled ***ICS daily dose:*** Low vs. medium	***Bud/for daily+PRN*** ***Relative measures:*** NR ***Count data:*** Number of hospital nights: 0 vs. 0 Number of ER visits: 9 vs. 11 Number of unscheduled MD visits: 11 vs. 17	NR	***Composite measures***: ACQ-5: MD -0.07 (-0.24 to 0.10) ***Spirometry:***: NR	NR	NR
		Bud/for twice daily+PRN ***Relative measures:*** NR ***Count data:*** Number of hospital nights: 3 vs. 0 Number of ER visits: 17 vs. 11 Number of unscheduled MD visits: 20 vs. 17	NR	***Composite measures***: ACQ-5: MD -0.10 (-0.26 to 0.07) ***Spirometry:***: NR	NR	NR

Study, Year, n, Study design, Duration	Population[a]	Exacerbations	Mortality	Asthma control	Quality of life	Healthcare utilization
Stallberg, 2008[100] n=1343 RCT, 12m	***Age****:* 12y+ ***Severity/control****:* Persistent asthma/ symptomatic or without symptoms ***ICS daily dose:*** Low vs. low to medium	***Relative Measures:*** Composite systemic corticosteroid, hospitalization, or ER visit: RR 0.77 (0.53 to 1.12) IRR 0.81 (0.61 to 1.09) ***Count Data:*** Hospitalization/pt/y: 0.007 vs. 0.000 Unplanned ER visit/ pt/y: 0.448 vs. 0.346	NR	***Composite measures***: NR ***Spirometry:***: NR	NR	NR

Abbreviations: ACQ=Asthma Control Questionnaire; Bud/for=budesonide/formoterol; d=day; EPR=Expert Panel Review (Guidelines for the Diagnosis and Management of Asthma); ER=emergency room; FEV1=forced expiratory volume in one second; HR=hazard ratio; ICS=inhaled corticosteroid; IRR= incident rate ratio; m=months; MD=mean difference; n=patient sample size; NR=not reported; OR=odds ratio; PRN=pro re nata (i.e., as-needed); pt=patient; RCT=randomized controlled trial; RR=relative risk; w=week; y=year

[a]Age is categorized using study inclusion criteria and the age categories used in EPR-3 of 0-4y, 5-11y and 12y+. Severity is as reported per the study. Control was usually not specified and rather details about patients being symptomatic or not at entry were given and reported here. ICS daily dose is categorized using the study's required ICS dose and the EPR-3 categories of low, medium and high

[b]Relative measures are presented first and include, when reported by the study, RR, HR for time to the event, and IRR for count data allowing multiple events over the period of follow-up. Count data is presented, when reported by the study, for number of hospitalizations, hospital days, and ER visits in association with exacerbations

[c]Defined as symptomatic as short-acting β_2-agonist use was required at least 5 of 7 days

Table C-19. Study level outcomes for KQ1c, ICS and LABA controller and quick relief vs. ICS and LABA controller and quick relief vs. ICS controller (same dose)

Study, Year, n, Study design, Duration	Population[a]	Exacerbations	Mortality	Asthma control	Quality of life	Healthcare utilization
Hozawa, 2016[117] n=30 RCT, 4w	***Age***: 12y+ ***Severity/control***: Persistent asthma/ symptomatic ***ICS daily dose:*** Medium vs. low	NR	NR	***Composite measures***: ACQ-5: MD -0.40 (-0.53 to -0.27) ***Spirometry:***: FEV1 % predicted: MD 3.10 (-1.36 to 7.56)	NR	PRN inhalations/w: MD -0.9 (-1.48 to -0.32)

Abbreviations: ACQ=Asthma Control Questionnaire; d=day; FEV1=forced expiratory volume in one second; ICS=inhaled corticosteroid; MD=mean difference; n=patient sample size; NR=not reported; PRN=pro re nata (i.e., as-needed); pt=patient; RCT=randomized controlled trial; w=week

[a]Age is categorized using study inclusion criteria and the age categories used in EPR-3 of 0-4y, 5-11y and 12y+. Severity is as reported per the study. Control was usually not specified and rather details about patients being symptomatic or not at entry were given and reported here. ICS daily dose is categorized using the study's required ICS dose and the EPR-3 categories of low, medium and high

Table C-20. Study level outcomes for KQ1c, ICS and LABA controller and quick relief vs. CBP

Study, Year, n, Study design, Duration	Population[a]	Exacerbations	Mortality	Asthma control	Quality of life	Healthcare utilization
Sears, 2008[97] n=1538 RCT, 6m	***Age***: 12y+ ***Severity/control***: Mild to severe persistent asthma/ with or without suboptimal control ***ICS daily dose:*** Low vs. mixed	***Relative Measures:*** Systemic corticosteroid: RR 1.03 (0.72 to 1.47) Hospitalization: OR 0.13 (0.00 to 6.77) ER visit: RR 0.69 (0.37 to 1.30) Composite systemic corticosteroid, hospitalization, or ER visit: RR 0.96 (0.69 to 1.35) HR 0.99 (0.85 to 1.15) IRR 0.92 (0.80 to 1.06) ***Count data:*** Hospitalization: 0 vs. 1 Hospital day: 0 vs. 5 ER visit: 16 vs. 28 Total number of oral corticosteroid days: 590 vs. 709, p=NR	All-cause: OR 0.51 (0.05 to 4.90) Asthma-specific: No deaths occurred	***Composite measures***: ACQ-5: MD -0.02 (-0.10 to 0.06) ACQ-5 responder: RR 1.22 (1.03 to 1.44) ***Spirometry:***: NR	NR	PRN inhalations/d: MD -0.16 (-0.26 to -0.05)
Stallberg, 2008[100] n=1776 RCT, 12m	***Age***: 12y+ ***Severity/control***: Persistent asthma/ symptomatic and without symptoms ***ICS daily dose:*** Low vs. mixed	***Relative Measures:*** Composite systemic corticosteroid, hospitalization, or ER visit: RR 0.72 (0.51 to 1.03) IRR 0.89 (0.78 to 1.01) ***Count Data:*** Hospitalization/pt/y: 0.007 vs. 0.010 Unplanned ER visit/pt/y: 0.448 vs. 0.295	NR	***Composite measures***: NR ***Spirometry:***: NR	NR	NR

Study, Year, n, Study design, Duration	Population[a]	Exacerbations	Mortality	Asthma control	Quality of life	Healthcare utilization
Louis, 2009[82] n=908 RCT, 26w	***Age****:* 12y+ ***Severity/control****:* Persistent asthma/ symptomatic and without symptoms ***ICS daily dose:*** Low vs. mixed	***Relative measures:*** Systemic corticosteroid: RR 0.70 (0.33 to 1.49) Hospitalization: OR 1.99 (0.21 to 19.14) ER visit: RR 0.25 (0.03 to 2.27) Composite systemic corticosteroid, hospitalization, or ER visit: RR 0.64 (0.32 to 1.31) ***Count data:*** Hospitalization: 2 vs. 1 Number of hospital days: 10 vs. 15 ER visit: 1 vs. 4 Total number of oral corticosteroid days: 132 vs. 244	All-cause: OR 7.54 (0.47 to 120.72) Asthma-specific: No deaths occurred	***Composite measures***: ACQ-5: MD -0.12 (-0.20 to -0.04) ***Spirometry:***: FEV1: MD -0.03 (-0.12 to 0.06)	NR	PRN inhalations/d: MD -0.10 (-0.24 to 0.03) ≥1 day with PRN inhalation: RR 2.96 (2.42 to 3.61)

Study, Year, n, Study design, Duration	**Population[a]**	**Exacerbations**	**Mortality**	**Asthma control**	**Quality of life**	**Healthcare utilization**
Quirce, 2011[91] n=654 RCT, 26w	***Age****:* 12y+ ***Severity/control****:* Mild to severe persistent asthma/ history of suboptimal control ***ICS daily dose:*** Low vs. mixed	***Relative measures:*** Systemic corticosteroid: RR 0.62 (0.33 to 1.16) Hospitalization: OR 7.34 (0.15 to 370.13) ER visit: RR 0.99 (0.47 to 2.11) Composite systemic corticosteroid, hospitalization, or ER visit: RR 0.71 (0.42 to 1.19) HR 0.75 (0.59 to 0.95) IRR 0.75 (0.60 to 0.95) ***Count data:*** Hospitalization: 1 vs. 0 ER visit: 14 vs. 15 Total number of oral corticosteroid days: 177 vs. 229, p<0.001	All-cause: No deaths occurred Asthma-specific: No deaths occurred	***Composite measures***: ACQ-5: MD -0.12 (-0.23 to -0.01) ACQ-5 responder: RR 1.09 (0.92 to 1.30) ***Spirometry:***: NR	NR	≥1 day with PRN inhalation: RR 2.96 (2.42 to 3.61) Total number of oral corticosteroid days: 177 vs. 229, p<0.001

Study, Year, n, Study design, Duration	Population[a]	Exacerbations	Mortality	Asthma control	Quality of life	Healthcare utilization
Soes-Peterson, 2011[98] n=1854 RCT, 26w	***Age***: 12y+ ***Severity/control***: Persistent asthma/ with and without history of suboptimal control ***ICS daily dose:*** Low vs. mixed	***Relative Measures:*** Systemic corticosteroid: RR 0.79 (0.55 to 1.13) Hospitalization: OR: 0.71 (0.23 to 2.21) ER visit: RR 0.80 (0.43 to 1.51) Composite systemic corticosteroid, hospitalization, or ER visit: RR 0.79 (0.57 to 1.10) HR 0.79 (0.68 to 0.92) IRR 0.74 (0.65 to 0.85) ***Count data:*** Hospitalization: 5 vs. 8 Hospital day: 29 vs. 33 ER visit: 18 vs. 22	All-cause: OR 7.33 (0.15 to 369.58) Asthma-specific: No deaths occurred	***Composite measures***: ACQ-5: MD -0.09 (-0.15 to -0.03) ***Spirometry:***: NR	NR	NR
Riemersma, 2012[95] n=102 RCT, 12m	***Age***: 12y+ ***Severity/control***: Mild to moderate persistent asthma/ history of suboptimal control ***ICS daily dose:*** Low vs. mixed	***Relative Measures:*** Composite systemic corticosteroid, hospitalization, or ER visit: RR 0.30 (0.06 to 1.40) Requiring ER or hospitalization: No events occurred ***Count data:*** Hospitalization: No events occurred ER visit: No events occurred	NR	***Composite measures***: ACQ-5: MD -0.06 (-0.31 to 0.19) ***Spirometry:***: FEV1 % predicted: MD 0.70 (-1.80 to 3.20)	NR	NR

Abbreviations: ACQ=Asthma Control Questionnaire; d=day; EPR=Expert Panel Review (Guidelines for the Diagnosis and Management of Asthma); ER=emergency room; FEV1=forced expiratory volume in one second; HR=hazard ratio; ICS=inhaled corticosteroid; IRR= incident rate ratio; m=months; MD=mean difference; n=patient sample size; NR=not reported; OR=odds ratio; PRN=pro re nata (as-needed); pt=patient; RCT=randomized controlled trial; RR=relative risk; w=week; y=year

[a]Age is categorized using study inclusion criteria and the age categories used in EPR-3 of 0-4y, 5-11y and 12y+. Severity is as reported per the study. Control was usually not specified and rather details about patients being symptomatic or not at entry were given and reported here. ICS daily dose is categorized using the study's required ICS dose and the EPR-3 categories of low, medium and high

[b]Relative measures are presented first and include, when reported by the study, RR, HR for time to the event, and IRR for count data allowing multiple events over the period of follow-up. Count data is presented, when reported by the study, for number of hospitalizations, hospital days, and ER visits in association with exacerbations

Table C-21. Study and population characteristics for KQ2a

Study, Year, n, Acronym, Study design, Duration Risk of bias	Study population	Intervention Comparisons	Age (y) [mean (SD)]	Males (%)	Duration of asthma (y) [mean (SD)]	FEV1 (L) [mean (SD)]	FEV1 % predicted (L) [mean (SD)]	Rescue inhaler use (puffs/d) [mean (SD)]	ICS dose during study (µg/d) [mean (SD)]
Peters, 2010[27] n=210 TALC RCT- crossover, 14w Low	≥18 years of age with moderately severe asthma not well controlled on a ICS alone	Tiotropium 18µg daily (Handihaler) n=210	42.2 (12.3)	32.9	26.1 (14.1)	2.31 (0.77)	71.5 (14.9)	1.71 (2.09)	NR
	Tiotropium or salmeterol were added on to run-in dose of beclomethasone 80µg BID	Doubling ICS dose to 160µg BID (MDI) n=210							NR
Bateman, 2011[118] n=254 RCT, 16w Low	18-65 years of age with moderate persistent asthma (GINA step 3) not controlled on ICS alone (400-1000µg/d budesonide or equivalent)	Tiotropium 5µg daily (Respimat) n=128	43.5 (12.6)	35.9	18.1 (12.1)	2.3 (0.77)	74.1 (16.1)	NR	NR
	Randomized therapy added on to ICS continued at prestudy dose	Placebo n=126	44.0 (11.9)	40.5	17.3 (12.2)	2.4 (0.8)	75.3 (19.0)	NR	NR
Kerstjens, 2015[119] Study 1 MezzoTinA-asthma 1 n=795 RCT, 24w Low	18-75 year of age with moderate persistent asthma according to GINA guidelines despite treatment with stable medium dose ICS (400-800µg/d budesonide or equivalent) alone or in fixed combination with LABA, symptomatic with ACQ-7 ≥1.5	Tiotropium 5µg daily (Respimat) n=264	44.4 (12.6)	41.7	22.9 (14.7)	2.2 (0.6)	72.2 (8.2)	NR	666.4 (216.2)[b]
	Randomized therapy was added to prestudy stable maintenance ICS dose[a]	Tiotropium 2.5µg daily (Respimat) n=262	43.7 (13.1)	40.5	22.2 (14.1)	2.2 (0.7)	73.1 (8.6)	NR	649.8 (196.2)[b]

Study, Year, n, Acronym, Study design, Duration Risk of bias	Study population	Intervention Comparisons	Age (y) [mean (SD)]	Males (%)	Duration of asthma (y) [mean (SD)]	FEV1 (L) [mean (SD)]	FEV1 % predicted (L) [mean (SD)]	Rescue inhaler use (puffs/d) [mean (SD)]	ICS dose during study (µg/d) [mean (SD)]
		Placebo n=269	42.5 (13.1)	38.3	20.2 (13.4)	2.3 (0.7)	73.0 (8.2)	NR	661.5 (209.5)[b]
Kerstjens, 2015[119] Study 2 MezzoTinA-asthma 2 n=764 RCT, 24w Low	18-75 year of age with moderate persistent asthma according to GINA guidelines despite treatment with stable medium dose ICS (400-800µg/d budesonide or equivalent) alone or in fixed combination with LABA, symptomatic with ACQ-7 ≥1.5 Randomized therapy was added to prestudy stable maintenance ICS dose[c]	Tiotropium 5µg daily (Respimat) n=253	44.3 (12.7)	42.3	23.1 (15.3)	2.3 (0.6)	72.2 (8.3)	NR	661.3 (216.1)[b]
		Tiotropium 2.5µg daily (Respimat) n=257	43.0 (12.6)	37.7	21.9 (14.5)	2.3 (0.7)	72.5 (8.0)	NR	662.1 (229.5)[b]
		Placebo n=254	43.0 (13.0)	42.9	22.0 (13.9)	2.3 (0.7)	73.0 (8.4)	NR	675.6 (225.4)[b]
Lee, 2015[120] n=362 RCT- crossover, 15d Unclear	18 years of age and older with symptomatic asthma despite ICS treatment, alone or in combination with LABA or leukotriene modifier	Umeclidinium/fluticasone 15.6/100µg daily (DPI) n=62	47.5 (13.8)	31	<1y=2% 1-4y=13% 5-9y=17% ≥10=69%	1.85 (0.53)	62.3 (10.3)	NR	NR
		Umeclidinium/fluticasone 31.25/100µg daily (DPI) n=60							
		Umeclidinium/fluticasone 62.5/100µg daily (DPI) n=63							
		Umeclidinium/fluticasone 125/100µg daily (DPI) n=58							
		Umeclidinium/fluticasone 250/100µg daily (DPI) n=55							

Study, Year, n, Acronym, Study design, Duration Risk of bias	Study population	Intervention Comparisons	Age (y) [mean (SD)]	Males (%)	Duration of asthma (y) [mean (SD)]	FEV1 (L) [mean (SD)]	FEV1 % predicted (L) [mean (SD)]	Rescue inhaler use (puffs/d) [mean (SD)]	ICS dose during study (µg/d) [mean (SD)]
		Fluticasone 100µg daily (DPI) n=64							
Ohta, 2015[121] n=285 RCT, 52w Low	18-75 years of age with moderate-severe asthma according to GINA guidelines despite receiving stable medium-dose ICS (400-800µg/d of budesonide or equivalent) alone or fixed combination with LABA, symptomatic with ACQ-7 ≥1.5 Randomized therapy was added to continued background ICS dose with or without LABA[d]	Tiotropium 2.5µg daily (Respimat) n=114	44.7 (12.1)	36.8	21.0 (0.8 to 57.8)[e]	NR	NR	NR	673.2 (247.4)[b,f]
		Tiotropium 5µg daily (Respimat) n=114	42.6 (12.8)	42.1	21.0 (0.3 to 54.0)[e]	NR	NR	NR	658.9 (220.5)[b,f]
		Placebo N=57	47.8 (13.0)	33.3	26.8 (0.8 to 63.0)[e]	NR	NR	NR	644.2 (220.9)[b,f]
Hammelmann, 2016[123] RubaTinA-asthma n=397 RCT, 48w Low	12-17 years of age with moderate symptomatic asthma with an ACQ ≥1.5 receiving maintenance therapy with ICS with or without LABA or LTRA Randomized therapy was added on to maintenance ICS dose with or without LTRA[g]	Tiotropium 5µg daily (Respimat) n=134	14.5 (1.6)	66.4	8.2 (4.2)	2.6 (0.6)	77.3 (8.6)	NR	536 (256)[b,f]
		Tiotropium 2.5µg daily (Respimat) n=125	14.2 (1.8)	64.8	7.7 (4.0)	2.5 (0.6)	78.1 (7.9)	NR	557 (346)[b,f]
		Placebo n=138	14.2 (1.7)	63.8	7.7 (4.2)	2.6 (0.6)	77.6 (7.5)	NR	527 (275)[b,f]

Study, Year, n, Acronym, Study design, Duration Risk of bias	Study population	Intervention Comparisons	Age (y) [mean (SD)]	Males (%)	Duration of asthma (y) [mean (SD)]	FEV1 (L) [mean (SD)]	FEV1 % predicted (L) [mean (SD)]	Rescue inhaler use (puffs/d) [mean (SD)]	ICS dose during study (µg/d) [mean (SD)]
Paggiaro, 2016[122] GraziaTinA-asthma n=464 RCT, 12w Low	18-75 years of age with mild symptomatic asthma with an ACQ ≥1.5 despite receiving maintenance therapy with low-moderate ICS (200-400µg/d budesonide or equivalent) that is GINA step 2 Randomized therapy was added on to continued low-medium ICS dose	Tiotropium 5µg daily (Respimat) n=155	41.9 (13.0)	38.1	15.2 (10.2)	2.3 (0.6)	74.9 (8.1)	NR	376.9 (59.7)[b,f]
		Tiotropium 2.5µg daily (Respimat) n=154	43.8 (14.0)	46.8	17.1 (13.0)	2.3 (0.7)	73.2 (8.6)	NR	384.4 (93.4)[b,f]
		Placebo n=155	42.8 (12.1)	33.5	16.2 (12.3)	2.2 (0.6)	73.7 (8.5)	NR	383.0 (77.1)[b,f]

ACQ=Asthma Control Questionnaire; BID=twice daily; d=day(s); DPI=dry powder inhaler; FEV1=forced expiratory volume in one second; GINA=Global Initiative for Asthma; ICS=inhaled corticosteroid; L=liter; LABA=long-acting ß-agonist; LTRA=leukotriene receptor antagonist; MDI=metered dose inhaler; n=patient sample size; NR=not reported; RCT=randomized controlled trial; SD=standard deviation; w=weeks; y=years

[a]Concurrent therapy during the study with leukotriene modifiers was 11.7% in the tiotropium 5µg daily arm, 8.8% in the tiotropium 2.5µg daily arm, 10.9% in the salmeterol 50µg BID arm and 10.8% in the placebo arm

[b]Data at baseline, randomized treatments were add-on to continued use of ICS

[c]Concurrent therapy during the study with leukotriene modifiers was 7.1% in the tiotropium 5µg daily arm, 9.7% in the tiotropium 2.5µg daily arm, 8.3% in the salmeterol 50µg BID arm and 7.5% in the placebo arm

[d]Concurrent therapies during the study in the tiotropium 2.5µg daily arm included LABAs (54.4%), leukotriene modifiers (31.6%) and methylxanthines (22.8%). Concurrent therapies during the study in the tiotropium 5µg daily arm included LABAs (57.0%), leukotriene modifiers (25.4%) and methylxanthines (16.7%). Concurrent therapies during the study in the placebo arm included LABAs (61.4%), leukotriene modifiers (24.6%) and methylxanthines (17.5%).

[e]Data reported as median (range)

[f]Budesonide equipotent dose in µg

[g]Concurrent therapy during the study with leukotriene modifiers was 11.2% in the tiotropium 5µg daily arm, 6.4% in the tiotropium 2.5µg daily arm and 10.1% in the placebo arm

Table C-22. Study level outcomes for KQ2a

Study, Year, n, Study design, Duration	Population[a]	Exacerbations	Mortality	Asthma control	Quality of life	Healthcare utilization
Peters, 2010[27] n=210 RCT-crossover, 14w	***Age**:* 12y+ ***Severity/control**:* Moderately severe/ not well controlled[b] ***ICS daily dose:*** Low vs. medium	Systemic corticosteroids: RR 0.48 (0.12 to 1.84) Oral corticosteroids or increase in ICS or other asthma medications: RR 0.32 (0.09 to 1.13)	NR	***Composite measures***: ACQ-6: MD -0.15 (-0.45 to 0.15) ***Spirometry:***: FEV1 trough: MD 0.09 (-0.20 to 0.38)	AQLQ: MD 0.04 (-0.32 to 0.40)	NR
Bateman, 2011[118] n=388 RCT, 16w	***Age**:* 12y+ ***Severity/control**:* Moderate persistent/ not controlled[c] ***ICS daily dose:*** Low to medium	Systemic corticosteroids: RR 0.93 (0.49 to 1.75)	NR	***Composite measures***: NR ***Spirometry:***: FEV1 trough: MD 0.15 (0.07 to 0.23) FVC trough: MD 0.14 (0.04 to 0.23)	AQLQ-mini: MD -0.091 (-0.265 to 0.082)	Rescue medication use: MD -0.37 (-0.90 to 0.16)
Kerstjens, 2015[119] Study 1 n=1071 RCT, 24w	***Age**:* 12y+ ***Severity/control**:* Moderate persistent/ uncontrolled[d] ***ICS daily dose:*** Low to medium	Systemic corticosteroids: RR 0.62 (0.42 to 0.92)[e] Asthma worsening: RR 0.79 (0.67 to 0.94)[e]	All-cause: No deaths occurred	***Composite measures***: ACQ-7 score: MD -0.21 (-0.30 to -0.12) ACQ-7 responder: RR 1.21 (1.07 to 1.38) ***Spirometry:***: FEV1 peak: MD 0.22 (0.17 to 0.27) FEV1 trough: MD 0.17 (0.11 to 0.22) FEV1 AUC: MD 0.21 (0.16 to 0.26) FVC peak: MD 0.14 (0.09 to 0.19) FVC trough: MD 0.10 (0.04 to 0.16) FVC AUC: MD 0.13 (0.08 to 0.19)	AQLQ: MD 0.07 (-0.06 to 0.2)	Rescue medication use: MD -0.01 (-0.26 to 0.23)

Study, Year, n, Study design, Duration	Population[a]	Exacerbations	Mortality	Asthma control	Quality of life	Healthcare utilization
Kerstjens, 2015[119] Study 2 n=1032 RCT, 24w	***Age**:* 12y+ ***Severity/ control**:* Moderate persistent/ uncontrolled[d] ***ICS daily dose:*** Low to medium	Systemic corticosteroids: RR 0.62 (0.42 to 0.92)[e] Asthma worsening: RR 0.79 (0.67 to 0.94)[e]	All-cause: No deaths occurred	***Composite measures***: ACQ-7 score: MD -0.07 (-0.16 to 0.02) ACQ-7 responder: RR 1.03 (0.92 to 1.15) ***Spirometry:***: FEV1 peak: MD 0.19 (0.15 to 0.24) FEV1 trough: MD 0.16 (0.10 to 0.21) FEV1 AUC: MD 0.18 (0.14 to 0.23) FVC peak: MD 0.10 (0.05 to 0.15) FVC trough: MD 0.08 (0.02 to 0.15) FVC AUC: MD 0.10 (0.04 to 0.16)	AQLQ: MD 0.11 (-0.03 to 0.25)	Rescue medication use: MD -0.03 (-0.25 to 0.19)
Lee, 2015[120] n=421 RCT-crossover, 15d	***Age**:* 12y+ ***Severity/control***: Not reported/ uncontrolled[f] ***ICS daily dose:*** Low	Systemic corticosteroids: RR 0.64 (0.07 to 6.09)	All-cause: No deaths occurred	***Composite measures***: NR ***Spirometry:***: FEV1 trough: MD 0.11 (0.01 TO 0.21)	NR	Rescue medication use: MD -0.29 (-0.69 to 0.10)
Ohta, 2015[121] n=285 RCT, 52w	***Age***: 12y+ ***Severity/ control***: Moderate-severe/ uncontrolled[d] ***ICS daily dose:*** Low to medium	NR	All-cause: No deaths occurred	***Composite measures***: ACQ-7 responder: RR 0.98 (0.83 to 1.16) ***Spirometry:***: FEV1 trough: MD 0.06 (-0.02 to 0.15) FVC trough: MD 0.02 (-0.07 to 0.12)	NR	Rescue medication use: MD -0.01 (-0.26 to 0.25)

Study, Year, n, Study design, Duration	Population[a]	Exacerbations	Mortality	Asthma control	Quality of life	Healthcare utilization
Hammel-mann, 2016[123] n=398 RCT, 48w	***Age****:* 12y+ ***Severity/ control****:* Moderate/ uncontrolled[d] ***ICS daily dose:*** Low to medium	Systemic corticosteroids: RR 0.41 (0.16 to 1.09) Asthma worsening: RR 0.92 (0.65 to 1.31)	All-cause: No deaths occurred	***Composite measures***: ACQ-7: MD -0.17 (-0.30 to -0.04) ACQ-7 responder: RR 1.16 (1.02 to 1.31) ***Spirometry:***: FEV1 peak: MD 0.16 (0.06 to 0.25) FEV1 trough: MD 0.10 (0.00 to 0.20) FEV1 AUC: MD 0.16 (0.07 to 0.24) FVC peak: MD 0.08 (-0.02 to 0.18) FVC trough: MD 0.05 (-0.06 to 0.16) FVC AUC: MD 0.08 (-0.02 to 0.18)	AQLQ(S) 12+ responder: RR 1.12 (0.92 to 1.37)	Rescue medication use: MD -0.29 (-0.53 to -0.05)
Paggiaro, 2016[122] n=465 RCT, 12w	***Age****:* 12y+ ***Severity/ control***: Mild/uncontrolled[d] ***ICS daily dose:*** Low	Systemic corticosteroid: RR 0.88 (0.26 to 2.95) Asthma worsening: RR 0.78 (0.47 to 1.28)	All-cause: No deaths occurred	***Composite measures***: ACQ-7: MD 0.03 (-0.07 to 0.14) ACQ-7 responder: RR 1.00 (0.86 to 1.18) ***Spirometry:***: FEV1 peak: MD 0.14 (0.08 to 0.21) FEV1 trough: MD 0.12 (0.05 to 0.18) FEV1 AUC: MD 0.14 (0.08 to 0.20) FEV1 % predicted: MD 3.5 (1.58 to 5.42)	NR	Rescue medication use: MD 0.09 (-0.13 to 0.32)

Abbreviations: ACQ=Asthma Control Questionnaire; AQLQ=Asthma Quality of Life Questionnaire; AUC=area under the curve; d=days; FEV1=forced expiratory volume in one second; FVC=forced vital capacity; EPR-3=Expert Panel Review-3 (guidelines for the diagnosis and management of asthma); ICS=inhaled corticosteroid; MD=mean difference; n=patient sample size; NR=not reported; RCT=randomized controlled trial; RR=relative risk; w=weeks

[a]Age is categorized using study inclusion criteria and the age categories used in EPR-3 of 0-4y, 5-11y and 12y+. Severity is as reported per the study. Control was not always explicitly stated thus study criteria were applied to EPR-3 categories of control to determine asthma control status. ICS daily dose is categorized using the study's required ICS dose and the EPR-3 categories of low, medium and high

[b]Defined as reported in the study, FEV1% predicted 70% or less or during final 2 week run-in symptoms 6 or more days per week or rescue inhaler used 6 or more days per week or were awakened by symptoms of asthma 2 nights or more per week.

[c]Defined as reported in the study, symptoms not well controlled on ICS alone
[d]Required ACQ≥1.5 for enrollment
[e]Outcome was not reported for study 1 and 2 separately, value reflects data from study 1 and 2 combined
[f]Patients were required to be symptomatic on ICS with FEV1% predicted 40-80% after run-in

Table C-23. Subgroup analysis by tiotropium dose for KQ2a

	Tiotropium vs. placebo RR or MD (95% CI) (base case analysis)	Tiotropium 2.5µg vs. placebo RR or MD (95% CI)	Tiotropium 5µg vs. placebo RR or MD (95% CI)	Tiotropium 2.5µg vs. 5µg RR or MD (95% CI)
Exacerbation requiring systemic corticosteroid	RR 0.67 (0.48 to 0.92)	RR 0.63 (0.20 to 2.04)	RR 0.69 (0.32 to 1.47)	RR 1.70 (0.11 to 25.55)
Asthma worsening	RR 0.81 (0.68 to 0.97)	RR 0.82 (0.49 to 1.38)	RR 0.85 (0.63 to 1.15)	RR 1.08 (0.45 to 2.57)
ACQ-7 score	MD -0.10 (-0.28 to 0.07)	MD -0.12 (-0.35 to 0.11)	MD -0.09 (-0.23 to 0.06)	MD -0.03 (-0.16 to 0.10)
ACQ-7 responder	RR 1.08 (0.96 to 1.21)	RR 1.08 (0.98 to 1.20)	RR 1.08 (0.95 to 1.24)	RR 0.99 (0.92 to 1.07)
FEV1 peak	MD 0.18 (0.13 to 0.24)	MD 0.20 (0.13 to 0.27)	MD 0.17 (0.13 to 0.21)	MD 0.03 (-0.01 to 0.07)
FEV1 trough	MD 0.13 (0.10 to 0.17)	MD 0.12 (0.03 to 0.21)	MD 0.13 (0.12 to 0.15)	MD -0.01 (-0.08 to 0.06)
FEV1 AUC	MD 0.18 (0.13 to 0.23)	MD 0.19 (0.12 to 0.25)	MD 0.17 (0.12 to 0.21)	MD 0.02 (-0.02 to 0.07)
FVC peak	MD 0.11 (0.05 to 0.18)	MD 0.13 (0.03 to 0.24)	MD 0.09 (0.06 to 0.12)	MD 0.04 (-0.04 to 0.12)
FVC trough	MD 0.08 (0.04 to 0.13)	MD 0.07 (-0.04 to 0.18)	MD 0.08 (0.05 to 0.12)	MD -0.01 (-0.13 to 0.11)
FVC AUC	MD 0.11 (0.05 to 0.17)	MD 0.13 (0.04 to 0.21)	MD 0.09 (0.05 to 0.13)	MD 0.03 (-0.02 to 0.08)
Rescue medication use, puffs/24 hours	MD -0.08 (-0.23 to 0.07)	MD -0.09 (-0.34 to 0.16)	MD -0.03 (-0.22 to 0.16)	MD -0.08 (-0.37 to 0.20)

Abbreviations: ACQ=Asthma Control Questionnaire; AUC=area under curve; CI=confidence interval; FVC=forced vital capacity; FEV1=forced expiratory volume in one second; MD=mean difference; RR=relative risk

Table C-24. Study and population characteristics for KQ2b

Study, Year, n, Acronym, Study design, Duration, Risk of bias	Study population	Intervention Comparisons	Age (y) [mean (SD)]	Males (%)	Duration of asthma (yr) [mean (SD)]	FEV_1 (L) [mean (SD)]	FEV_1 % predicted (L) [mean (SD)]	Rescue inhaler use (puffs/d) [mean (SD)]	ICS dose during study (µg/d) [mean (SD)]
Peters, 2010[27] TALC n=210 RCT- crossover, 14w Low	≥18 years of age with moderately severe asthma not well controlled on ICS alone Tiotropium or salmeterol were added on to run-in dose of beclomethasone 80µg BID	Tiotropium 18µg daily (Handihaler) n=210	42.2 (12.3)	32.9	26.1 (14.1)	2.31 (0.77)	71.5 (14.9)	1.71 (2.09)	NR
		Salmeterol 50µg BID (DPI) n=210							NR
Bateman, 2011[118] n=262 RCT, 16w Low	18-65 years of age with moderate persistent asthma (GINA step 3) not controlled on ICS alone (400-1000µg/d budesonide or equivalent) Randomized therapy added on to ICS continued at prestudy dose	Tiotropium 5µg daily (Respimat) n=128	43.5 (12.6)	35.9	18.1 (12.1)	2.3 (0.77)	74.1 (16.1)	NR	NR
		Salmeterol 50µg BID (MDI) n=134	42.3 (13.4)	38.1	15.4 (10.7)	2.4 (0.8)	75.6 (17.6)	NR	NR
Rajanandh, 2014[146] n=123 RCT, 90d High	18-60 years of age with uncontrolled, mild to moderate persistent asthma according to the GINA guidelines[a]	Tiotropium 18µg daily (HandiHaler) + budesonide 400µg daily n=31	40.4 (13.6)	64.5	5.4 (2.7)	NR	66.9 (1.7)	NR	NR
		Formoterol 6µg BID + budesonide 400µg daily n=32	37.2 (14.9)	56.3	5.6 (2.7)	NR	66.6 (2.0)	NR	NR
		Doxofylline 400mg daily + budesonide 400µg daily n=30	37.1 (18.8)	36.7	5.2 (2.7)	NR	66.8 (1.5)	NR	NR

Study, Year, n, Acronym, Study design, Duration, Risk of bias	Study population	Intervention Comparisons	Age (y) [mean (SD)]	Males (%)	Duration of asthma (yr) [mean (SD)]	FEV_1 (L) [mean (SD)]	FEV_1 % predicted (L) [mean (SD)]	Rescue inhaler use (puffs/d) [mean (SD)]	ICS dose during study (µg/d) [mean (SD)]
		Montelukast 10mg daily + budesonide 400µg daily n=30	39.3 (17.0)	40.0	5.6 (3.0)	NR	67.2 (1.4)	NR	NR
Kerstjens, 2015[119] Study 1 MezzoTinA-asthma 1 n=801 RCT, 24w Low	18-75 year of age with moderate persistent asthma according to GINA guidelines despite treatment with stable medium dose ICS (400-800µg/d budesonide or equivalent) alone or in fixed combination with LABA, symptomatic with ACQ-7 ≥1.5. Randomized therapy was added to prestudy stable maintenance ICS dose[b]	Tiotropium 5µg daily (Respimat) n=264	44.4 (12.6)	41.7	22.9 (14.7)	2.2 (0.6)	72.2 (8.2)	NR	666.4 (216.2)[c]
		Tiotropium 2.5µg daily (Respimat) n=262	43.7 (13.1)	40.5	22.2 (14.1)	2.2 (0.7)	73.1 (8.6)	NR	649.8 (196.2)[c]
		Salmeterol 50µg BID (MDI) n=275	42.6 (12.6)	42.2	21.4 (14.5)	2.3 (0.6)	72.8 (8.5)	NR	656.7 (193.1)[c]
Kerstjens, 2015[119] Study 2 MezzoTinA-asthma 2 n=776 RCT, 24w Low	18-75 year of age with moderate persistent asthma according to GINA guidelines despite treatment with stable medium dose ICS (400-800µg/d budesonide or equivalent) alone or in fixed combination with LABA, symptomatic with ACQ-7 ≥1.5 Randomized therapy was added to prestudy stable maintenance ICS dose[d]	Tiotropium 5µg daily (Respimat) n=253	44.3 (12.7)	42.3	23.1 (15.3)	2.3 (0.6)	72.2 (8.3)	NR	661.3 (216.1)[c]
		Tiotropium 2.5µg daily (Respimat) n=257	43.0 (12.6)	37.7	21.9 (14.5)	2.3 (0.7)	72.5 (8.0)	NR	662.1 (229.5)[c]
		Salmeterol 50µg BID (MDI) n=266	41.5 (13.1)	42.5	20.4 (14.1)	2.4 (0.7)	73.1 (8.1)	NR	644.7 (217.2)[c]

Study, Year, n, Acronym, Study design, Duration, Risk of bias	Study population	Intervention Comparisons	Age (y) [mean (SD)]	Males (%)	Duration of asthma (yr) [mean (SD)]	FEV_1 (L) [mean (SD)]	FEV_1 % predicted (L) [mean (SD)]	Rescue inhaler use (puffs/d) [mean (SD)]	ICS dose during study (µg/d) [mean (SD)]
Lee, 2015[120] n=357 RCT- crossover, 15d Unclear	18 years of age and older with symptomatic asthma despite ICS treatment, alone or in combination with LABA or leukotriene modifier	Umeclidinium/fluticasone 15.6/100µg daily (DPI) n=62	47.5 (13.8)	31	<1y=2% 1-4y=13% 5-9y=17% ≥10=69%	1.85 (0.53)	62.3 (10.3)	NR	NR
		Umeclidinium/fluticasone 31.25/100µg daily (DPI) n=60							
		Umeclidinium/fluticasone 62.5/100µg daily (DPI) n=63							
		Umeclidinium/fluticasone 125/100µg daily (DPI) n=58							
		Umeclidinium/fluticasone 250/100µg daily (DPI) n=55							
		Vilanterol/fluticasone 125/100µg daily (DPI) n=59							
Rajanandh, 2015[147] n=297 RCT, 180d Medium	18-60 years of age with uncontrolled, mild-moderate persistent asthma according to GINA guidelines[a]	Tiotropium 18µg daily (Handihaler) + budesonide 400µg daily n=72	37.4 (13.6)	52.8	5.8 (8.7)	NR	66.1 (6.4)	4.4 (1.1)	NR
		Formoterol 6µg BID + budesonide 400µg daily n=68	38.4 (14.9)	55.4	6.6 (6.7)	NR	66.2 (8.3)	4.4 (1.1)	NR
		Montelukast 10mg daily + budesonide 400µg daily n=81	36.3 (17.0)	44.4	5.9 (8.0)	NR	67.2 (6.5)	4.5 (1.2)	NR
		Doxofylline 400mg daily + budesonide 400µg daily n=76	38.3 (18.8)	53.9	6.2 (9.7)	NR	66.3 (7.0)	4.5 (1.1)	NR

Study, Year, n, Acronym, Study design, Duration, Risk of bias	Study population	Intervention Comparisons	Age (y) [mean (SD)]	Males (%)	Duration of asthma (yr) [mean (SD)]	FEV_1 (L) [mean (SD)]	FEV_1 % predicted (L) [mean (SD)]	Rescue inhaler use (puffs/d) [mean (SD)]	ICS dose during study (µg/d) [mean (SD)]
Wechsler, 2015[148] BELT n=1070 RCT, 18m Low	18-75 years of age with asthma currently on or eligible for step 3 or 4 combination ICS/LABA according to the NHLBI guidelines Randomized therapy was added to continued baseline ICS dose	Tiotropium 18µg daily (HandiHaler) n=532	45.2 (12.6)	23.9	23.3 (15.8)	2.1 (0.7)	78.6 (17.6)	3.4 (3.5)	NR[f]
		LABA BID[e] n=538	45.1 (12.6)	24.2	25.6 (16.0)	2.1 (0.6)	78.7 (18.6)	3.5 (3.7)	NR[f]

Abbreviations: ACQ=Asthma Control Questionnaire; BID=twice daily; d=day; DPI=dry powder inhaler; FEV1=forced expiratory volume in one second; GINA=Global Initiative for Asthma; ICS=inhaled corticosteroid; L=liter; LABA=long-acting β_2-agonist; =months; MDI=metered dose inhaler; n=patient sample size; NHLBI=National Heart, Lung, and Blood Institute; NR=not reported; RCT=randomized controlled trial; SD=standard deviation; µg=microgram; w=week; y=year

[a]Confirmed through author correspondence

[b]Concurrent therapy during the study with leukotriene modifiers was 11.7% in the tiotropium 5µg daily arm, 8.8% in the tiotropium 2.5µg daily arm, 10.9% in the salmeterol 50µg BID arm and 10.8% in the placebo arm

[c]Data at baseline, randomized treatments were add-on to continued use of ICS

[d]Concurrent therapy during the study with leukotriene modifiers was 7.1% in the tiotropium 5µg daily arm, 9.7% in the tiotropium 2.5µg daily arm, 8.3% in the salmeterol 50µg BID arm and 7.5% in the placebo arm

[e]Either salmeterol 50µg or formoterol 9µg BID, based on baseline usage of LABA. 116/538 (21.6%) for formoterol & 422/538 (78.4%) for salmeterol

[f]Mean/median ICS dose was not reported, although patients continued baseline ICS dose. Of those taking an ICS without LABA at baseline (28%), 88% were taking low-dose ICS <500µg. Of those taking ICS+LABA, 70% were using a single inhaler to delivery both medications. Approximately half were taking fluticasone/salmeterol 250/50µg

Table C-25. Study level outcomes for KQ2b

Study, Year, n, Study design, Duration	Population[a]	Exacerbations	Mortality	Asthma control	Quality of life	Healthcare utilization
Peters, 2010[27] n=210 RCT-crossover, 14w	***Age**:* 12y+ ***Severity/control**:* Moderately severe/ not well controlled[b] ***ICS daily dose:*** Low vs. medium	Systemic corticosteroid: RR 0.60 (0.15 to 2.42) Oral corticosteroid or increase in ICS or other asthma medication: RR 0.60 (0.15 to 2.42)	NR	***Composite measures***: ACQ-6: MD 0.30 (0.00 to 0.60) ***Spirometry:***: FEV1 trough: MD 0.12 (-0.15 to 0.39)	AQLQ: MD -0.22 (-0.60 to 0.16)	NR
Bateman, 2011[118] n=388 RCT, 16w	***Age**:* 12y+ ***Severity/control**:* Moderate persistent/ not controlled[c] ***ICS daily dose:*** Low to medium	Systemic corticosteroid: RR 0.99 (0.52 to 1.87)	NR	***Composite measures***: NR ***Spirometry:***: FEV1 trough: MD -0.02 (-0.10 to 0.06) FVC trough: MD 0.01 (-0.08 to 0.11)	AQLQ-mini: MD -0.149 (-0.320 to 0.222)	Rescue medication use: MD 0.20 (-0.32 to 0.72)
Rajanandh, 2014[146] n=167 RCT, 90d	***Age**:* 12y+ ***Severity/control**:* Mild to moderate persistent/ uncontrolled[d] ***ICS daily dose:*** Low to medium	NR	NR	***Composite measures***: NR ***Spirometry:***: FEV1 % predicted: LAMA vs. LABA: MD -7.34 (-8.30 to -6.38) LAMA vs. montelukast: MD -2.14 (-2.93 to -1.35) LAMA vs. doxofylline: MD -3.87 (-4.6 to -3.14)	NR	Rescue medication use: LAMA vs. LABA: MD 1.38 (0.89 to 1.87) LAMA vs. montelukast: MD 0.26 (-0.25 to 0.77) LAMA vs. doxofylline: MD 1.21 (0.89 to 1.53)

Study, Year, n, Study design, Duration	Population[a]	Exacerbations	Mortality	Asthma control	Quality of life	Healthcare utilization
Kerstjens, 2015[119] Study 1 n=1071 RCT, 24w	***Age**:* 12y+ ***Severity/control**:* Moderate persistent/ uncontrolled[e] ***ICS daily dose:*** Low to medium	Systemic corticosteroid: RR 0.81 (0.54 to 1.24)[f] Asthma worsening: RR 1 (0.84 to 1.12)[f]	All-cause: No deaths occurred	***Composite measures***: ACQ-7 score: MD 0.04 (-0.05 to 0.13) ACQ-7 responder: RR 1.06 (0.96 to 1.18) ***Spirometry:***: FEV1 peak: MD 0.004 (-0.05 to 0.05) FEV1 trough: MD 0.05 (-0.01 to 0.10) FEV1 AUC: MD -0.004 (-0.05 to 0.04) FVC peak: MD 0.016 (-0.04 to 0.07) FVC trough: MD 0.03 (-0.03 to 0.10) FVC AUC: MD 0.005 (-0.05 to 0.06)	AQLQ: MD -0.07 (-0.20 to 0.06)	Rescue medication use: MD 0.44 (0.20 to 0.68)
Kerstjens, 2015[119] Study 2 n=1032 RCT, 24w	***Age**:* 12y+ ***Severity/ control**:* Moderate persistent/ uncontrolled[e] ***ICS daily dose:*** Low to medium	Systemic corticosteroid: RR 0.81 (0.54 to 1.24)[f] Asthma worsening: RR 1.00 (0.84 to 1.12)[f]	All-cause: No deaths occurred	***Composite measures***: ACQ-7 score: MD 0 (-0.09 to 0.09) ACQ-7 responder: RR 1.00 (0.90 to 1.12) ***Spirometry:***: FEV1 peak: MD 0.014 (-0.03 to 0.06) FEV1 trough: MD 0.05 (0.00 to 0.10) FEV1 AUC: MD 0.004 (-0.04 to 0.05) FVC peak: MD -0.017 (-0.07 to 0.03) FVC trough: MD 0.02 (-0.05 to 0.08) FVC AUC: MD -0.032 (-0.09 to 0.03)	AQLQ: MD -0.05 (0.18 to 0.08)	Rescue medication use: MD 0.09 (-0.13 to 0.31)

[f]Concurrent therapies during the study in the tiotropium arm included leukotriene modifiers (16.4%), theophylline (14.2%), omalizumab (2.7%), systemic steroids (3.7%) and antihistamines (14.2%). Concurrent therapies during the study in the placebo arm included leukotriene modifiers (19.7%), theophylline (12.8%), omalizumab (6.0%), systemic steroids (5.6%) and antihistamines (8.1%)

[g]Data reported as mean (standard error)

[h]ICS dose assumed due to fixed dosing with add-on therapy (tiotropium arm) or increased dose (salmeterol/fluticasone arm) used in trial

[i]Concurrent therapies during the treatment period in the tiotropium 5µg arm were systemic corticosteroids (3%), short acting anticholinergic (0.8%), long-acting β_2-agonists (82.3%), theophylline (6.2%) and leukotriene modifiers (78.5%). In this arm, 33.1% of patients were on 2 controllers while 66.9% were on three controllers. Concurrent therapies during the treatment period in the tiotropium 2.5µg arm were systemic corticosteroids (0.8%), long-acting β_2-agonists (79.5%), theophylline (4.7%) and leukotriene modifiers (81.9%). In this arm, 33.9% of patients were on 2 controllers while 66.1% were on three controllers. Concurrent therapies during the treatment period in the placebo arm were systemic corticosteroids (1.5%), long-acting β_2-agonists (85.9%), theophylline (5.2%) and leukotriene modifiers (80.7%). In this arm, 28.2% of patients were on 2 controllers while 71.9% were on three controllers

Table C-27. Study level outcomes for KQ2c

Study, Year, n, Study design, Duration	Population[a]	Exacerbations	Mortality	Asthma control	Quality of life	Healthcare utilization
Kerstjens, 2012[150] Study 1 n=459 RCT, 48w	***Age****:* 12y+ ***Severity/control****:* Severe persistent/ uncontrolled[b] ***ICS daily dose:*** Medium to high	Systemic corticosteroid: RR 0.73 (0.54 to 0.99) Asthma worsening: RR 0.79 (0.67 to 0.94) Requiring hospitalization: RR 1.33 (0.54 to 3.32)	All-cause: No deaths occurred	***Composite measures***: ACQ-7 score: MD -0.12 (-0.27 to 0.03) ACQ-7 responder: RR 0.78 (0.68 to 0.88)[c] ACQ-6 responder: OR 1.49 (1.14 to 1.9)[c] ACQ-5 responder: OR 1.42 (1.08 to 1.86)[c] ***Spirometry:***: FEV1 peak: MD 0.07 (0.00 to 0.14) FEV1 trough: MD 0.04 (-0.03 to 0.11) FEV1 AUC: MD 0.07 (0.00 to 0.14) FVC peak: MD 0.12 (0.03 to 0.22) FVC trough: MD 0.11 (0.02 to 0.20) FVC AUC: MD 0.12 (0.04 to 0.21)	AQLQ: MD 0.038 (-0.13 to 0.2) AQLQ responder: RR 1.62 (1.34 to 1.96)[c]	Rescue medication use: MD -0.09 (-0.47 to 0.29)

Study, Year, n, Study design, Duration	Population[a]	Exacerbations	Mortality	Asthma control	Quality of life	Healthcare utilization
Kerstjens, 2012[150] Study 2 n=453 RCT, 48w	***Age***: 12y+ ***Severity /control***: Severe persistent/ uncontrolled[b] ***ICS daily dose:*** Medium to high	Systemic corticosteroid: RR 0.91 (0.70 to 1.19) Asthma worsening: RR 0.79 (0.67 to 0.93) Requiring hospitalization: RR 1.16 (0.47 to 2.89)	All-cause: No deaths occurred	***Composite measures***: ACQ-7 score: MD -0.13 (-0.27 to 0.01) ACQ-7 responder: RR 0.78 (0.68 to 0.88)[c] ACQ-6 responder: OR 1.49 (1.14 to 1.9)[c] ACQ-5 responder: OR 1.42 (1.08 to 1.86)[c] ***Spirometry:***: FEV1 peak: MD 0.15 (0.08 to 0.22) FEV1 trough: MD 0.09 (0.03 to 0.16) FEV1 AUC: MD 0.14 (0.07 to 0.20) FVC peak: MD 0.12 (0.02 to 0.21) FVC trough: MD 0.07 (-0.02 to 0.16) FVC AUC: MD 0.11 (0.02 to 0.20)	AQLQ: MD 0.14 (-0.03 to 0.31) AQLQ responder: RR 1.62 (1.34 to 1.96)[c]	Rescue medication use: MD -0.26 (-0.71 to 0.18)
Wang, 2015[151] n=63 RCT, 12w	***Age***: 12y+ ***Severity/ control***: Moderate persistent/ uncontrolled[d] ***ICS daily dose:*** Medium vs. high	NR	NR	***Composite measures***: ACT score: MD -0.61 (-4.82 to 3.6) ***Spirometry:***: NR	NR	NR

Study, Year, n, Study design, Duration	Population[a]	Exacerbations	Mortality	Asthma control	Quality of life	Healthcare utilization
Hamelmann, 2016[152] n=392 RCT, 12w	***Age**:* 12y+ ***Severity/control**:* Severe persistent/ uncontrolled[b] ***ICS daily dose:*** Medium to high	Systemic corticosteroid: RR 1.58 (0.17 to 15.00) Asthma worsening: RR 0.69 (0.43 to 1.12)	All-cause: No deaths occurred	***Composite measures***: ACQ-7 score: MD 0.05 (-0.11 to 0.20) ACQ-7 responder: RR 0.99 (0.88 to 1.12) ACQ-6 score: MD 0.085 (-0.08 to 0.25) ACQ-6 responder: RR 1.00 (0.88 to 1.12) ***Spirometry:*** FEV1 peak: MD 0.10 (-0.01 to 0.21) FEV1 trough: MD 0.08 (-0.03 to 0.20) FEV1 AUC: MD 0.10 (0.00 to 0.20) FVC peak: MD 0.08 (-0.04 to 0.19) FVC trough: MD 0.08 (-0.04 to 0.20) FVC AUC: MD 0.07 (-0.04 to 0.18)	NR	Rescue medication use: MD -0.03 (-0.32 to 0.26)

Abbreviations: ACQ=Asthma Control Questionnaire; ACT=Asthma Control Test; AQLQ=Asthma Quality of Life Questionnaire; AUC=area under the curve; FEV1=forced expiratory volume in one second; FVC=forced vital capacity; EPR=Expert Panel Review (Guidelines for the Diagnosis and Management of Asthma); ICS=inhaled corticosteroid; MD=mean difference; n=patient sample size; NR=not reported; OR=odds ratio; PEF=peak expiratory flow; RCT=randomized controlled trial; RR=relative risk; SABA=short-acting β-agonist; w=weeks

[a]Age is categorized using study inclusion criteria and the age categories used in EPR-3 of 0-4y, 5-11y and 12y+. Severity is as reported per the study. Control was not always explicitly stated thus study criteria were applied to EPR-3 categories of control to determine asthma control status. ICS daily dose is categorized using the study's required ICS dose and the EPR-3 categories of low, medium and high

[b]Required ACQ≥1.5 for enrollment

[c]Outcome was not reported for study 1 and 2 separately, value reflects data from study 1 and 2 combined

[d]Daily symptoms, daily SABA use, FEV1 % predicted or PEF 60-80%

Appendix D. Risk of Bias Assessment

Table D-1. Risk of bias assessment for KQ1a

Study, Year	Sequence Generation	Allocation concealment	Blinding of participants, personnel	Blinding of Outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias	Overall risk of bias
Svedmyr, 1999[48]	Unclear	Unclear	Unclear	Unclear	High	Unclear	Low	Unclear
Ghirga, 2002[46]	Unclear	Unclear	High	High	Low	Unclear	Low	Medium
Bacharier, 2008[44]	Low	Low	Low	Low	Low	Unclear	Low	Low
Ducharme, 2009[45]	Low	Low	Low	Low	High	Low	Low	Low
Papi, 2009[47]	Unclear	Unclear	Low	Low	Low	Low	Low	Low
Zeiger, 2011[49]	Low	Low	Low	Low	Low	Low	Low	Low

Table D-2. Risk of bias assessment for KQ1b

Study, Year	Sequence Generation	Allocation concealment	Blinding of participants, personnel	Blinding of Outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias	Overall risk of bias
Lahdensuo, 1996[59]	Low	Low	Unclear	Unclear	Low	Unclear[a]	Low	Medium
Foresi, 2000[48]	Unclear	Unclear	Unclear	Unclear	Low	Unclear[a]	Low	Unclear
Colland, 2004[46]	Unclear	Unclear	Unclear	Unclear	Low	Unclear[a]	Low	Unclear
FitzGerald, 2004[47]	Low	Unclear	Low	Low	High	Unclear[a]	Low	Low
Harrison, 2004[51]	Low	Low	Low	Low	Low	Unclear[a]	Low	Low
Boushey, 2005[43]	Low	Unclear	Low	Low	Low	Unclear[a]	Low	Low
Papi, 2007[55]	Low	Low	Low	Low	Low	Low	Low	Low
Turpeinen, 2007[56]	Low	Unclear	Low	Low	Low	Unclear[a]	Low	Low
Oborne, 2009[58]	Low	Low	Low	Low	Low	Low	Low	Low
Martinez, 2011[52]	Low	Low	Low	Low	Low	Low[b]	Low	Low
Calhoun, 2012[44]	Unclear	Low	Low	Low	Low	Low	Low	Low

[a]Endpoints are not specified as pre-planned, and could not identify published protocol (or clinicaltrials.gov)
[b]All outcomes awarded a "Yes" with the exception of Asthma Control Test, which is listed as an endpoint on clinicaltrials.gov but results on this outcome is not reported (unclear)

Table D-3. Risk of bias assessment for KQ1c, ICS and LABA controller and quick relief vs. ICS controller (same dose)

Study, Year	Sequence Generation	Allocation concealment	Blinding of participants, personnel	Blinding of Outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias	Overall risk of bias
Scicchitano, 2004[88]	Low	Low	Low	Low	Low	Unclear[a]	Low	Low
Rabe, 2006[86]	Unclear	Unclear	Low	Low	Low	Unclear[a]	Low	Low
Sovani, 2008[91]	Low	Low	High	High	High	Unclear[a]	Low	High

[a]Endpoints are not specified as pre-planned, and could not identify published protocol (or clinicaltrials.gov)

Table D-4. Risk of bias assessment for KQ1c, ICS and LABA controller and quick relief vs. ICS controller (higher dose)

Study, Year	Sequence Generation	Allocation concealment	Blinding of participants, personnel	Blinding of Outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias	Overall risk of bias
O'Byrne, 2005[75]	Low	Unclear	Low	Low	Low	Low	Low	Low

Table D-5. Risk of bias assessment for KQ1c, ICS and LABA controller and quick relief vs. ICS and LABA controller (same dose)

Study, Year	Sequence Generation	Allocation concealment	Blinding of participants, personnel	Blinding of Outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias	Overall risk of bias
O'Byrne, 2005[75]	Low	Unclear	Low	Low	Low	Low	Low	Low
Vogelmeier, 2005[96]	Low	Low	High	High	Low	Unclear[a]	Low	Medium[b]
Rabe, 2006[85]	Low	Low	Low	Low	Low	Unclear[c]	Low	Low
Atienza, 2013[62]	Low	Low	Low	Low	Low	Low	Low	Low
Papi, 2013[76]	Low	Low	Unclear	Unclear	Low	Low	Low	Low
Patel, 2013[78]	Low	Low	High	High	Low	Low	Low	Medium[b]
Hozawa, 2014[70]	Unclear	Unclear	High	High	Low	Unclear[c]	Low	Medium
Takeyama, 2014[93]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear[c]	Low	Unclear
Stallberg, 2008[92]	Low	Low	High	High	Low	Low	Low	Medium

[a]All outcomes were awarded an "unclear" with the exception of exacerbations, which is listed as being determined a priori (yes)
[b]All outcomes were awarded "medium" with the exception of death (low)
[c]Endpoints are not specified as pre-planned, and could not identify published protocol (or clinicaltrials.gov)

Table D-6. Risk of bias assessment for KQ1c, ICS and LABA controller and quick relief vs. ICS and LABA controller (higher dose)

Study, Year	Sequence Generation	Allocation concealment	Blinding of participants, personnel	Blinding of Outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias	Overall risk of bias
Bousquet, 2007[68]	Low	Low	Low	Low	Low	Low	Low	Low
Kuna, 2007[73]	Low	Low	Low	Low	Low	Unclear[a]	Low	Low
Pavord, 2009[81]	Low	Unclear	Low	Low	Low	Low	Low	Low
Lundborg, 2006[107]	Low	Unclear	High	High	Low	Unclear[a]	Low	Medium
Stallberg, 2008[92]	Low	Low	High	High	Low	Low	Low	Medium

[a]Endpoints are not specified as pre-planned, and could not identify published protocol (or clinicaltrials.gov)

Table D-7. Risk of bias assessment for KQ1c, ICS and LABA controller and quick relief vs. ICS and LABA controller (lower dose)

Study, Year	Sequence Generation	Allocation concealment	Blinding of participants, personnel	Blinding of Outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias	Overall risk of bias
Hozawa, 2016[xx]	Unclear	Unclear	High	High	Low	Unclear[a]	Low	Medium

[a]Endpoints are not specified as pre-planned, and could not identify published protocol (or clinicaltrials.gov)

Table D-8. Risk of bias assessment for KQ1c, ICS and LABA controller and quick relief vs. CBP

Study, Year	Sequence Generation	Allocation concealment	Blinding of participants, personnel	Blinding of Outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias	Overall risk of bias
Sears, 2008[89]	Unclear	Unclear	High	High	Low	Low	Low	Medium[a]
Stallberg, 2008[92]	Low	Low	High	High	Low	Low	Low	Medium
Louis, 2009[74]	Unclear	Unclear	High	High	Low	Low[b]	Low	Medium[a]
Quirce, 2011[83]	Unclear	Unclear	High	High	Low	Unclear[c]	Low	Medium[a]
Soes-Peterson, 2011[90]	Unclear	Unclear	High	High	Low	Low	Low	Medium[a]
Riemersma, 2012[87]	Unclear	Unclear	High	High	Low	Low	Low	Medium

[a]All outcomes were awarded "medium" with the exception of death (low)

[b]All outcomes awarded a "yes," with the exception of the Asthma Control Questionnaire and forced expiratory volume. These were reported but not specified as endpoints on clinicaltrials.gov (unclear)
[c]There is inconsistency between original and current secondary outcomes on clinicaltrials.gov (unclear). The primary endpoint is reported consistently across original and current secondary outcomes on clinicaltrials.gov (yes)

Table D-9. Risk of bias assessment for non-randomized studies, KQ1c

Study, Year	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study	Comparability of cohorts	Assessment of outcome	Follow-up long enough	Adequacy of follow-up of cohorts	Overall risk of bias
Loh, 2008[106]	Low	Low	Low	N/A	High[a]	Low	Low	Low	Medium
Kardos, 2013[71]	Low	Low	Low	N/A	Low[b]	Medium	Low	Low	Low

[a]No information about matching of patient cohorts either for inclusion or analysis
[b]Cohorts controlled/matched for analysis, but not inclusion

Table D-10. Risk of bias assessment for KQ2a

Study, Year	Sequence Generation	Allocation concealment	Blinding of participants, personnel	Blinding of Outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias	Overall risk of bias
Peters, 2010[19]	Unclear	Unclear	Low	Low	Low	Low	Low	Low
Bateman, 2011[108]	Low	Low	Low	Low	Low	Low	Low	Low
Kerstjens, 2015[109] (Study 1)	Low	Low	Low	Low	Low	Low	Low	Low
Kerstjens, 2015[109] (Study 2)	Low	Low	Low	Low	Low	Low	Low	Low
Lee, 2015[110]	Low	Low	Unclear	Unclear	Low	Low	Low	Unclear
Ohta, 2015[111]	Low	Low	Low	Low	Low	Low[a]	Low	Low
Hamelmann, 2016[113]	Low	Unclear	Low	Low	Low	Low[b]	Low	Low
Paggiaro, 2016[112]	Low	Low	Low	Low	Low	Low	Low	Low

[a]Exacerbations were not reported but are an objective in the clinicaltrials.gov protocol (no)
[b]Spirometry is not reported at the end of the treatment period and there is inconsistency on the timing of spirometry assessment on clinicaltrials.gov (unclear)

Table D-11. Risk of bias assessment for KQ2b

Study, Year	Sequence Generation	Allocation concealment	Blinding of participants, personnel	Blinding of Outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias	Overall risk of bias
Peters, 2010[19]	Unclear	Unclear	Low	Low	Low	Low	Low	Low
Bateman, 2011[108]	Low	Low	Low	Low	Low	Low	Low	Low
Rajanandh, 2014[136]	Low	Low	High	High	High	Unclear[a]	Low	High
Kerstjens, 2015[109] (Study 1)	Low	Low	Low	Low	Low	Low	Low	Low
Kerstjens, 2015[109] (Study 2)	Low	Low	Low	Low	Low	Low	Low	Low
Lee, 2015[110]	Low	Low	Unclear	Unclear	Low	Low	Low	Unclear
Rajanandh, 2015[137]	Low	Low	High	High	Low	Unclear[b]	Low	Medium
Wechsler, 2015[138]	Low	Low	High	Low[c]	Low	Low	Low	Low

[a]Endpoints are not specified as pre-planned, and could not identify published protocol (or clinicaltrials.gov)
[b]Endpoints are not specified as pre-planned, and could not identify published protocol (or clinicaltrials.gov)
[c]Blinded adjudication was used for exacerbation, hospitalization and death endpoints (yes). It is unclear if this blinding was present for the remaining outcomes (unclear)

Table D-12. Risk of bias assessment for KQ2c

Study, Year	Sequence Generation	Allocation concealment	Blinding of participants, personnel	Blinding of Outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias	Overall risk of bias
Kerstjens, 2012[140] (Study 1)	Low	Low	Low	Low	Low	Low	Low	Low
Kerstjens, 2012[140] (Study 2)	Low	Low	Low	Low	Low	Low	Low	Low
Wang, 2015[141]	Unclear	Unclear	Unclear	Unclear	Low	Unclear[a]	Low	Unclear
Hamelmann, 2016[142]	Low	Low	Low	Low	Low	Low	Low	Low

[a]Endpoints are not specified as pre-planned, and no published protocol (or clinicaltrials.gov) is available

Appendix E. Strength of Evidence Assessments

Table E-1. Strength of evidence KQ1a, intermittent ICS with as-needed SABA vs. as-needed SABA

Outcome	N of studies (n of patients)	Study limitations	Consistency	Directness	Precision	Publication bias	Strength of evidence (rational)
Exacerbations							
Requiring oral corticosteroid	3 (324)	Low	Consistent	Direct	Imprecise	Undetected	Moderate (imprecise)
Requiring hospitalization	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Requiring ER visit	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Requiring ICU/ ventilation	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma-related hospitalization	3 (324)	Low	Inconsistent	Direct	Imprecise	Undetected	Low (inconsistent, imprecise)
Asthma-related ER visit	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma-related outpatient visit	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma-related acute care visit	3 (324)	Low	Consistent	Direct	Precise	Undetected	High
Mortality							
All-cause	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma-specific	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma control- composite measures							
ACT	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
ACQ-7 score	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
ACQ-7 responder	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma control- spirometry							
FEV1 peak	0	NA	NA	NA	NA	NA	Insufficient (no evidence)

Outcome	N of studies (n of patients)	Study limitations	Consistency	Directness	Precision	Publication bias	Strength of evidence (rational)
FEV1 trough	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
FEV1 AUC	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
FEV1 % predicted	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
FVC peak	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
FVC trough	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
FVC AUC	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
FEV1/FVC	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Quality of life							
AQLQ score	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
AQLQ responder	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
PACQLQ score	2 (270)	Low	Unknown consistency (single study)	Direct	Imprecise	Undetected	Low (unknown consistency, imprecise)
Healthcare utilization							
Daytime rescue medication use, mean puffs/day	1 (166)	Low	Unknown consistency (single study)	Direct	Precise	Undetected	Low
Nighttime rescue medication use, mean puffs/night	1 (166)	Low	Unknown consistency (single study)	Direct	Precise	Undetected	Low
Resource use	0	NA	NA	NA	NA	NA	Insufficient (no evidence)

Abbreviations: ACQ=Asthma Control Questionnaire; ACT=Asthma Control Test; AQLQ=Asthma Quality of Life Questionnaire; AUC=area under the curve; ER=emergency room; FVC=forced vital capacity; FEV1=forced expiratory volume in one second; ICU=intensive care unit; n=patient sample size; N=number of studies; NA=not applicable; PACQLQ=Pediatric Asthma Caregiver's Quality of Life Questionnaire

Table E-2. Strength of evidence KQ1a, intermittent ICS with as-needed SABA vs. ICS controller with as-needed SABA

Outcome	N of studies (n of patients)	Study limitations	Consistency	Directness	Precision	Publication bias	Strength of evidence (rationale)
Exacerbations							
Requiring oral corticosteroid	1 (278)	Low	Unknown consistency (single study)	Direct	Precise	Undetected	Low (unknown consistency)
Requiring hospitalization	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Requiring ER visit	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Requiring ICU/ ventilation	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma-related hospitalization	1 (278)	Low	Unknown consistency (single study)	Direct	Imprecise	Undetected	Low (unknown consistency, imprecise)
Asthma-related ER visit	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma-related outpatient visit	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma-related acute care visits	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Mortality							
All-cause	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma-specific	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma control-composite measures							
ACT	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
ACQ-7 score	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
ACQ-7 responder	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma control-spirometry							
FEV1 peak	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
FEV1 trough	0	NA	NA	NA	NA	NA	Insufficient (no evidence)

Outcome	N of studies (n of patients)	Study limitations	Consistency	Directness	Precision	Publication bias	Strength of evidence (rationale)
FEV1 AUC	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
FEV1 % predicted	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
FVC peak	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
FVC trough	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
FVC AUC	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
FEV1/FVC	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Quality of life							
AQLQ score	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
AQLQ responder	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
PACQLQ score	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Healthcare utilization							
Daytime rescue medication use, mean puffs/day	1 (220)	Low	Unknown consistency (single study)	Direct	Imprecise	Undetected	Low (unknown consistency, imprecise)
Nighttime rescue medication use, mean puffs/night	1 (220)	Low	Unknown consistency (single study)	Direct	Imprecise	Undetected	Low (unknown consistency, imprecise)
Resource use	0	NA	NA	NA	NA	NA	Insufficient (no evidence)

Abbreviations: ACQ=Asthma Control Questionnaire; ACT=Asthma Control Test; AQLQ=Asthma Quality of Life Questionnaire; AUC=area under the curve; ER=emergency room; FVC=forced vital capacity; FEV1=forced expiratory volume in one second; ICU=intensive care unit; n= patient sample size; N=number of studies; NA=not applicable; PACQLQ=Pediatric Asthma Caregiver's Quality of Life Questionnaire

Table E-3. Strength of evidence KQ1a, intermittent ICS vs. no therapy

Outcome	N of studies (n of patients)	Study limitations	Consistency	Directness	Precision	Publication bias	Strength of evidence
Exacerbations							
Requiring systemic corticosteroid	1 (26)	Low	Unknown consistency (single study)	Direct	Imprecise	Undetected	Insufficient
Requiring hospitalization	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Requiring ED visit	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Requiring ICU/ ventilation	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma-related hospitalization	1 (26)	Low	Unknown consistency (single study)	Direct	Imprecise	Undetected	Insufficient
Asthma-related ER visit	1 (26)	Low	Unknown consistency (single study)	Direct	Imprecise	Undetected	Insufficient
Asthma-related outpatient visit	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma-related acute care visits	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Mortality							
All-cause	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma-specific	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma control-composite measures							
ACT	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
ACQ-7 score	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
ACQ-7 responder	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma control-spirometry							
FEV1 peak	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
FEV1 trough	0	NA	NA	NA	NA	NA	Insufficient (no evidence)

Outcome	N of studies (n of patients)	Study limitations	Consistency	Directness	Precision	Publication bias	Strength of evidence
FEV1 AUC	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
FEV1 % predicted	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
FVC peak	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
FVC trough	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
FVC AUC	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
FEV1/FVC	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Quality of life							
AQLQ score	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
AQLQ responder	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
PACQLQ score	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Healthcare utilization							
Daytime rescue medication use, mean puffs/day	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Nighttime rescue medication use, mean puffs/night	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Resource use	0	NA	NA	NA	NA	NA	Insufficient (no evidence)

Abbreviations: ACQ=Asthma Control Questionnaire; ACT=Asthma Control Test; AQLQ=Asthma Quality of Life Questionnaire; AUC=area under the curve; ER=emergency room; FVC=forced vital capacity; FEV1=forced expiratory volume in one second; ICU=intensive care unit; n= patient sample size; N=number of studies; NA=not applicable; PACQLQ=Pediatric Asthma Caregiver's Quality of Life Questionnaire;

Table E-4. Strength of evidence KQ1b, intermittent ICS and ICS controller vs. ICS controller

Outcome	N of studies (n of patients)	Study limitations	Consistency	Directness	Precision	Publication bias	Strength of evidence
Exacerbations ≥12y							
Requiring oral corticosteroid (full population)	3 (908)	Low	Inconsistent	Direct	Imprecise	Undetected	Low (inconsistent, imprecise)
Requiring oral corticosteroid (of those that started study inhaler)	3 (399)	Low	Inconsistent	Direct	Imprecise	Undetected	Low (inconsistent, imprecise)
Requiring hospitalization	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Requiring ER visit	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Requiring ICU/ ventilation	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Requiring oral corticosteroid, unscheduled doctor visit, ER, or unstable asthma[a]	1 (98)	Low	Unknown (single study)	Direct	Imprecise	Undetected	Low (unknown consistency, imprecise)
Asthma-related hospitalization	1 (115)	Medium	Unknown (single study)	Direct	Imprecise	Undetected	Insufficient (risk of bias, unknonw consistency, imprecise)
Asthma-related ER visits	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma-related outpatient visit	2 (505)	Low	Inconsistent	Direct	Imprecise	Undetected	Low (inconsistent, imprecise)
Asthma-related acute care visit	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Unstable asthma[a]	1 (98)	Low	Unknown (single study)	Direct	Imprecise	Undetected	Low (unknown consistency, imprecise)
2 or 3 exacerbations requiring oral corticosteroid (full population)	1 (403)	Low	Unknown (single study)	Direct	Imprecise	Undetected	Low (unknown consistency, imprecise)

Outcome	N of studies (n of patients)	Study limitations	Consistency	Directness	Precision	Publication bias	Strength of evidence
2 or 3 exacerbations requiring oral corticosteroid (of those starting the study inhaler)	1 (403)	Low	Unknown (single study)	Direct	Imprecise	Undetected	Low (unknown consistency, imprecise)
Fall in PEF <70% from baseline	1 (134)	Unclear	Unknown (single study)	Direct	Imprecise	Undeteced	Low (unknown consistency, imprecise)
Exacerbations 4 to 11y							
Requiring oral corticosteroid	1 (143)	Low	Unknown (single study)	Indirect	Imprecise	Undetected	Insufficient (unknonw consistency, indirect)
Requiring hospitalization	1 (29)	Unclear	Unknown (single study)	Direct	Imprecise	Undetected	Insufficient (unknonw consistency, imprecise)
Asthma-related hospitalization	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma-related ER visit	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma-related hospitalization or ER visit	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma-related outpatient visit	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Treatment failure[b]	1 (143)	Low	Unknown (single study)	Indirect	Imprecise	Undetected	Insufficient (unknonw consistency, indirect, imprecise)
Mortality							
All-cause	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma-specific	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma control-composite measures							

Outcome	N of studies (n of patients)	Study limitations	Consistency	Directness	Precision	Publication bias	Strength of evidence
ACT	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
ACQ-7 score	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
ACQ-7 responder	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma control-spirometry ≥12y							
FEV1 peak	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
FEV1 trough	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
FEV1 AUC	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
FEV1 % predicted	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
FVC peak	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
FVC trough	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
FVC AUC	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
FEV1/FVC	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma control-spirometry 4 to 11y							
FEV1 % predicted	1 (29)	Unclear	Unknown (single study)	Direct	Imprecise	Undetected	Insufficient (Unclear ROB, unknown consistency, imprecise)
Quality of life ≥12y							
AQLQ score	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
AQLQ responder	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
PACQLQ score	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Quality of life 4 to 11y							

Outcome	N of studies (n of patients)	Study limitations	Consistency	Directness	Precision	Publication bias	Strength of evidence
PAQLQ score	1 (143)	Low	Unknown (single study)	Indirect	Precise	Undetected	Low (unknown consistency, indirect)
Healthcare utilization ≥12y							
Daytime rescue medication use mean puffs /day	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Nighttime rescue medication use mean puffs /night	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Resource use	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Healthcare utilization 4 to 11y							
Albuterol puffs/ day	1 (143)	Low	Unknown (single study)	Indirect	Imprecise	Undetected	Insufficient (unknonw consistency, indirect, imprecise)

Abbreviations: ACQ=Asthma Control Questionnaire; ACT=Asthma Control Test; AQLQ=Asthma Quality of Life Questionnaire; AUC=area under the curve; ER=emergency room; FVC=forced vital capacity; FEV1=forced expiratory volume in one second; ICU=intensive care unit; n= patient sample size; N=number of studies; NA=not applicable; PACQLQ=Pediatric Asthma Caregiver's Quality of Life Questionnaire; PAQLQ=Pediatric Asthma Quality of Life Questionnaire; y=years

[a]Defined as absence of stability, where stability was defined as morning peak expiratory flow 90% or more of mean baseline value on either of the two previous days, <4 inhalations of inhaled corticosteroid per day over the past 2 days, no nocturnal awakenings in the prior 2 nights and a total symptom score not exceeding mean baseline value more than 2 ordinal values over the previous 2 days

[b]Defined as any of following: (1) Hospitalization due to asthma; (2) Hypoxic seizure due to asthma; (3) Intubation due to asthma; (4) Requirement for a second burst of prednisone within any 6 months period; (5) Significant adverse event related to the use of a study medication. The only criterion for assignment of treatment failure during the trial was the requirement for a second burst of prednisone within any 6 month period

Table E-4. Strength of evidence KQ1b, intermittent ICS vs. ICS controller

Outcome	N of studies (n of patients)	Study limitations	Consistency	Directness	Precision	Publication bias	Strength of evidence
Exacerbations ≥12y							
Requiring oral corticosteroid	1 (149)	Low	Unknown (single study)	Direct	Imprecise	Undetected	Low (unknown consistency, imprecise)
Requiring hospitalization	1 (149)	Low	Unknown (single study)	Direct	Precise	Undetected	Insufficient (no events occurred)
Requiring ER visit	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Requiring ICU/ ventilation	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma-related hospitalization	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma-related ER visit	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma-related outpatient visit	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma-related urgent care visit	1 (227)	Low	Unknown (single study)	Direct	Imprecise	Undetected	Low (unknown consistency, imprecise)
Mild[c] or severe[d] exacerbation	1 (228)	Low	Unknown (single study)	Direct	Imprecise	Undetected	Low (unknown consistency, imprecise)
Severe exacerbation[d]	1 (228)	Low	Unknown (single study)	Direct	Imprecise	Undetected	Low (unknown consistency, imprecise)
Exacerbations 4 to 11y							
Requiring oral corticosteroid	1 (143)	Low	Unknown (single study)	Indirect	Imprecise	Undetected	Insufficient (unknown consistency, indirect, imprecise)
Treatment failure[a]	1 (143)	Low	Unknown (single study)	Indirect	Imprecise	Undetected	Insufficient (unknown consistency, indirect, imprecise)
Mortality							

Outcome	N of studies (n of patients)	Study limitations	Consistency	Directness	Precision	Publication bias	Strength of evidence
All-cause mortality	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma-specific death	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma control-composite measures							
ACT	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
ACQ-7 score	1 (149)	Low	Unknown (single study)	Direct	Precise	Undetected	Low (unknown consistency)
ACQ-7 responder	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
ACQ-5 score	1 (227)	Low	Unknown (single study)	Direct	Precise	Undetected	Low (unknown consistency)
ACQ-5 responder	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma control-spirometry ≥12y							
FEV1 peak	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
FEV1 trough	2 (564)	Low	Consistent	Direct	Precise	Undetected	High
FEV1 AUC	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
FEV1 % predicted	3 (713)	Low	Consistent	Direct	Imprecise	Undetected	Moderate (imprecise)
FVC peak	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
FVC trough	1 (228)	Low	Unknown (single study)	Direct	Precise	Undetected	Low (unknonw consistency)
FVC AUC	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
FEV1/FVC	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
FVC % predicted	1 (228)	Low	Unknown (single study)	Direct	Imprecise	Undetected	Low (unknown consistenct, imprecsie)

Outcome	N of studies (n of patients)	Study limitations	Consistency	Directness	Precision	Publication bias	Strength of evidence
Asthma control-spirometry 4 to 11y							
FEV1 % predicted	1 (143)	Low	Unknown (single study)	Indirect	Imprecise	Undetected	Insufficient (unknown consistency, indirect, imprecise)
Quality of life ≥12y							
AQLQ score	2 (376)	Low	Inconsistent	Direct	Precise	Undetected	Moderate (inconsistent)
AQLQ responder	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
PACQLQ score	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Quality of life 4 to 11y							
PAQLQ score	1 (143)	Low	Unknown (single study)	Indirect	Precise	Undetected	Low (unknown consistency, indirect)
Healthcare utilization ≥12y							
Albuterol puffs/day	2 (564)	Low	Consistent	Direct	Imprecise	Undetected	Moderate (imprecise)
Resource use	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Healthcare utilization 4 to 11y							
Albuterol puffs/day	1 (143)	Low	Unknown (single study)	Indirect	Precise	Undetected	Low

Abbreviations: ACQ=Asthma Control Questionnaire; ACT=Asthma Control Test; AQLQ=Asthma Quality of Life Questionnaire; AUC=area under the curve; ER=emergency room; FVC=forced vital capacity; FEV1=forced expiratory volume in one second; ICU=intensive care unit; n= patient sample size; N=number of studies; NA=not applicable; PACQLQ=Pediatric Asthma Caregiver's Quality of Life Questionnaire; PAQLQ=Pediatric Asthma Quality of Life Questionnaire; y=years

[a]Defined as any of following: (1) Hospitalization due to asthma; (2) Hypoxic seizure due to asthma; (3) Intubation due to asthma; (4) Requirement for a second burst of prednisone within any 6 months period; (5) Significant adverse event related to the use of a study medication. The only criterion for assignment of treatment failure during the trial was the requirement for a second burst of prednisone within any 6 month period

[c]Defined as awakening at night owing to asthma or as a decrease in the morning peak expiratory flow rate to more than 20% below the baseline value, the use of more than three additional puffs per day of rescue medication (either albuterol or beclomethasone and albuterol) as compared with during the baseline for 2 or more consecutive days, or both. Single, isolated days on which mild exacerbation occurred were not counted

[d]Defined as a decrease in the morning peak expiratory flow rate to more than 30% below the baseline value on 2 consecutive days or more than 8 puffs per day of rescue medication for 3 consecutive days or the need for treatment with oral corticosteroids, as judged by the investigator

Table E-5. Strength of evidence KQ1c, ICS and LABA controller and quick relief vs. ICS controller (same dose)

Outcome	N of studies (n of patients)	Risk of bias	Consistency	Directness	Precision	Publication bias	Strength of evidence
Exacerbations							
Requiring systemic corticosteroid	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Requiring hospitalization	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Requiring ER visit	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Requiring ICU/ ventilation	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma-related hospitalization	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma-related ER visit	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma-related hospitalization or ER visit	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma-related outpatient visit	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Requiring systemic corticosteroid, hospitalization, or ER visit	1 (1890)	Low	Unknown (single study)	Direct	Precise	Undetected	Moderate (unknown consistency)
Requiring systemic corticosteroid, hospitalization, ER visit, or PEF<70%	2 (2586)	Low	Consistent	Direct	Imprecise	Undetected	Moderate (imprecise)
Mortality							
All-cause	1 (1890)	Low	Unknown (single study)	Direct	Imprecise	Undetected	Insufficient (unknown consistency, imprecise)
Asthma-specific	1 (1890)	Low	Consistent	Direct	Precise	Undetected	Insufficient (no events occurred)
Asthma control-composite measures							
ACT	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
ACQ-5 score	0	NA	NA	NA	NA	NA	Insufficient (no evidence)

Outcome	N of studies (n of patients)	Risk of bias	Consistency	Directness	Precision	Publication bias	Strength of evidence
ACQ-5 responder	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma control-spirometry							
FEV1	1 (1890)	Low	Unknown (single study)	Direct	Precise	Undetected	Moderate (unknown consistency)
FEV1 % predicted	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
FVC	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
FEV1/ FVC	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Quality of Life							
AQLQ score	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
AQLQ responder	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Healthcare Utilization							
Mean PRN inhalations/ day	1 (697)	Low	Unknown (single study)	Direct	Imprecise	Undetected	Low (unknown consistency, imprecise)
Mean PRN inhalations/ week	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Resource use	0	NA	NA	NA	NA	NA	Insufficient (no evidence)

Abbreviations: ACQ=Asthma Control Questionnaire; ACT=Asthma Control Test; AQLQ=Asthma Quality of Life Questionnaire; ER=emergency room; FVC=forced vital capacity; FEV1=forced expiratory volume in one second; ICU=intensive care unit; n=patient sample size; N=number of studies; NA=not applicable; PRN=pro re nata (i.e., as-needed

Table E-6. Strength of evidence KQ1c, ICS and LABA controller and quick relief vs. ICS controller (higher dose)

Outcome	N of studies (n of patients)	Risk of bias	Consistency	Directness	Precision	Publication bias	Strength of evidence
Exacerbations ≥12 years							
Requiring systemic corticosteroid	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Requiring hospitalization	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Requiring ED visit	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Requiring ICU/ ventilation	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Requiring systemic corticosteroid, hospitalization, ER visit, or PEF<70% (increase in ICS or other medication as well for 4 to 11 year olds)	1 (1851)	Low	Unknown (single study)	Indirect	Precise	Undetected	Low (unknown consistency, indirect)
Requiring systemic corticosteroids, hospitalization, or ER visit (increase in ICS or other medication as well for 4 to 11 year olds)	1 (1851)	Low	Unknown (single study)	Indirect	Precise	Undetected	Low (unknown consistency, indirect)
Asthma-related hospitalization	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma-related ER visit	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma-related hospitalization or ER visit	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma-related outpatient visit	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Exacerbations 4 to 11 years							
Requiring systemic corticosteroid, hospitalization, ER visit, increase in ICS or other medication, or PEF <70%	1 (224)	Low	Unknown (single study)	Indirect	Imprecise	Undetected	Low (unknown consistency, indirect)
Requiring systemic corticosteroid, hospitalization, or ER visit	1 (224)	Low	Unknown (single study)	Indirect	Imprecise	Undetected	Low (unknown consistency, indirect)

Outcome	N of studies (n of patients)	Risk of bias	Consistency	Directness	Precision	Publication bias	Strength of evidence
Asthma-related hospitalization	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma-related ER visit	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma-related hospitalization or ER visit	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma-related outpatient visit	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Mild exacerbation	1 (224)	Low	Unknown (single study)	Indirect	Precise	Undetected	Low (unknown consistency, indirect)
Mortality							
All-cause	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma-specific	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma control-composite measures							
ACT	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
ACQ-5 score	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
ACQ-5 responder	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma control-spirometry							
FEV1	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
FEV1 % predicted	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
FVC	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
FEV1/ FVC	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Quality of Life							
AQLQ score	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
AQLQ responder	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Healthcare utilization							

Outcome	N of studies (n of patients)	Risk of bias	Consistency	Directness	Precision	Publication bias	Strength of evidence
Mean PRN inhalations/ day	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Mean PRN inhalations/ week	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Resource use	0	NA	NA	NA	NA	NA	Insufficient (no evidence)

Abbreviations: ACQ=Asthma Control Questionnaire; ACT=Asthma Control Test; AQLQ=Asthma Quality of Life Questionnaire; ER=emergency room; FVC=forced vital capacity; FEV1=forced expiratory volume in one second; ICU=intensive care unit; n=patient sample size; N=number of studies; NA=not applicable; PRN=pro re nata (i.e., as-needed)

Table E-7. Strength of evidence KQ1c, ICS and LABA controller and quick relief vs. ICS and LABA controller (same dose)

Outcome	N of studies (n of patients)	Risk of bias	Consistency	Directness	Precision	Publication bias	Strength of evidence
Exacerbations ≥12y							
Requiring systemic corticosteroid	2 (3792)	Low	Consistent	Direct	Precise	Undetected	High
Requiring hospitalization	2 (2224)	Low	Inconsistent	Direct	Imprecise	Undetected	Low (inconsistent, imprecise)
Requiring ER visit	1 (2091)	Low	Unknown (single study)	Direct	Precise	Undetected	Moderate (unknown consistency)
Requiring ICU/ ventilation	1 (1701)	Low	Unknown (single study)	Direct	Precise	Undetected	Insufficient (no events occurred)
Requiring systemic corticosteroid, hospitalization, or ER visit	5 (8483)	Low	Consistent	Direct	Precise	Undetected	High
Requiring hospitalization or ER visit	5 (8313)	Low	Consistent	Direct	Precise	Undetected	High
Asthma-related outpatient visits	0	NA	NA	NA	NA	NA	Insufficient (no data)
Requiring systemic corticosteroid, hospitalization, ER visit, or unscheduled visit	1 (2143)	Medium	Unknown (single study)	Direct	Precise	Undetected	Moderate (unknown consistency)
Mild exacerbation	3 (6037)	Low	Inconsistent	Direct	Precise	Undetected	Moderate (unknown consistency)
Exacerbations 4 to 11y							

Outcome	N of studies (n of patients)	Risk of bias	Consistency	Directness	Precision	Publication bias	Strength of evidence
Requiring systemic corticosteroid, hospitalization, ER visit, increase in ICS or other medication, or PEF <70%	1 (341)	Low	Unknown (single study)	Indirect	Precise	Undetected	Low (unknown consistency, indirect)
Exacerbations requiring hospitalization, systemic corticosteroids, ER, or increase in ICS or other medications	1 (341)	Low	Unknown (single study)	Indirect	Precise	Undetected	Low (unknown consistency, indirect)
Mild exacerbations	1 (341)	Low	Unknown (single study)	Indirect	Precise	Undetected	Low (unknown consistency, indirect)
Mortality ≥12y							
All-cause	4 (6782)	Low	Consistent	Direct	Imprecise	Undetected	Moderate (imprecise)
Asthma-specific	4 (6782)	Low	Consistent	Direct	Precise	Undetected	Insufficient (no events occurred)
Asthma control-composite measures ≥ 12y							
ACT	1 (63)	Unclear	Unknown (single study)	Direct	Precise	Undetected	Insufficient (unknown consistency)
ACQ-5 score	3 (4353)	Low	Inconsistent	Direct	Imprecise	Undetected	Low (inconsistent, imprecise)
ACQ-5 responder	1 (2091)	Low	Unknown (single study)	Direct	Precise	Undetected	Moderate (unknown consistency)
Asthma control-spirometry ≥12y							
FEV1	5 (6343)	Low	Inconsistent	Direct	Imprecise	Undetected	Low (inconsistent, imprecise)
FEV1 % predicted	2 (304)	Medium	Consistent	Direct	Precise	Undetected	Moderate (risk of bias)

Outcome	N of studies (n of patients)	Risk of bias	Consistency	Directness	Precision	Publication bias	Strength of evidence
FVC	1 (1701)	Low	Unknown (single study)	Direct	Imprecise	Undetected	Low (unknown consistency, imprecise)
FEV1/ FVC	0	NA	NA	NA	NA	NA	Insufficient (no data)
Quality of life ≥12y							
AQLQ score	0	NA	NA	NA	NA	NA	Insufficient (no data)
AQLQ responder	0	NA	NA	NA	NA	NA	Insufficient (no data)
Healthcare utilization ≥12y							
Mean PRN inhalations/ day	3 (6006)	Low	Inconsistent	Direct	Imprecise	Undetected	Low (inconsistent, imprecise)
Mean PRN inhalations/ week	2 (93)	Medium	Consistent	Direct	Imprecise	Undetected	Low (risk of bias, imprecise)
Resource use	0	NA	NA	NA	NA	NA	Insufficient (no data)

Abbreviations: ACQ=Asthma Control Questionnaire; ACT=Asthma Control Test; AQLQ=Asthma Quality of Life Questionnaire; ER=emergency room; FVC=forced vital capacity; FEV1=forced expiratory volume in one second; ICS=inhaled corticosteroid; ICU=intensive care unit; n= patient sample size; N=number of studies; NA=not applicable; PEF=peak expiratory flow; PRN=pro re nata (i.e., as-needed); y=year

Table E-8. Strength of evidence KQ1c, ICS and LABA controller and quick relief vs. ICS and LABA controller (higher dose)

Outcome	N of studies (n of patients)	Risk of bias	Consistency	Directness	Precision	Publication bias	Strength of evidence
Exacerbations							
Requiring systemic corticosteroid	1 (2304)	Low	Unknown (single study)	Direct	Precise	Undetected	Moderate (unknown consistency)
Requiring hospitalization	0	NA	NA	NA	NA	NA	Insufficient (no data)
Requiring ER visit	0	NA	NA	NA	NA	NA	Insufficient (no data)
Requiring ICU/ ventilation	0	NA	NA	NA	NA	NA	Insufficient (no data)
Asthma-related hospitalization	0	NA	NA	NA	NA	NA	Insufficient (no data)
Asthma-related ER visit	0	NA	NA	NA	NA	NA	Insufficient (no data)
Asthma-related outpatient visit	0	NA	NA	NA	NA	NA	Insufficient (no data)
Requiring systemic corticosteroid, hospitalization, or ER visit	3 (6742)	Low	Consistent	Direct	Precise	Undetected	High
Requiring hospitalization or ER visit	3 (6742)	Low	Consistent	Direct	Imprecise	Undetected	Moderate (imprecise)
Mild exacerbation	2 (3321)	Low	Unknown[a]	Direct	Precise	Undetected	Moderate (unknown consistency)
Mortality							
All-cause	4 (5757)	Low	Consistent	Direct	Imprecise	Undetected	Moderate (imprecise)
Asthma-specific	4 (5757)	Low	Consistent	Direct	Precise	Undetected	Insufficient (no events occurred)
Asthma control-composite measures							
ACT	0	NA	NA	NA	NA	NA	Insufficient (no data)
ACQ-5 score	3 (6559)	Low	Consistent	Direct	Precise	Undetected	High

Outcome	N of studies (n of patients)	Risk of bias	Consistency	Directness	Precision	Publication bias	Strength of evidence
ACQ-5 responder	0	NA	NA	NA	NA	NA	Insufficient (no data)
Asthma control-spirometry							
FEV1	2 (4424)	Low	Unknown[a]	Direct	Precise	Undetected	Moderate (unknown consistency)
FVC	0	NA	NA	NA	NA	NA	Insufficient (no data)
FEV1/FVC	0	NA	NA	NA	NA	NA	Insufficient (no data)
Quality of life							
AQLQ(S) score	2 (4270)	Low	Unknown[a]	Direct	Precise	Undetected	Moderate (unknown consistency)
AQLQ responder	0	NA	NA	NA	NA	NA	Insufficient (no data)
Healthcare utilization							
Mean PRN inhalations/day	3 (6559)	Low	Consistent	Direct	Precise	Undetected	High
Resource use	0	NA	NA	NA	NA	NA	Insufficient (no data)

Abbreviations: ACQ=Asthma Control Questionnaire; ACT=Asthma Control Test; AQLQ=Asthma Quality of Life Questionnaire; AQLQ(S)=standardized Asthma Quality of Life Questionnaire; ER=emergency room; FVC=forced vital capacity; FEV1=forced expiratory volume in one second; ICU=intensive care unit; n=patient sample size; N=number of studies; NA=not applicable; PRN=pro re nata (i.e., as-needed)

[a]A single 3-arm trial contributed two unique comparisons for this outcome. Thus, the consistency with an independent trial population is unknown

Table E-9. Strength of evidence KQ1c, ICS and LABA controller and quick relief vs. ICS and LABA controller (lower dose)

Outcome	N of studies (n of patients)	Risk of bias	Consistency	Directness	Precision	Publication bias	Strength of evidence
Exacerbations							
Requiring systemic corticosteroid	0	NA	NA	NA	NA	NA	Insufficient (no data)
Requiring hospitalization	0	NA	NA	NA	NA	NA	Insufficient (no data)
Requiring ER visit	0	NA	NA	NA	NA	NA	Insufficient (no data)
Requiring ICU/ ventilation	0	NA	NA	NA	NA	NA	Insufficient (no data)
Asthma-related hospitalization	0	NA	NA	NA	NA	NA	Insufficient (no data)

Outcome	N of studies (n of patients)	Risk of bias	Consistency	Directness	Precision	Publication bias	Strength of evidence
Asthma-related ER visit	0	NA	NA	NA	NA	NA	Insufficient (no data)
Asthma-related outpatient visit	0	NA	NA	NA	NA	NA	Insufficient (no data)
Mortality							
All-cause	0	NA	NA	NA	NA	NA	Insufficient (no data)
Asthma-specific	0	NA	NA	NA	NA	NA	Insufficient (no data)
Asthma control-composite measures							
ACT	0	NA	NA	NA	NA	NA	Insufficient (no data)
ACQ-5 score	1 (30)	Medium	Unknown (single study)	Direct	Imprecise	Undetected	Insufficient (risk of bias, unknown consistency, imprecise)
ACQ-5 responder	0	NA	NA	NA	NA	NA	Insufficient (no data)
Asthma control-spirometry							
FEV1 % predicted	1 (30)	Medium	Unknown (single study)	Direct	Precise	Undetected	Insufficient (risk of bias, unknown consistency, imprecise)
FVC	0	NA	NA	NA	NA	NA	Insufficient (no data)
FEV1/FVC	0	NA	NA	NA	NA	NA	Insufficient (no data)
Quality of life							
AQLQ(S) score	0	NA	NA	NA	NA	NA	Insufficient (no data)
AQLQ responder	0	NA	NA	NA	NA	NA	Insufficient (no data)
Healthcare utilization							

Outcome	N of studies (n of patients)	Risk of bias	Consistency	Directness	Precision	Publication bias	Strength of evidence
Mean PRN inhalations/week	1 (30)	Medium	Unknown (single study)	Direct	Imprecise	Undetected	Insufficient (risk of bias, unknown consistency, imprecise)
Resource use	0	NA	NA	NA	NA	NA	Insufficient (no data)

Table E-10. Strength of evidence KQ1c, ICS and LABA controller and quick relief vs. CBP

Outcome	N of studies (n of patients)	Risk of bias	Consistency	Directness	Precision	Publication bias	Strength of evidence
Exacerbations							
Requiring systemic corticosteroid	4 (4935)	Medium	Consistent	Direct	Imprecise	Undetected	Low (risk of bias, imprecise)
Requiring hospitalization	4 (4935)	Medium	Consistent	Direct	Imprecise	Undetected	Low (risk of bias, imprecise)
Requiring ER visit	4 (4935)	Medium	Consistent	Direct	Imprecise	Undetected	Low (risk of bias, imprecise)
Requiring ICU/ ventilation	0	NA	NA	NA	NA	NA	Insufficient (no data)
Asthma-related hospitalization	0	NA	NA	NA	NA	NA	Insufficient (no data)
Asthma-related ER visit	0	NA	NA	NA	NA	NA	Insufficient (no data)
Asthma-related outpatient visit	0	NA	NA	NA	NA	NA	Insufficient (no data)
Requiring systemic corticosteroid, hospitalization, or ER visit	6 (6354)	Medium	Consistent	Direct	Precise	Undetected	Moderate (risk of bias)
Mortality							
All-cause	4 (4935)	Low	Consistent	Direct	Imprecise	Undetected	Moderate (imprecise)
Asthma-specific	4 (4935)	Low	Consistent	Direct	Precise	Undetected	Insufficient (no events occurred)
Asthma control-composite measures							

Outcome	N of studies (n of patients)	Risk of bias	Consistency	Directness	Precision	Publication bias	Strength of evidence
ACT	0	NA	NA	NA	NA	NA	Insufficient (no data)
ACQ-5 score	5 (4996)	Medium	Consistent	Direct	Precise	Undetected	Moderate (risk of bias)
ACQ-5 responder	2 (2166)	Medium	Consistent	Direct	Precise	Undetected	Moderate (risk of bias)
Asthma control-spirometry							
FEV1	1 (271)	Medium	Unknown (single study)	Direct	Precise	Undetected	Low (unknown consistency)
FEV1 % predicted	1 (102)	Medium	Unknown (single study)	Direct	Precise	Undetected	Low (unknown consistency)
FVC	0	NA	NA	NA	NA	NA	Insufficient (no data)
FEV1/ FVC	0	NA	NA	NA	NA	NA	Insufficient (no data)
Quality of life							
AQLQ score	0	NA	NA	NA	NA	NA	Insufficient (no data)
AQLQ responder	0	NA	NA	NA	NA	NA	Insufficient (no data)
Healthcare utilization							
Mean PRN inhalations/ day	2 (2404)	Medium	Consistent	Direct	Precise	Undetected	Moderate (risk of bias)
≥1 day w/PRN inhalation	2 (1562)	Medium	Inconsistent	Direct	Imprecise	Undetected	Low (inconsistent, imprecise)
Resource use	0	NA	NA	NA	NA	NA	Insufficient (no data)

Abbreviations: ACQ=Asthma Control Questionnaire; ACT=Asthma Control Test; AQLQ=Asthma Quality of Life Questionnaire; ER=emergency room; FVC=forced vital capacity; FEV1=forced expiratory volume in one second; ICU=intensive care unit; n= patient sample size; N=number of studies; NA=not applicable; PRN=pro re nata (i.e., as-needed)

Table E-11. Strength of evidence KQ 2a, LAMA as add-on to ICS vs. doubling ICS dose

Outcome	N of studies (n of patients)	Risk of bias	Consistency	Directness	Precision	Publication bias	Strength of evidence
Exacerbations							
Requiring systemic corticosteroid	1 (210)	Low	Unknown (single study)	Direct	Imprecise	Undetected	Low (unknown consistency, imprecise)
Requiring hospitalization	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Requiring ER visit	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Requiring ICU/ ventilation	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma-related hospitalization	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma-related ER visit	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma-related outpatient visit	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma worsening	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Requiring oral corticosteroid or increase in ICS or other asthma medication	1 (210)	Low	Unknown (single study)	Direct	Imprecise	Undetected	Low (unknown consistency, imprecise)
Mortality							
All-cause	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma-specific	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma control-composite measures							
ACT	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
ACQ-6 score	1 (127)	Low	Unknown (single study)	Direct	Precise	Undetected	Low (unknown consistency)
ACQ-6 responder	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma control-spirometry							

Outcome	N of studies (n of patients)	Risk of bias	Consistency	Directness	Precision	Publication bias	Strength of evidence
FEV1 peak	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
FEV1 trough	1 (118)	Low	Unknown (single study)	Direct	Imprecise	Undetected	Low (unknown consistency, imprecise)
FEV1 AUC	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
FEV1 % predicted	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
FVC peak	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
FVC trough	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
FVC AUC	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
FEV1/FVC	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Quality of life							
AQLQ score	1 (122)	Low	Unknown (single study)	Direct	Precise	Undetected	Low (unknown consistency)
AQLQ responder	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Healthcare utilization							
Rescue medication use, puffs/24 hours	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Resource use	0	NA	NA	NA	NA	NA	Insufficient (no evidence)

Abbreviations: ACQ=Asthma Control Questionnaire; ACT=Asthma Control Test; AQLQ=Asthma Quality of Life Questionnaire; AUC=area under curve; ER=emergency room; FVC=forced vital capacity; FEV1=forced expiratory volume in one second; ICS=inhaled corticosteroid; ICU=intensive care unit; n= patient sample size; N=number of studies; NA=not applicable;

Table E-12. Strength of evidence KQ2a, LAMA vs. placebo as add-on to ICS

Outcome	N of studies (n of patients)	Risk of bias	Consistency	Directness	Precision	Publication bias	Strength of evidence
Exacerbations							
Requiring systemic corticosteroid	5 (3036)	Low	Consistent	Direct	Precise	Undetected	High
Requiring hospitalization	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Requiring ED visit	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Requiring ICU/ ventilation	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma-related hospitalization	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma-related ER visit	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma-related outpatient visit	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma worsening	4 (2420)	Low	Consistent	Direct	Precise	Undetected	High
Mortality							
All-cause mortality	6 (3065)	Low	Consistent	Direct	Precise	Undetected	Insufficient (no events occurred)
Asthma-specific deaths	6 (3065)	Low	Consistent	Direct	Precise	Undetected	Insufficient (no events occurred)
Asthma control-composite measures							
ACT	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
ACQ-5 score	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
ACQ-5 responder	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
ACQ-6 score	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
ACQ-6 responder	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
ACQ-7 score	4 (2304)	Low	Inconsistent	Direct	Precise	Undetected	Moderate (inconsistent)
ACQ-7 responder	5 (2680)	Low	Inconsistent	Direct	Precise	Undetected	Moderate (inconsistent)

Outcome	N of studies (n of patients)	Risk of bias	Consistency	Directness	Precision	Publication bias	Strength of evidence
Asthma control-spirometry							
FEV1 peak	4 (2310)	Low	Consistent	Direct	Precise	Undetected	High
FEV1 trough	7 (3173)	Low	Consistent	Direct	Precise	Undetected	High
FEV1 AUC	3 (2310)	Low	Consistent	Direct	Precise	Undetected	High
FEV1 % predicted	1 (457)	Low	Unknown (single study)	Direct	Precise	Undetected	Low (unknown consistency)
FVC peak	3 (1853)	Low	Consistent	Direct	Precise	Undetected	High
FVC trough	5 (2390)	Low	Consistent	Direct	Precise	Undetected	High
FVC AUC	3 1859)	Low	Consistent	Direct	Precise	Undetected	High
FEV1/FVC	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Quality of life							
AQLQ score	2 (1461)	Low	Consistent	Direct	Precise	Undetected	High
AQLQ responder	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
AQLQ-mini score	1 (253)	Low	Unknown (single study)	Direct	Precise	Undetected	Low (unknown consistency)
AQLQ-S 12+ responder	1 (397)	Low	Unknown (single study)	Direct	Precise	Undetected	Low (unknown consistency)
Healthcare utilization							
Rescue medication use, puffs/24 hours	7 (3104)	Low	Inconsistent	Direct	Precise	Undetected	Moderate (inconsistent)
Resource use	0	NA	NA	NA	NA	NA	Insufficient (no evidence)

Abbreviations: ACQ=Asthma Control Questionnaire; ACT=Asthma Control Test; AQLQ=Asthma Quality of Life Questionnaire; AQLQ-S=Standardized Asthma Quality of Life Questionnaire; AUC=area under curve; ER=emergency room; FVC=forced vital capacity; FEV1=forced expiratory volume in one second; ICU=intensive care unit; n= patient sample size; N=number of studies; NA=not applicable

Table E-13. Strength of evidence KQ2b, LAMA vs. LABA as add-on to ICS

Outcome	N of studies (n of patients)	Risk of bias	Consistency	Directness	Precision	Publication bias	Strength of evidence
Exacerbations							
Requiring systemic corticosteroid	4 (2574)	Low	Inconsistent	Direct	Imprecise	Undetected	Low (inconsistent, imprecise)
Requiring hospitalization	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Requiring ER visit	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Requiring ICU/ ventilation	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma-related hospitalization	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma-related ER visit	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma-related outpatient visit	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma worsening	1 (1577)	Low	Unknown (single study)	Direct	Precise	Undetected	Moderate (unknown consistency)
Requiring oral corticosteroid or increase in ICS or other asthma medication	1 (210)	Low	Unknown (single study)	Direct	Imprecise	Undetected	Low (unknown consistency, imprecise)
Mortality							
All-cause	4 (3572)	Low	Inconsistent	Direct	Imprecise	Undetected	Low (inconsistent, imprecise)
Asthma-specific	4 (3572)	Low	Inconsistent	Direct	Imprecise	Undetected	Low (inconsistent, imprecise)
Asthma control-composite measures							
ACT	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
ACQ-5 score	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
ACQ-5 responder	0	NA	NA	NA	NA	NA	Insufficient (no evidence)

Outcome	N of studies (n of patients)	Risk of bias	Consistency	Directness	Precision	Publication bias	Strength of evidence
ACQ-6 score	1 (126)	Low	Unknown (single study)	Direct	Imprecise	Undetected	Low (unknown consistency, imprecise)
ACQ-6 responder	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
ACQ-7 score	2 (1577)	Low	Consistent	Direct	Precise	Undetected	High
ACQ-7 responder	2 (1577)	Low	Consistent	Direct	Precise	Undetected	High
Asthma control-spirometry							
FEV1 peak	2 (1483)	Low	Consistent	Direct	Precise	Undetected	High
FEV1 trough	6 (3261)	Low	Consistent	Direct	Precise	Undetected	High
FEV1 AUC	2 (1483)	Low	Consistent	Direct	Precise	Undetected	High
FEV1 % predicted	3 (542)	Medium	Inconsistent	Direct	Precise	Undetected	Low (risk of bias, inconsistent)
FVC peak	2 (1483)	Low	Consistent	Direct	Precise	Undetected	High
FVC trough	2 (1745)	Low	Consistent	Direct	Precise	Undetected	High
FVC AUC	2 (1483)	Low	Consistent	Direct	Precise	Undetected	High
FEV1/FVC	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Quality of life							
AQLQ score	4 (1982)	Low	Consistent	Direct	Precise	Undetected	High
AQLQ responder	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
AQLQ-mini score	1 (262)	Low	Unknown (single study)	Direct	Precise	Undetected	Low (unknown consistency)
AQLQ-S 12+ responder	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Healthcare utilization							

Outcome	N of studies (n of patients)	Risk of bias	Consistency	Directness	Precision	Publication bias	Strength of evidence
Rescue medication use, puffs/24 hours	7 (2450)	Low	Inconsistent	Direct	Imprecise	Undetected	Low (inconsistent, imprecise)
Resource use	0	NA	NA	NA	NA	NA	Insufficient (no evidence)

Abbreviations: ACQ=Asthma Control Questionnaire; ACT=Asthma Control Test; AQLQ=Asthma Quality of Life Questionnaire; AQLQ-S= Standardized Asthma Quality of Life Questionnaire; AUC=area under curve; ER=emergency room; FVC=forced vital capacity; FEV1=forced expiratory volume in one second; h=hour; ICU=intensive care unit; LAMA=long acting muscarinic antagonist; n= patient sample size; N=number of studies; NA=not applicable

Table E-14. Strength of evidence KQ2a, LAMA vs. controller other than LABA as add-on to ICS

Outcome	N of studies (n of patients)	Study limitations	Consistency	Directness	Precision	Publication bias	Strength of evidence
Exacerbations							
Requiring systemic corticosteroid	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Requiring hospitalization	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Requiring ER visit	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Requiring ICU/ ventilation	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma-related hospitalization	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma-related ER visit	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma-related outpatient visit	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma worsening	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Mortality							
All-cause	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma-specific	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma control-composite measures							
ACT	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
ACQ-5 score	0	NA	NA	NA	NA	NA	Insufficient (no evidence)

Outcome	N of studies (n of patients)	Study limitations	Consistency	Directness	Precision	Publication bias	Strength of evidence
ACQ-5 responder	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
ACQ-6 score	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
ACQ-6 responder	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
ACQ-7 score	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
ACQ-7 responder	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma control-spirometry							
FEV1 peak	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
FEV1 trough	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
FEV1 AUC	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
FEV1 % predicted LAMA vs. montelukast	2 (214)	Medium	Consistent	Direct	Precise	Undetected	Moderate (risk of bias)
FEV1 % predicted LAMA vs. doxofylline	2 (209)	Medium	Consistent	Direct	Precise	Undetected	Moderate (risk of bias)
FVC peak	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
FVC trough	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
FVC AUC	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
FEV1/FVC	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Quality of life							
AQLQ score	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
AQLQ responder	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
AQLQ-mini score	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
AQLQ-S 12+ responder	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Healthcare utilization							

Outcome	N of studies (n of patients)	Study limitations	Consistency	Directness	Precision	Publication bias	Strength of evidence
Rescue medication use, puffs/24 hours LAMA vs. montelukast	2 (214)	Medium	Inconsistent	Direct	Precise	Undetected	Low (risk of bias, inconsistent)
Rescue medication use, puffs/24 hours LAMA vs. doxofylline	2 (209)	Medium	Inconsistent	Direct	Precise	Undetected	Low (risk of bias inconsistent)
Resource use	0	NA	NA	NA	NA	NA	Insufficient (no evidence)

Abbreviations: ACQ=Asthma Control Questionnaire; ACT=Asthma Control Test; AQLQ=Asthma Quality of Life Questionnaire; AQLQ-S= Standardized Asthma Quality of Life Questionnaire; AUC=area under curve; ER=emergency room; FVC=forced vital capacity; FEV1=forced expiratory volume in one second; h=hour; ICU=intensive care unit; LAMA=long acting muscarinic antagonist; n=patient sample size; N=number of studies; NA=not applicable

Table E-15. Strength of evidence KQ2c, LAMA and ICS and LABA vs. ICS and LABA

Outcome	N of studies (n of patients)	Study limitations	Consistency	Directness	Precision	Publication bias	Strength of evidence
Exacerbations							
Requiring systemic corticosteroid	3 (1299)	Low	Consistent	Direct	Imprecise	Undetected	Moderate (imprecise)
Requiring hospitalization	2 (907)	Low	Consistent	Direct	Imprecise	Undetected	Moderate (imprecise)
Requiring ER visit	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Requiring ICU/ ventilation	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma-related hospitalization	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma-related ER visit	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma-related outpatient visit	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Asthma worsening	3 (1299)	Low	Consistent	Direct	Precise	Undetected	High
Mortality							
All-cause	3 (1299)	Low	Consistent	Direct	Precise	Undetected	Insufficient (no events occurred)
Asthma-specific	3 (1299)	Low	Consistent	Direct	Precise	Undetected	Insufficient (no events occurred)
Asthma control-composite measures							

Outcome	N of studies (n of patients)	Study limitations	Consistency	Directness	Precision	Publication bias	Strength of evidence
ACT	1 (63)	Unclear	Unknown (single study)	Direct	Imprecise	Undetected	Low (unknown consistency, imprecise)
ACQ-5 score	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
ACQ-5 responder	1 (907)	Low	Unknown (single study)	Direct	Imprecise	Undetected	Low (unknown consistency, imprecise)
ACQ-6 score	1 (338)	Low	Unknown (single study)	Direct	Precise	Undetected	Low (unknown consistency)
ACQ-6 responder	2 (1299)	Low	Inconsistent	Direct	Imprecise	Undetected	Low (inconsistent, imprecise)
ACQ-7 score	3 (1301)	Low	Inconsistent	Direct	Precise	Undetected	Moderate (inconsistent)
ACQ-7 responder	2 (1299)	Low	Inconsistent	Direct	Precise	Undetected	Moderate (inconsistent)
Asthma control-spirometry							
FEV1 peak	3 (1295)	Low	Inconsistent	Direct	Precise	Undetected	Moderate (inconsistent)
FEV1 trough	3 (1295)	Low	Inconsistent	Direct	Precise	Undetected	Moderate (inconsistent)
FEV1 AUC	3 (1295)	Low	Consistent	Direct	Precise	Undetected	High
FEV1 % predicted	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
FVC peak	3 (1295)	Low	Consistent	Direct	Precise	Undetected	High
FVC trough	3 (1295)	Low	Consistent	Direct	Precise	Undetected	High
FVC AUC	3 (1295)	Low	Consistent	Direct	Precise	Undetected	High
FEV1/FVC	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Quality of life							
AQLQ score	2 (907)	Low	Consistent	Direct	Precise	Undetected	High

Outcome	N of studies (n of patients)	Study limitations	Consistency	Directness	Precision	Publication bias	Strength of evidence
AQLQ responder	1 (907)	Low	Unknown (single study)	Direct	Imprecise	Undetected	Moderate (unknown consistency imprecise)
Healthcare utilization							
Rescue medication use, puffs/24 hours	3 (1302)	Low	Inconsistent	Direct	Precise	Undetected	Moderate (inconsistent)
Resource use	0	NA	NA	NA	NA	NA	Insufficient (no evidence)

Abbreviations: ACQ=Asthma Control Questionnaire; ACT=Asthma Control Test; AQLQ=Asthma Quality of Life Questionnaire; AUC=area under curve; ER=emergency room; FVC=forced vital capacity; FEV1=forced expiratory volume in one second; h=hour; ICU=intensive care unit; n=patient sample size; N=number of studies; NA=not applicable

Appendix F. Forest Plots

Figure F-1. Asthma-related acute care visit: intermittent ICS with as-needed SABA vs. as-needed SABA

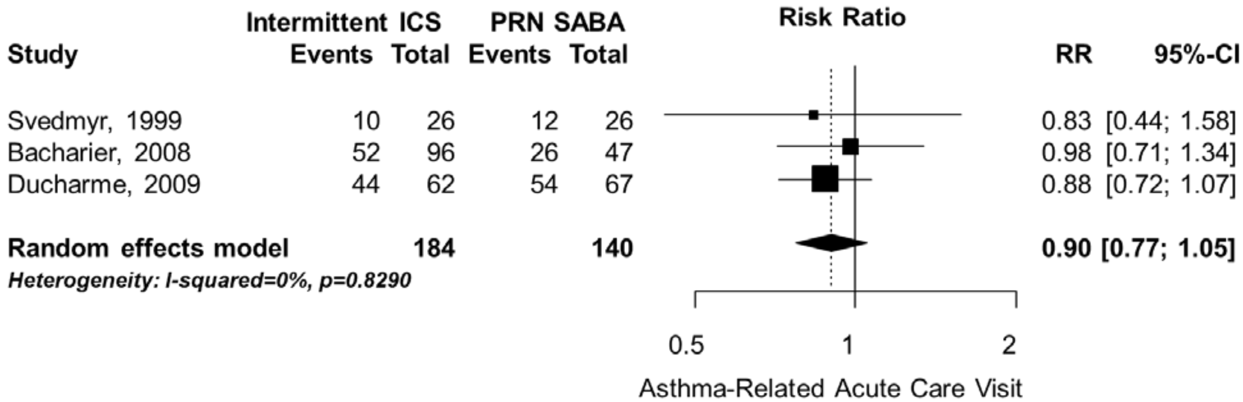

Figure F-2. Hospital admissions due to asthma: intermittent ICS with as-needed SABA vs. as-needed SABA

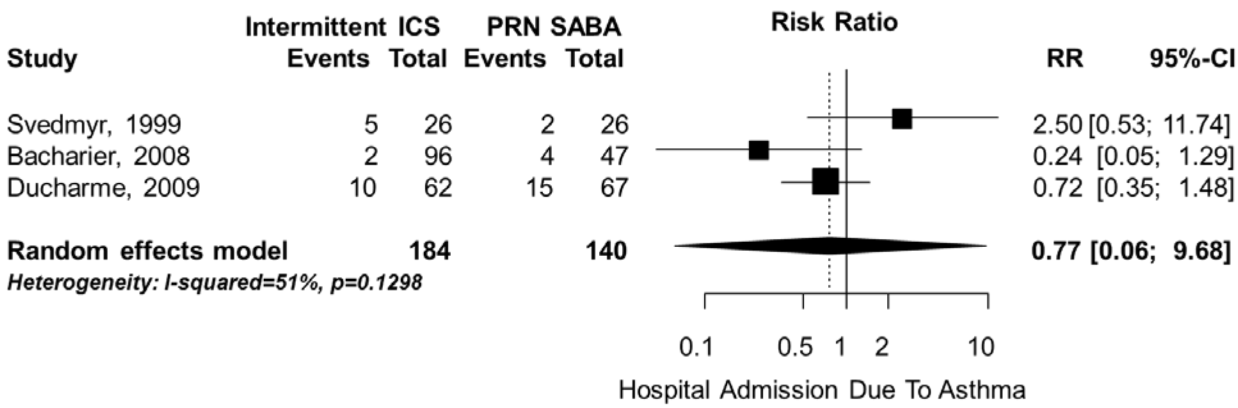

Figure F-3. All-cause death: ICS and LABA controller and quick reliever vs. ICS and LABA controller (same dose)

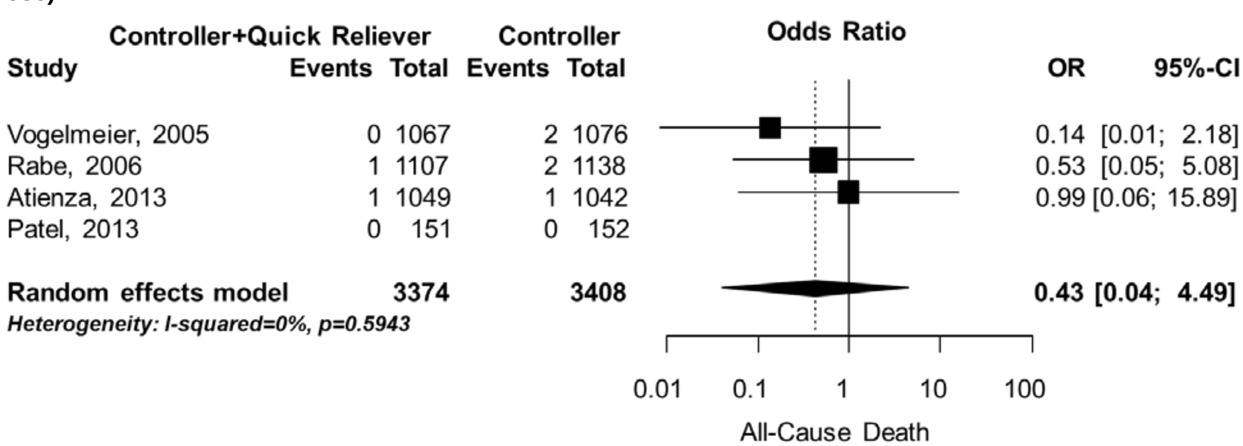

Figure F-4. Change in ACQ-5 mean score from baseline: ICS and LABA controller and quick reliever vs. ICS and LABA controller (same dose)

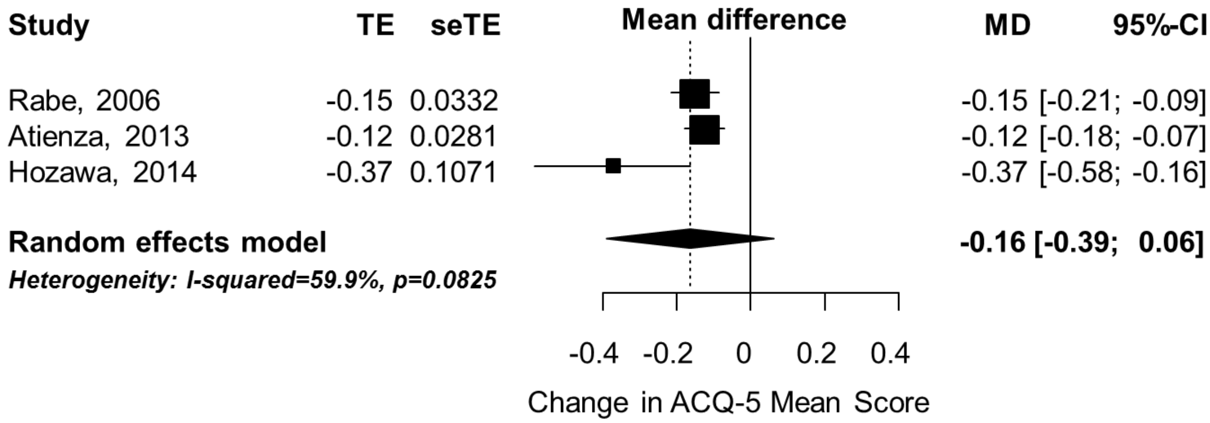

Figure F-5. Change in on-treatment FEV1 from baseline: ICS and LABA controller and quick reliever vs. ICS and LABA controller (same dose)

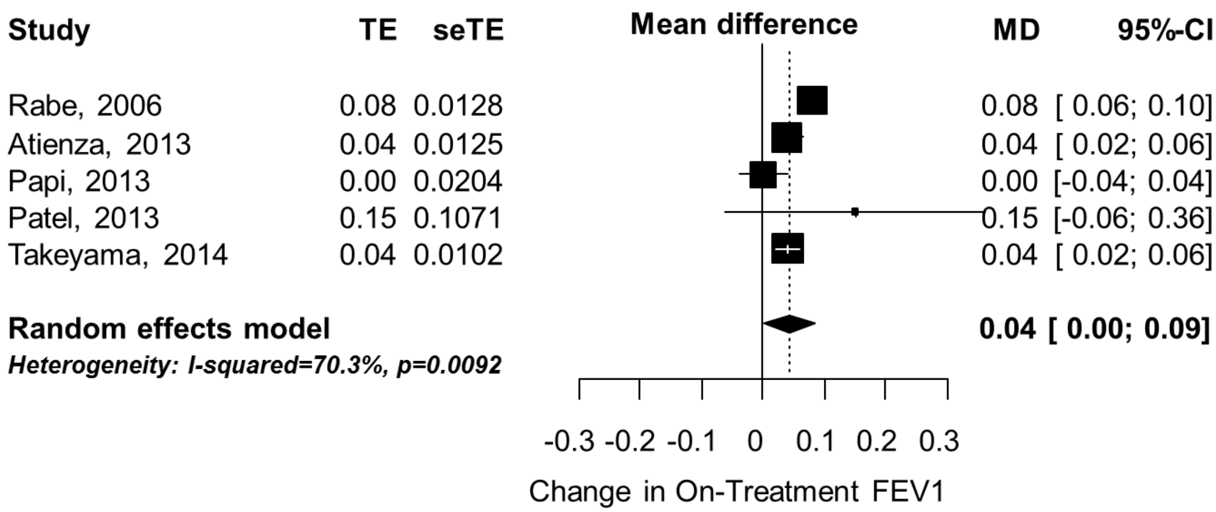

Figure F-6. Change in rescue medication use from baseline, mean inhalations per day: ICS and LABA controller and quick reliever vs. ICS and LABA controller (same dose)

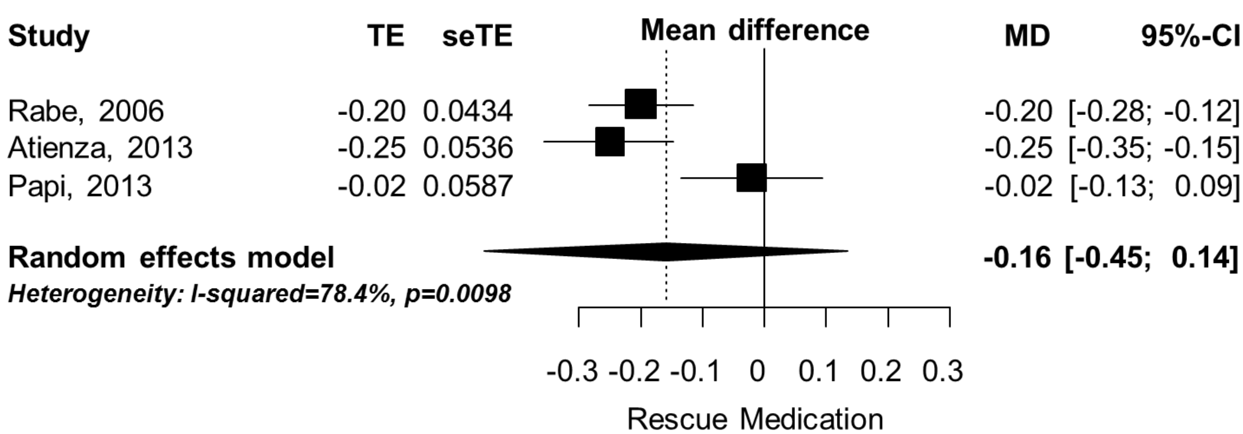

Figure F-7. All-cause death: ICS and LABA controller and quick reliever vs. ICS and LABA controller (higher dose)

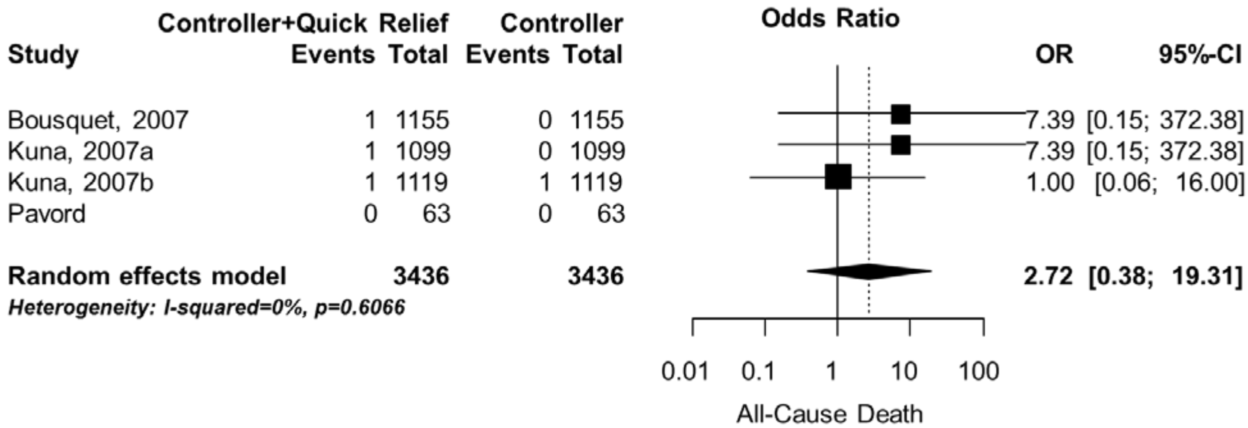

Figure F-8. All-cause death: ICS and LABA controller and quick reliever vs. CBP

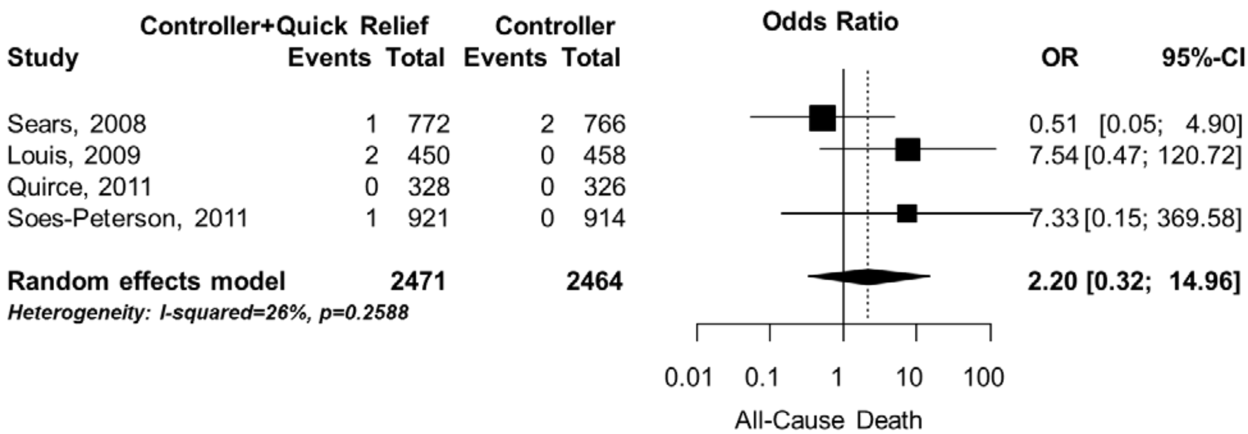

Figure F-9. Change in ACQ-5 mean score from baseline: ICS and LABA controller and quick reliever vs. CBP

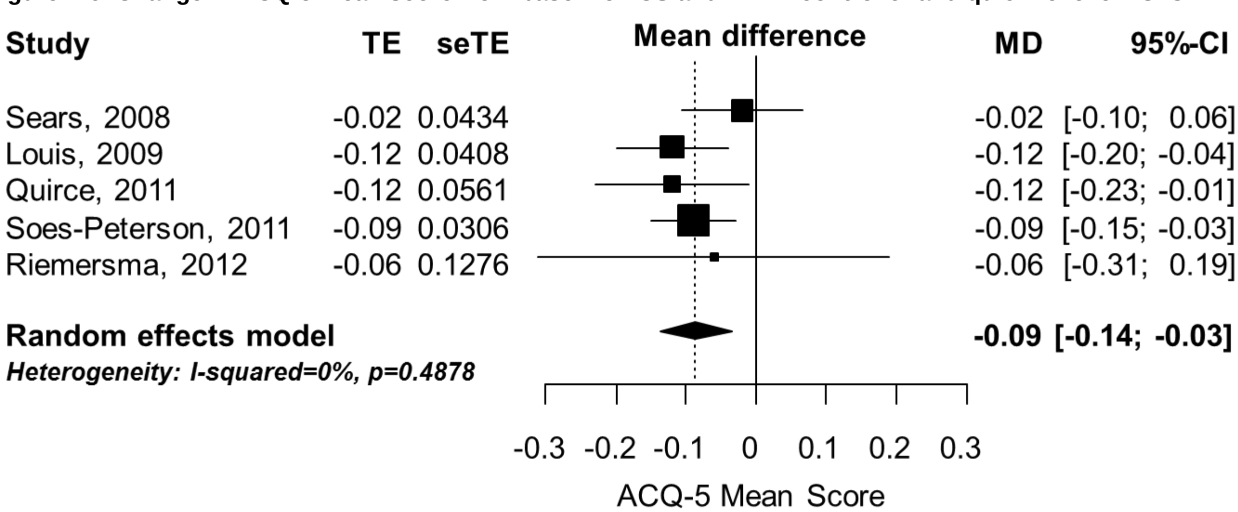

Figure F-10. Change in ACQ-7 score from baseline: LAMA vs. placebo as add-on to ICS

Study	TIO Total	TIO Mean	TIO SD	Placebo Total	Placebo Mean	Placebo SD	MD	95%-CI
Paggiaro, 2016	301	-0.685	0.530	154	-0.72	0.53	0.03	[-0.07; 0.14]
Kerstjens Trial 1, 2015	489	-0.810	0.605	247	-0.60	0.60	-0.21	[-0.30; -0.12]
Kerstjens Trial 2, 2015	485	-0.840	0.556	240	-0.77	0.62	-0.07	[-0.16; 0.02]
Hamelmann, 2016	252	-0.961	0.649	136	-0.79	0.62	-0.17	[-0.30; -0.04]
Random effects model	**1527**			**777**			**-0.10**	**[-0.28; 0.07]**

Heterogeneity: I-squared=78%, p=0.0035

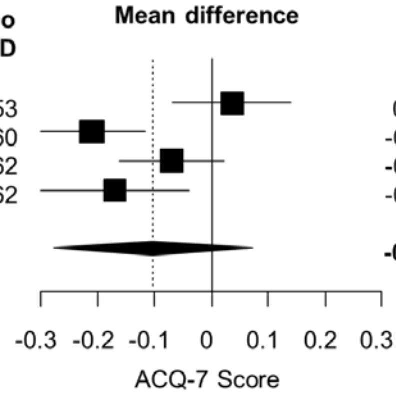

Figure F-11. ACQ-7 responder: LAMA vs. placebo as add-on to ICS

Study	TIO Events	TIO Total	Placebo Events	Placebo Total	RR	95%-CI
Ohta, 2015	168	228	42	56	0.98	[0.83; 1.16]
Paggiaro, 2016	181	301	91	152	1.00	[0.86; 1.18]
Kerstjens Trial 1, 2015	336	520	141	265	1.21	[1.07; 1.38]
Kerstjens Trial 2, 2015	326	508	158	253	1.03	[0.92; 1.15]
Hamelmann, 2016	206	259	95	138	1.16	[1.02; 1.31]
Random effects model		**1816**		**864**	**1.08**	**[0.96; 1.21]**

Heterogeneity: I-squared=41.9%, p=0.1418

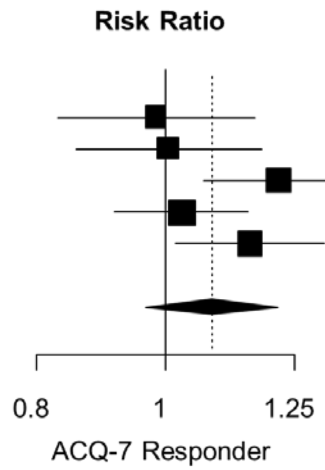

Figure F-12. Change in FEV1 peak from baseline: LAMA vs. placebo as add-on to ICS

Study	TIO Total	TIO Mean	TIO SD	Placebo Total	Placebo Mean	Placebo SD	MD	95%-CI
Paggiaro, 2016	303	0.277	0.320	154	0.134	0.323	0.14	[0.08; 0.21]
Kerstjens Trial 1, 2015	488	0.270	0.330	250	0.053	0.330	0.22	[0.17; 0.27]
Kerstjens Trial 2, 2015	485	0.266	0.245	242	0.075	0.310	0.19	[0.15; 0.24]
Hamelmann, 2016	251	0.528	0.437	137	0.373	0.430	0.16	[0.06; 0.25]
Random effects model	**1527**			**783**			**0.18**	**[0.13; 0.24]**

Heterogeneity: I-squared=20.7%, p=0.2859

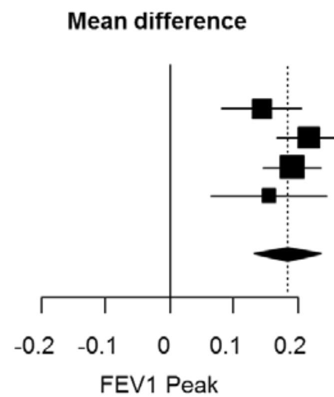

Figure F-13. Change in FEV1 trough from baseline: LAMA vs. placebo as add-on to ICS

Study	TIO Total	TIO Mean	TIO SD	Placebo Total	Placebo Mean	Placebo SD	MD	95%-CI
Bateman, 2011	128	0.044	0.340	125	-0.105	0.340	0.15	[0.07; 0.23]
Lee, 2015	271	0.311	0.353	55	0.205	0.340	0.11	[0.01; 0.21]
Ohta, 2015	228	0.137	0.294	56	0.075	0.290	0.06	[-0.02; 0.15]
Paggiaro, 2016	303	0.131	0.326	154	0.015	0.323	0.12	[0.05; 0.18]
Kerstjens Trial 1, 2015	488	0.132	0.345	250	-0.036	0.350	0.17	[0.11; 0.22]
Kerstjens Trial 2, 2015	485	0.143	0.330	242	-0.012	0.330	0.16	[0.10; 0.21]
Hamelmann, 2016	251	0.384	0.475	137	0.283	0.468	0.10	[0.00; 0.20]
Random effects model	**2154**			**1019**			**0.13**	**[0.10; 0.17]**

Heterogeneity: I-squared=2.6%, p=0.4056

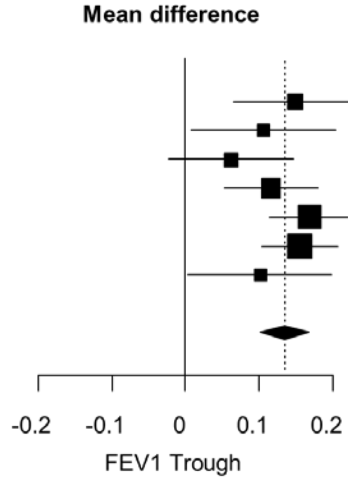

Figure F-14. Change in FEV1 AUC from baseline: LAMA vs. placebo as add-on to ICS

Study	TIO Total	TIO Mean	TIO SD	Placebo Total	Placebo Mean	Placebo SD	MD	95%-CI
Paggiaro, 2016	303	0.186	0.301	154	0.048	0.298	0.14	[0.08; 0.20]
Kerstjens Trial 1, 2015	488	0.178	0.310	250	-0.033	0.320	0.21	[0.16; 0.26]
Kerstjens Trial 2, 2015	485	0.177	0.295	242	-0.005	0.300	0.18	[0.14; 0.23]
Hamelmann, 2016	251	0.438	0.414	137	0.281	0.410	0.16	[0.07; 0.24]
Random effects model	**1527**			**783**			**0.18**	**[0.13; 0.23]**

Heterogeneity: I-squared=22.6%, p=0.2750

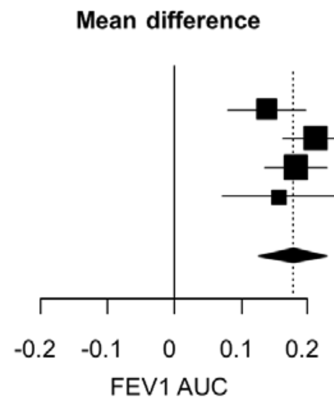

Figure F-15. Change in FVC peak from baseline: LAMA vs. placebo as add-on to ICS

Study	TIO Total	TIO Mean	TIO SD	Placebo Total	Placebo Mean	Placebo SD	MD	95%-CI
Kerstjens Trial 1, 2015	488	0.184	0.356	250	0.045	0.35	0.14	[0.09; 0.19]
Kerstjens Trial 2, 2015	485	0.171	0.340	242	0.071	0.34	0.10	[0.05; 0.15]
Hamelmann, 2016	251	0.411	0.492	137	0.331	0.48	0.08	[-0.02; 0.18]
Random effects model	**1224**			**629**			**0.11**	**[0.05; 0.18]**

Heterogeneity: I-squared=0%, p=0.4621

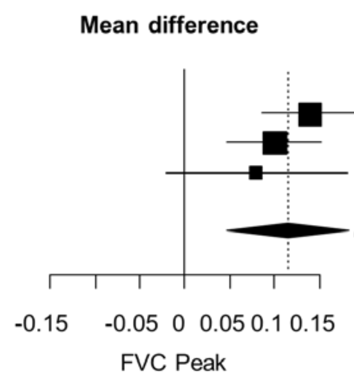

Figure F-16. Change in FVC trough from baseline: LAMA vs. placebo as add-on to ICS

Study	TIO Total	TIO Mean	TIO SD	Placebo Total	Placebo Mean	Placebo SD	MD	95%-CI
Bateman, 2011	128	0.035	0.380	125	-0.100	0.380	0.14	[0.04; 0.23]
Ohta, 2015	228	0.145	0.330	56	0.122	0.330	0.02	[-0.07; 0.12]
Kerstjens Trial 1, 2015	488	0.061	0.405	250	-0.039	0.400	0.10	[0.04; 0.16]
Kerstjens Trial 2, 2015	485	0.037	0.420	242	-0.048	0.420	0.08	[0.02; 0.15]
Hamelmann, 2016	251	0.330	0.530	137	0.281	0.503	0.05	[-0.06; 0.16]
Random effects model	**1580**			**810**			**0.08**	**[0.04; 0.13]**

Heterogeneity: I-squared=0%, p=0.5012

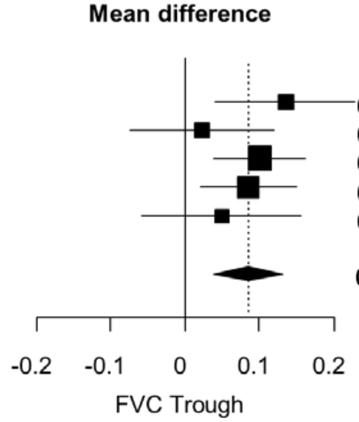

Figure F-17. Change in FVC AUC from baseline: LAMA vs. placebo as add-on to ICS

Study	TIO Total	TIO Mean	TIO SD	Placebo Total	Placebo Mean	Placebo SD	MD	95%-CI
Kerstjens Trial 1, 2015	494	0.067	0.371	250	-0.066	0.360	0.13	[0.08; 0.19]
Kerstjens Trial 2, 2015	485	0.034	0.385	242	-0.065	0.370	0.10	[0.04; 0.16]
Hamelmann, 2016	251	0.320	0.458	137	0.240	0.456	0.08	[-0.02; 0.18]
Random effects model	**1230**			**629**			**0.11**	**[0.05; 0.17]**

Heterogeneity: I-squared=0%, p=0.5541

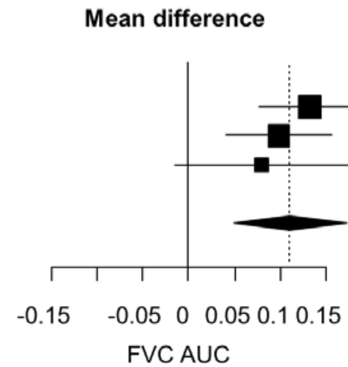

Figure F-18. Difference in rescue medication mean puffs in 24 hours: LAMA vs. placebo as add-on to ICS

Study	TIO Total	TIO Mean	TIO SD	Placebo Total	Placebo Mean	Placebo SD	MD	95%-CI
Bateman, 2011	128	-0.074	2.180	125	0.294	2.140	-0.37	[-0.90; 0.16]
Ohta, 2015	208	-0.255	0.984	50	-0.250	0.770	-0.01	[-0.26; 0.25]
Paggiaro, 2016	302	-0.722	1.150	153	-0.815	1.150	0.09	[-0.13; 0.32]
Kerstjens Trial 1, 2015	483	-0.974	1.596	239	-0.962	1.580	-0.01	[-0.26; 0.23]
Kerstjens Trial 2, 2015	474	-0.984	1.430	237	-0.952	1.430	-0.03	[-0.25; 0.19]
Lee, 2015	284	-0.674	1.606	64	-0.380	1.406	-0.29	[-0.69; 0.10]
Hamelmann, 2016	231	-0.663	1.108	126	-0.372	1.110	-0.29	[-0.53; -0.05]
Random effects model	**2110**			**994**			**-0.08**	**[-0.23; 0.07]**

Heterogeneity: I-squared=27.8%, p=0.2161

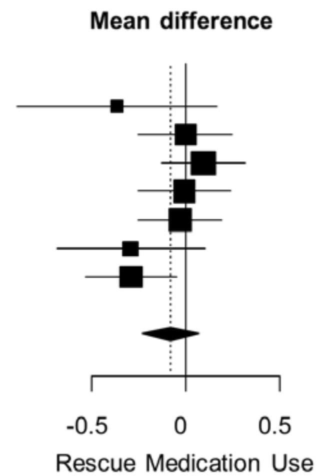

Figure F-19. All-cause death: LAMA vs. LABA as add-on to ICS

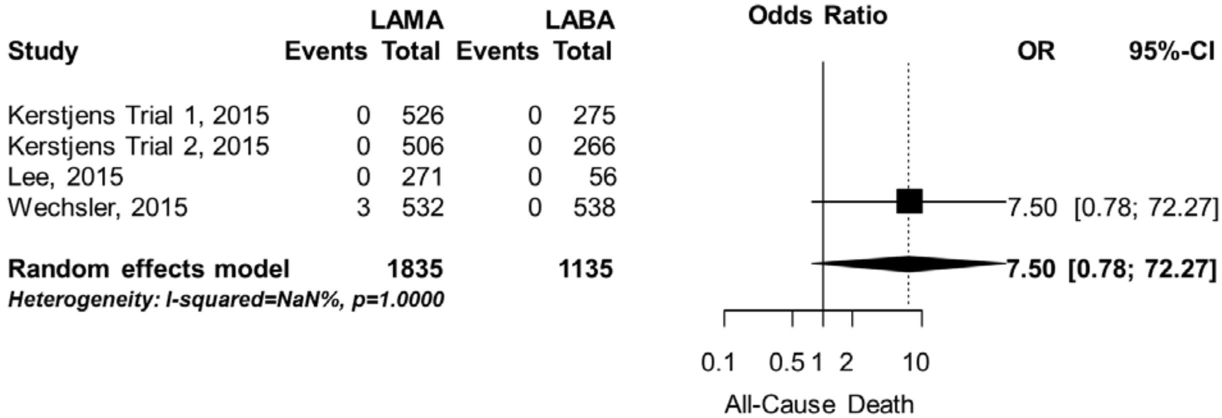

Figure F-20. Asthma-specific death: LAMA vs. LABA as add-on to ICS

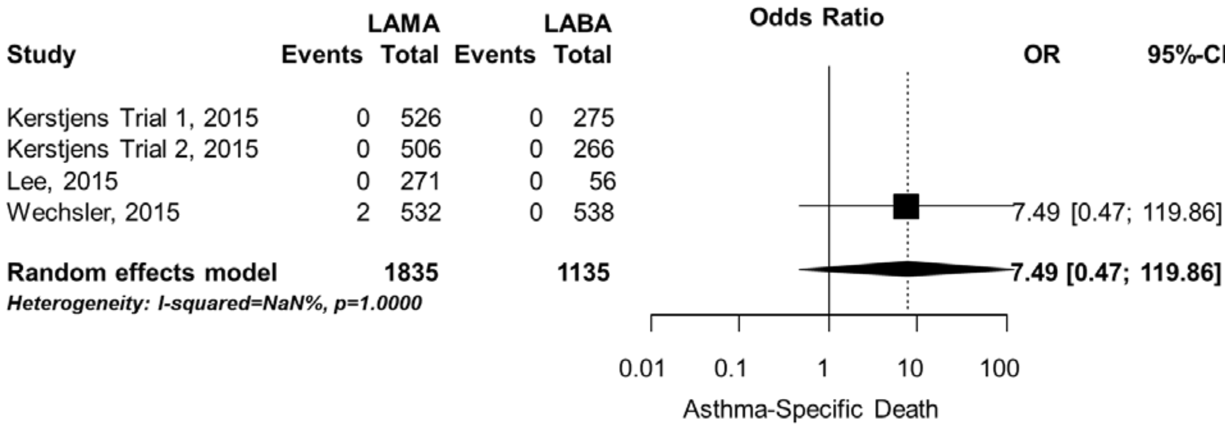

Figure F-21. Change in FEV1 trough from baseline: LAMA vs. LABA as add-on to ICS

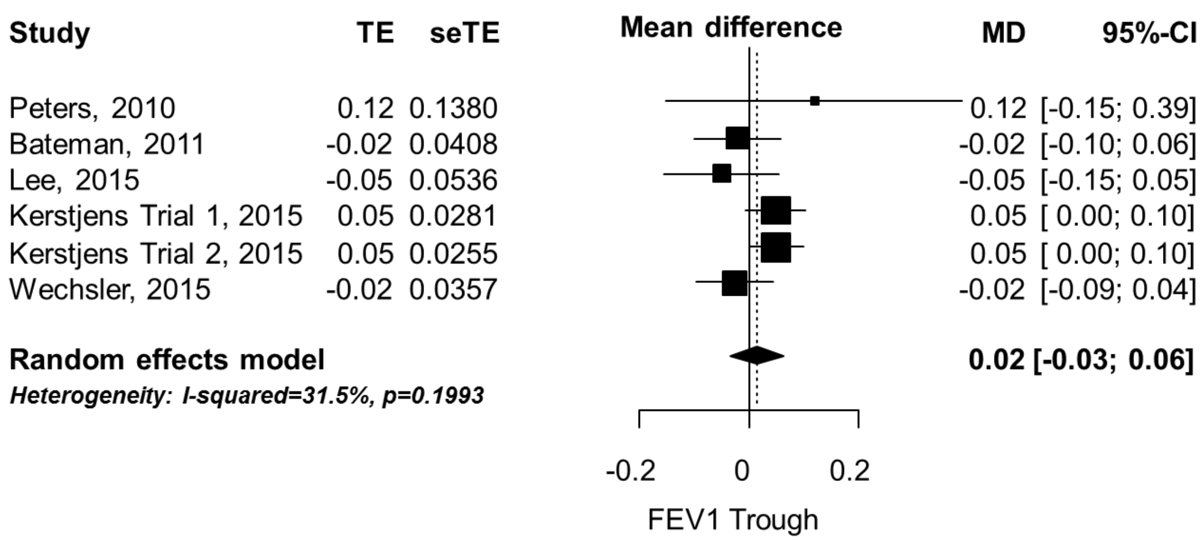

Figure F-22. Change in FEV1 % predicted from baseline: LAMA vs. LABA as add-on to ICS

Study	LAMA Total	LAMA Mean	LAMA SD	LABA Total	LABA Mean	LABA SD	MD	95%-CI
Rajanandh, 2014	31	4.06	1.54	32	11.40	2.28	-7.34	[-8.30; -6.38]
Rajanandh, 2015	72	4.51	5.54	68	8.97	7.80	-4.46	[-6.71; -2.21]
Wechsler, 2015	162	-2.97	19.25	177	-2.34	15.93	-0.63	[-4.41; 3.15]
Random effects model	**265**			**277**			**-4.54**	**[-12.69; 3.61]**

Heterogeneity: I-squared=87%, p=0.0005

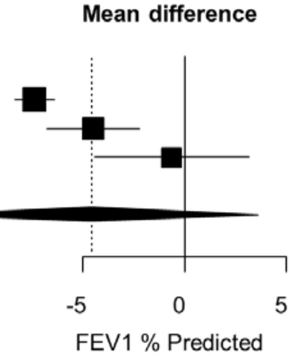

Figure F-23. Change in FVC trough from baseline: LAMA vs. LABA as add-on to ICS

Study	LAMA Total	LAMA Mean	LAMA SD	LABA Total	LABA Mean	LABA SD	MD	95%-CI
Bateman, 2011	128	0.035	0.380	134	0.021	0.38	0.01	[-0.08; 0.11]
Kerstjens Trial 1, 2015	488	0.061	0.405	259	0.028	0.45	0.03	[-0.03; 0.10]
Kerstjens Trial 2, 2015	485	0.037	0.420	251	0.020	0.43	0.02	[-0.05; 0.08]
Random effects model	**1101**			**644**			**0.02**	**[0.00; 0.05]**

Heterogeneity: I-squared=0%, p=0.9237

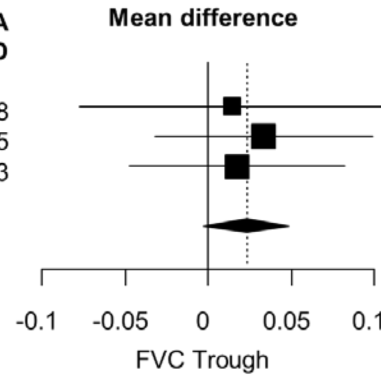

Figure F-24. Change in AQLQ score from baseline: LAMA vs. LABA as add-on to ICS

Study	LAMA Total	LAMA Mean	LAMA SD	LABA Total	LABA Mean	LABA SD	MD	95%-CI
Peters, 2010	64	0.28	0.990	58	0.50	1.12	-0.22	[-0.60; 0.16]
Wechsler, 2015	180	0.99	1.340	197	0.94	1.39	0.05	[-0.23; 0.33]
Kerstjens Trial 1, 2015	488	0.69	0.855	260	0.76	0.85	-0.07	[-0.20; 0.06]
Kerstjens Trial 2, 2015	485	0.79	0.905	250	0.84	0.83	-0.05	[-0.18; 0.08]
Random effects model	**1217**			**765**			**-0.06**	**[-0.15; 0.03]**

Heterogeneity: I-squared=0%, p=0.7178