ICS-SABA – Which Patients?

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Objectives

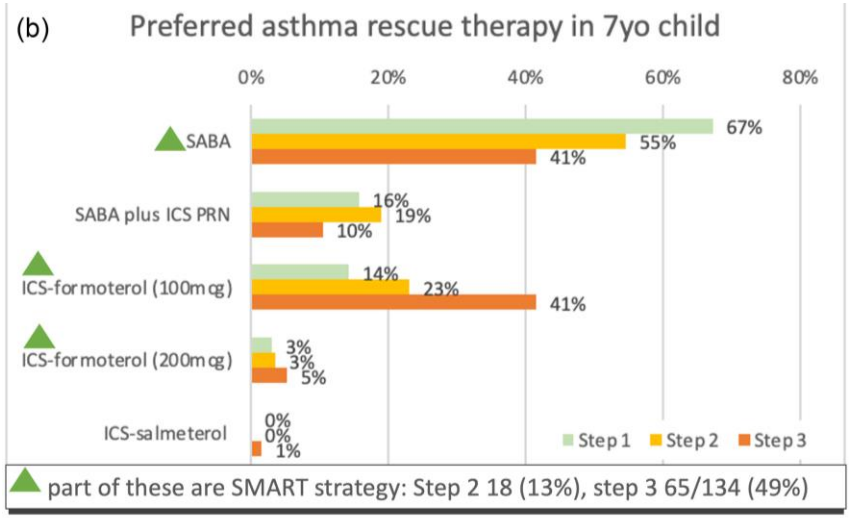
- Describe the options for anti-inflammatory reliever (AIR) therapy
- Identify patients who are appropriate candidates for various AIR approaches

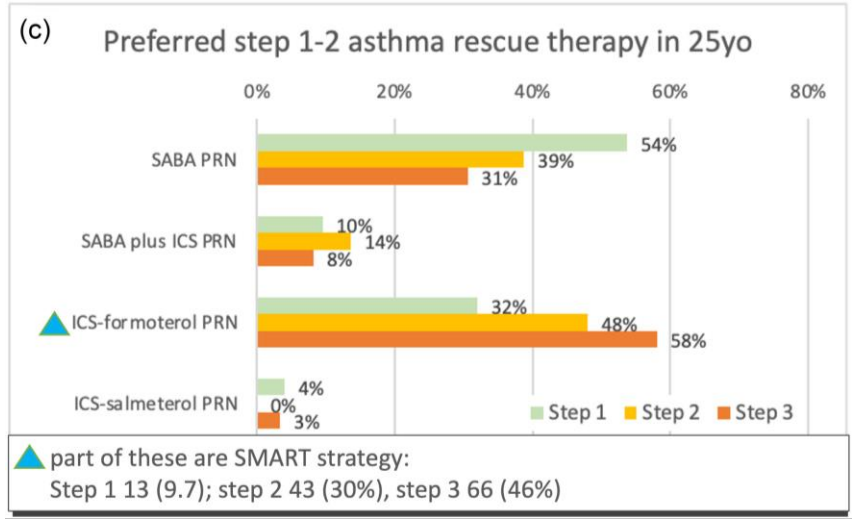
Need for Improved Reliever Strategies

- Exacerbations remain a major source of morbidity
- Despite substantial advances in treatment options, no asthma controller regimen to date has been shown to entirely eliminate exacerbations
- Adherence to all controller regimens is suboptimal
- All patients with asthma need a reliever
- Inhaled SABA has been 1st line treatment for 50 years
- SABAs do not treat inflammation and do not prevent against exacerbation
- Reliever only use is associated with increased health care utilization (Reddel BMJ Open 2017)
- Greater SABA use associated with annual systemic corticosteroid exposure (Lugogo et al. ATS 2021 Poster; Quint et al. SABINA + *JACI-IP 2022*)
- Regardless of SABA or maintenance therapy use, roughly half of all patients are at risk of experiencing at least one exacerbation in any given year (Lugogo N, *Ann Allergy Asthma Immunol*)

Current Reliever Preferences

- 147 ACAAI Members completed online survey in Summer of 2022
- In children, SABA alone was the most commonly preferred reliever (Steps 1-2), 10-19% preferred ICS-SABA, while ICS-formoterol and SABA were preferred by 41% at Step 3
- In adults, SABA alone was the most commonly preferred reliever in Step 1, although 10% preferred ICS-SABA and 32% preferred ICS-formoterol for Step 1
- In adults, ICS-formoterol was the most commonly preferred reliever for Steps 2 and 3





Larenas-Linnemann D et al. Ann Allergy Asthma Immunol 2023

Two Approaches to the Concomitant Treatment of Symptoms and Inflammation with ICS/Beta-agonists

Table 1. Differences between Current Asthma Treatment Regimens Containing an AIR

	Anti-inflammatory Reliever (AIR) Therapy Alone (*GINA Steps 1–2*)	Maintenance-and-Reliever Therapy (MART*) (*GINA Steps 3–5*)
Definition	Combination ICS–formoterol taken as needed for symptom relief,† without maintenance therapy. *Or, if not available, low-dose ICS taken whenever SABA is taken for symptom relief.*	Daily maintenance ICS–formoterol. **PLUS** Low-dose ICS–formoterol taken as needed for symptom relief.†
Indications	**Mild asthma: GINA Steps 1–2**	**Moderate-to-severe asthma: GINA Steps 3–5**
Explanation	Whenever symptom relief is needed, the patient takes an inhaler containing a combination of a low dose of ICS and formoterol (instead of a SABA), without daily maintenance treatment. *Or, if ICS–formoterol is not available, they take a low dose of ICS whenever SABA is taken.*	The patient takes **regular daily maintenance** controller treatment with low-dose (Step 3) or medium-dose (Step 4) combination ICS–formoterol. **PLUS** Whenever needed for symptom relief, the patient uses an inhaler containing a combination of a low dose of ICS and formoterol (instead of a SABA).
Medications and age groups studied	Budesonide–formoterol (≥12 yr). There have been smaller studies with beclometasone–albuterol in combination or separate inhalers in adults ≥18 yr, adolescents and children ≥4 yr.	Budesonide–formoterol (ages ≥4 yr). Or beclometasone–formoterol (adults ≥18 yr).
Rationale	In patients with mild asthma, as-needed-only budesonide–formoterol reduced severe exacerbations by ≥60% compared with SABA alone, with similar symptom control and lung function as maintenance ICS plus as-needed SABA. *With as-needed-only ICS + SABA in patients with mild asthma, some studies showed fewer exacerbations than SABA alone; other studies showed similar outcomes to physician-adjusted ICS treatment.*	In moderate-to-severe asthma, MART with ICS–formoterol reduced severe exacerbations compared with the same dose or high-dose ICS or ICS–LABA plus as-needed SABA, with similar symptom control and lung function. *There have been no studies with ICS + SABA both used as MART, and some evidence suggests that taking ICS + SABA regularly may increase exacerbation risk.*

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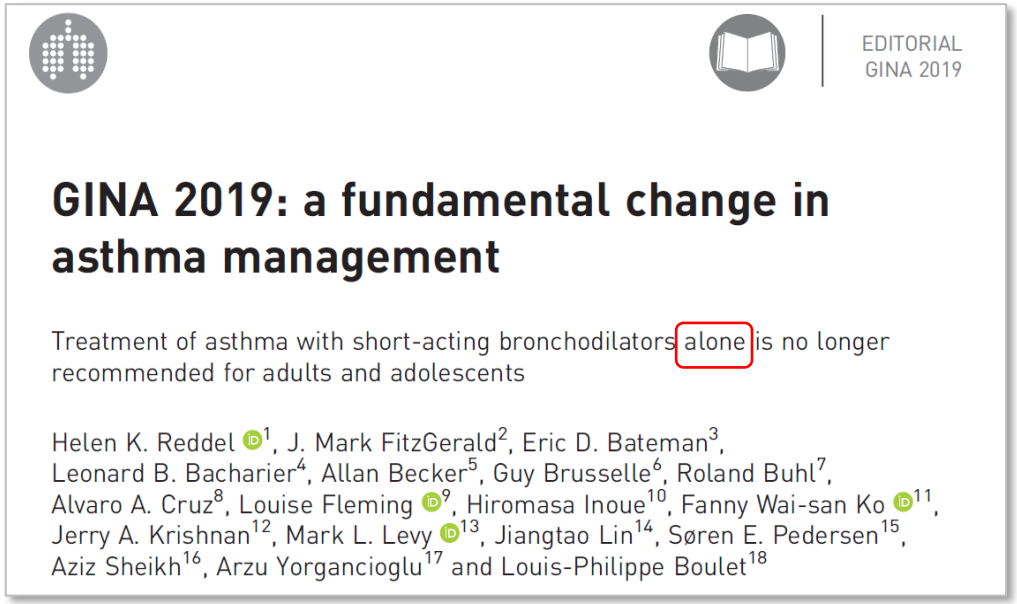
Why not treat with SABA alone?

- People with apparently mild asthma can have severe or fatal exacerbations *(Dusser, 2007; Bergstrom, 2008)*
  - Exacerbation triggers are unpredictable
  - Even 4–5 lifetime OCS courses increase the risk of osteoporosis, diabetes, cataract *(Price et al, J Asthma Allerg 2018)*
- There is no evidence for safety or efficacy of SABA-only treatment
- Regular use of SABA, even for 1–2 weeks, is associated with increased AHR, reduced bronchodilator effect, increased allergic response, increased eosinophils *(e.g. Hancox, 2000; Aldridge, 2000)*
  - Can lead to a vicious cycle encouraging overuse
  - Over-use of SABA associated with ↑ exacerbations and ↑ mortality *(e.g. Suissa 1994, Nwaru 2020)*
- Starting treatment with SABA trains the patient to regard it as their primary asthma treatment
- The only previous alternative was daily ICS even when no symptoms, but adherence is extremely poor
- GINA changed its recommendation once evidence for a safe and effective alternative was available



EDITORIAL
GINA 2019

GINA 2019: a fundamental change in asthma management

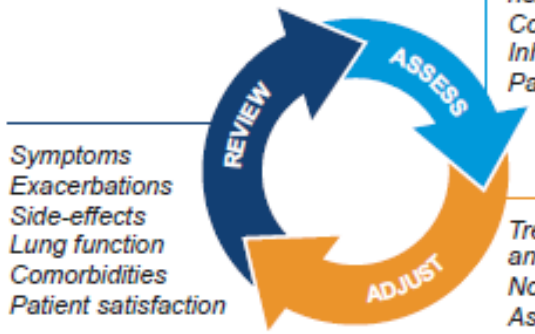
Treatment of asthma with short-acting bronchodilators alone is no longer recommended for adults and adolescents

Helen K. Reddel[1], J. Mark FitzGerald[2], Eric D. Bateman[3], Leonard B. Bacharier[4], Allan Becker[5], Guy Brusselle[6], Roland Buhl[7], Alvaro A. Cruz[8], Louise Fleming[9], Hiromasa Inoue[10], Fanny Wai-san Ko[11], Jerry A. Krishnan[12], Mark L. Levy[13], Jiangtao Lin[14], Søren E. Pedersen[15], Aziz Sheikh[16], Arzu Yorgancioglu[17] and Louis-Philippe Boulet[18]

GINA 2023 – Adults & adolescents 12+ years

Personalized asthma management
Assess, Adjust, Review
for individual patient needs

UPDATE WITH GINA 2024



Symptoms
Exacerbations
Side-effects
Lung function
Comorbidities
Patient satisfaction

Confirmation of diagnosis if necessary
Symptom control & modifiable risk factors (see Box 2-2)
Comorbidities
Inhaler technique & adherence
Patient preferences and goals

Treatment of modifiable risk factors and comorbidities
Non-pharmacological strategies
Asthma medications (adjust down/up/between tracks)
Education & skills training

TRACK 1: PREFERRED CONTROLLER and RELIEVER
Using ICS-formoterol as the reliever* reduces the risk of exacerbations compared with using a SABA reliever, and is a simpler regimen

STEPS 1 – 2	STEP 3	STEP 4	STEP 5
As-needed-only low dose ICS-formoterol	Low dose maintenance ICS-formoterol	Medium dose maintenance ICS-formoterol	Add-on LAMA Refer for assessment of phenotype. Consider high dose maintenance ICS-formoterol, ± anti-IgE, anti-IL5/5R, anti-IL4Rα, anti-TSLP

RELIEVER: As-needed low-dose ICS-formoterol*

See GINA severe asthma guide

TRACK 2: Alternative CONTROLLER and RELIEVER
Before considering a regimen with SABA reliever, check if the patient is likely to adhere to daily controller treatment

STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
Take ICS whenever SABA taken*	Low dose maintenance ICS	Low dose maintenance ICS-LABA	Medium/high dose maintenance ICS-LABA	Add-on LAMA Refer for assessment of phenotype. Consider high dose maintenance ICS-LABA, ± anti-IgE, anti-IL5/5R, anti-IL4Rα, anti-TSLP

RELIEVER: as-needed SABA, or as-needed ICS-SABA*

Other controller options (limited indications, or less evidence for efficacy or safety – see text)	*Low dose ICS whenever SABA taken*, or daily LTRA, or add HDM SLIT*	*Medium dose ICS, or add LTRA, or add HDM SLIT*	*Add LAMA or LTRA or HDM SLIT, or switch to high dose ICS*	*Add azithromycin (adults) or LTRA. As last resort consider adding low dose OCS but consider side-effects*

*Anti-inflammatory relievers (AIR)

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Two Approaches to the Concomitant Treatment of Symptoms and Inflammation with ICS/Beta-agonists

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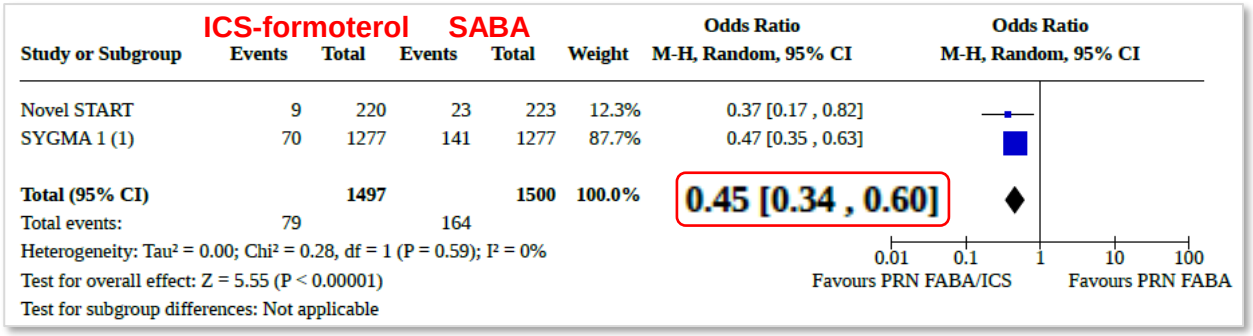
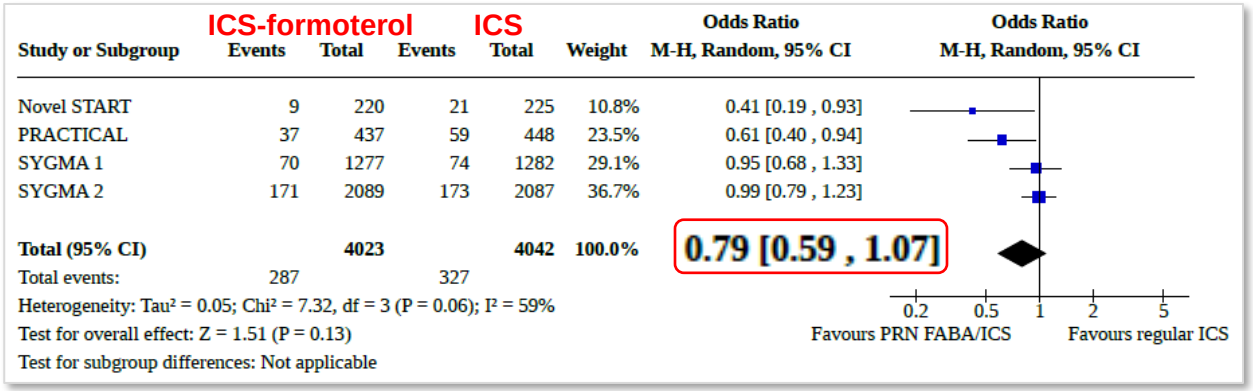
Reddel H et al. AJRCCM 2022

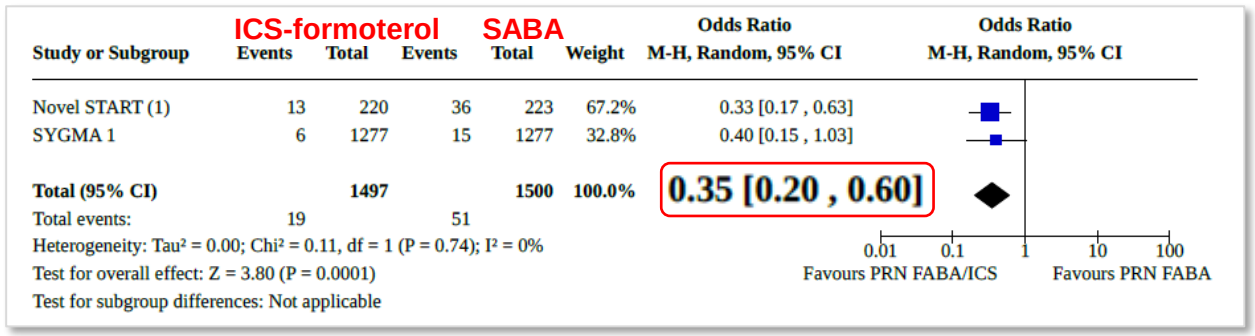
As-needed-only ICS-formoterol in Steps 1–2 (n=9,565)

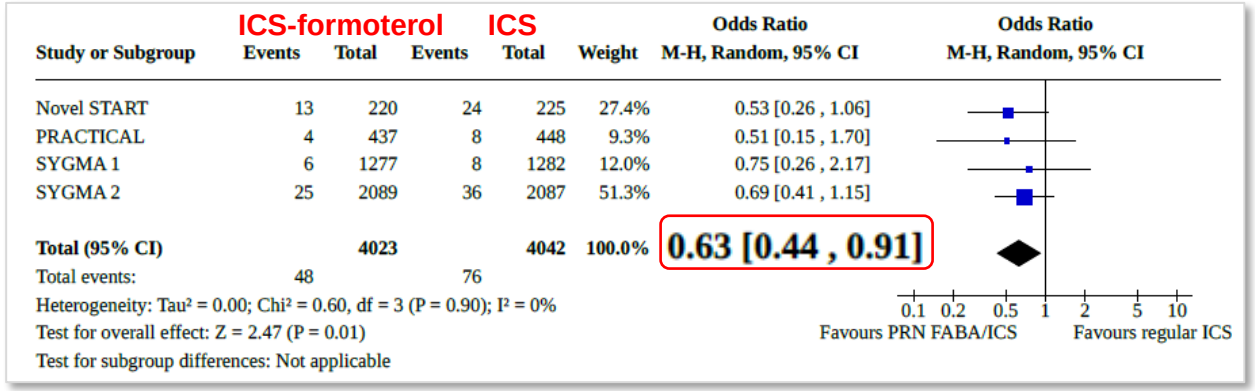
SEVERE EXACERBATIONS





ED VISITS AND HOSPITALIZATIONS

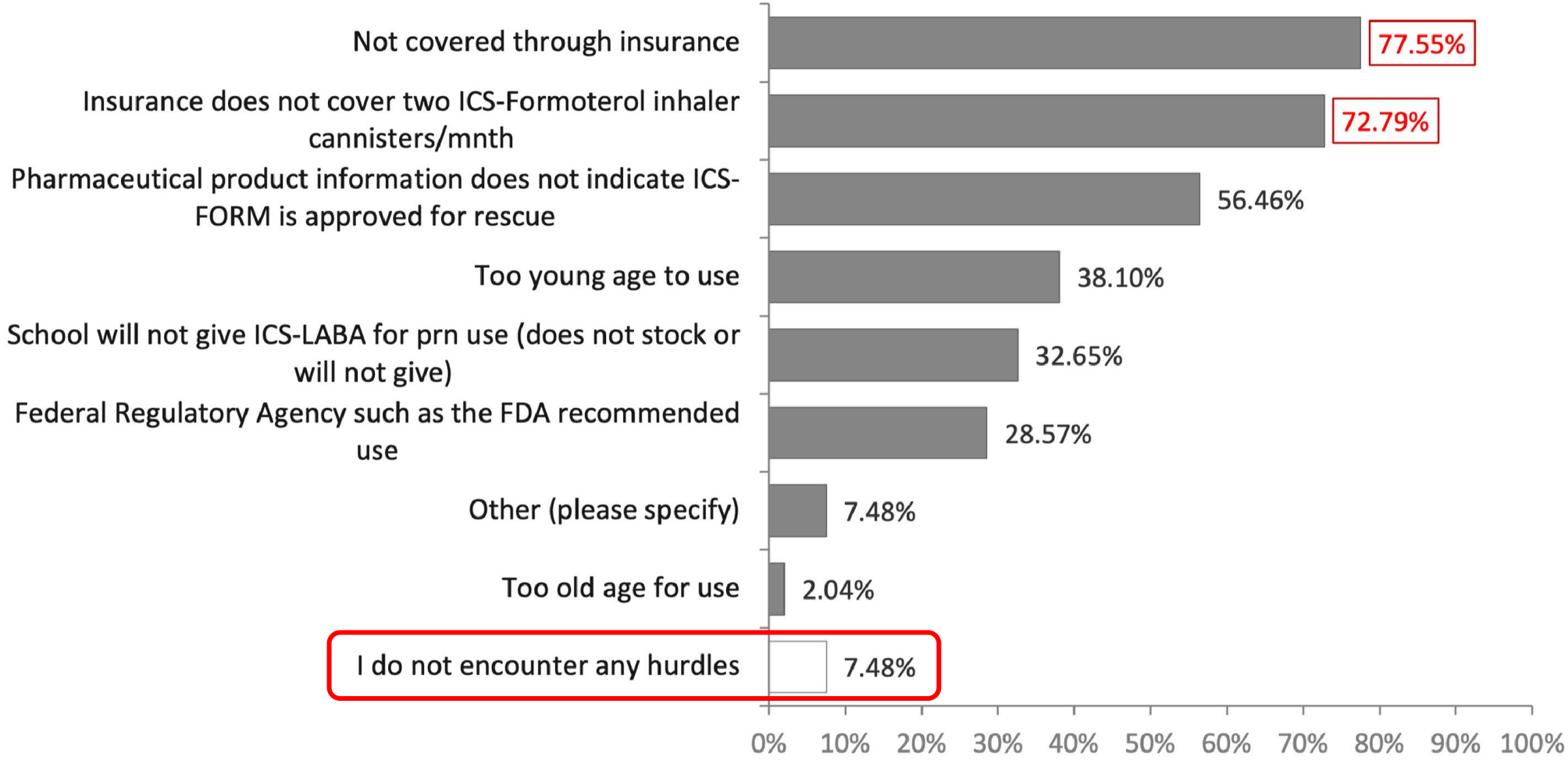




ICS: inhaled corticosteroid; SABA: short-acting beta$_2$-agonist; FABA: fast-acting beta2-agonist, used by Cochrane authors for both SABA and formoterol

Crossingham et al, Cochrane 2021

Hurdles for Prescribing One's Preferred ICS-Formoterol Use



Larenas-Linnemann D et al. Ann Allergy Asthma Immunol 2023

ICS/Formoterol is **Effective** as Both an Anti-Inflammatory Reliever and as MART at All Levels of Asthma Severity

But access and uptake are problems in the US

Are there other options for AIR?

Two Approaches to the Concomitant Treatment of Symptoms and Inflammation with ICS/Beta-agonists

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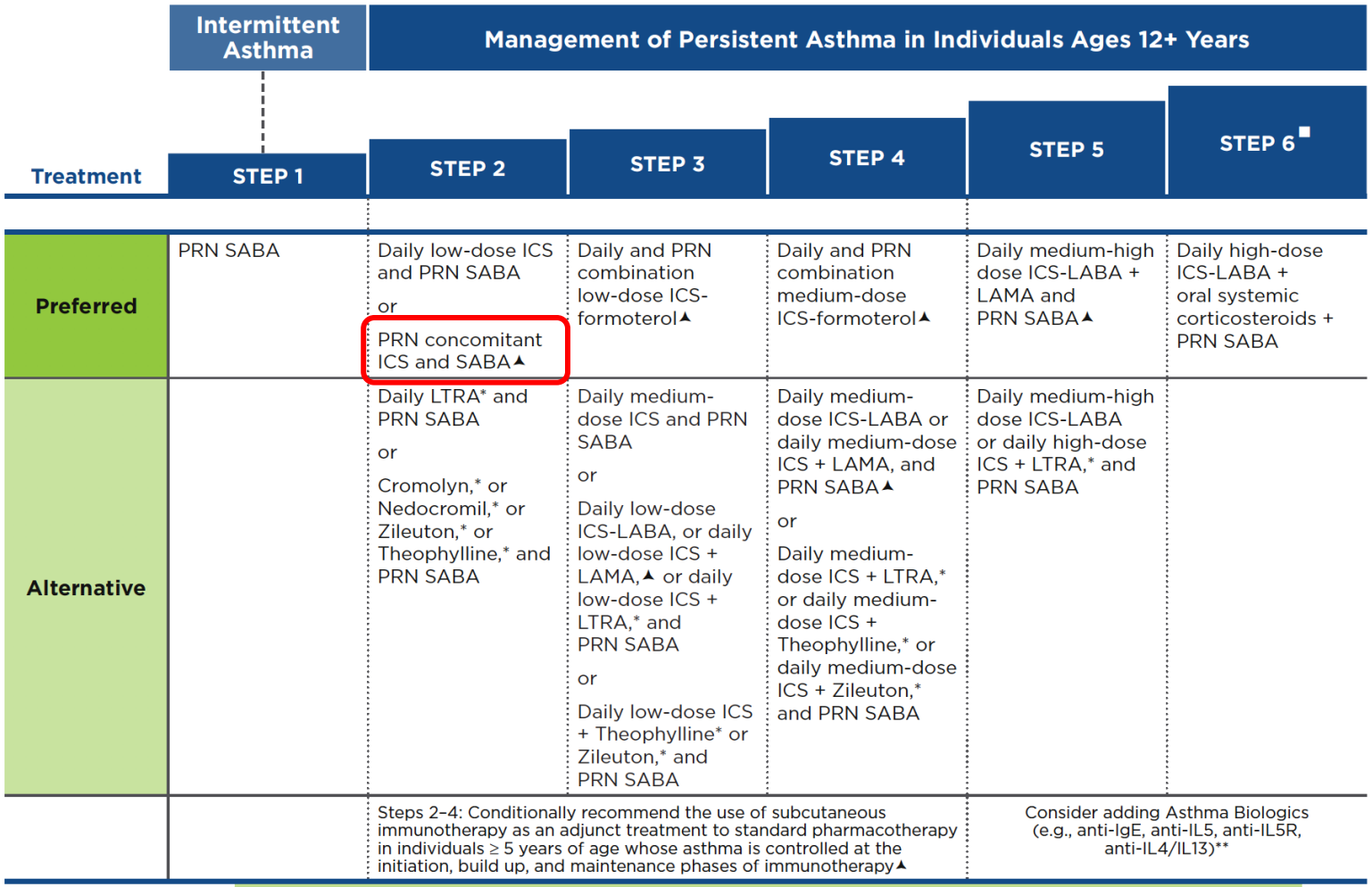
Reddel H et al. AJRCCM 2022

AGES 12+ YEARS: STEPWISE APPROACH FOR MANAGEMENT OF ASTHMA



Assess Control

- First check adherence, inhaler technique, environmental factors,▲ and comorbid conditions.
- **Step up** if needed; reassess in 2–6 weeks
- **Step down** if possible (if asthma is well controlled for at least 3 consecutive months)

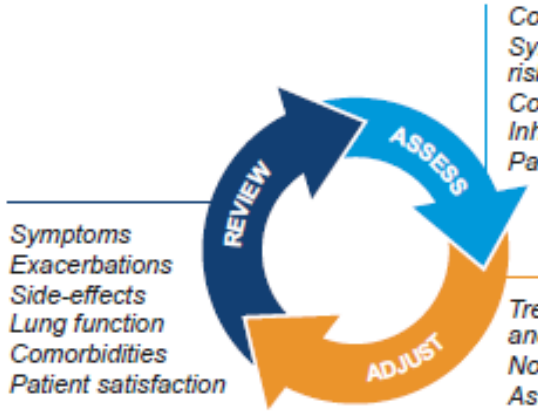
Consult with asthma specialist if Step 4 or higher is required. Consider consultation at Step 3.

Control assessment is a key element of asthma care. This involves both impairment and risk. Use of objective measures, self-reported control, and health care utilization are complementary and should be employed on an ongoing basis, depending on the individual's clinical situation.

GINA 2023 – Adults & adolescents 12+ years

Personalized asthma management
Assess, Adjust, Review
for individual patient needs

UPDATE WITH GINA 2024



Confirmation of diagnosis if necessary
Symptom control & modifiable risk factors (see Box 2-2)
Comorbidities
Inhaler technique & adherence
Patient preferences and goals

Symptoms
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Side-effects
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RELIEVER: As-needed low-dose ICS-formoterol*

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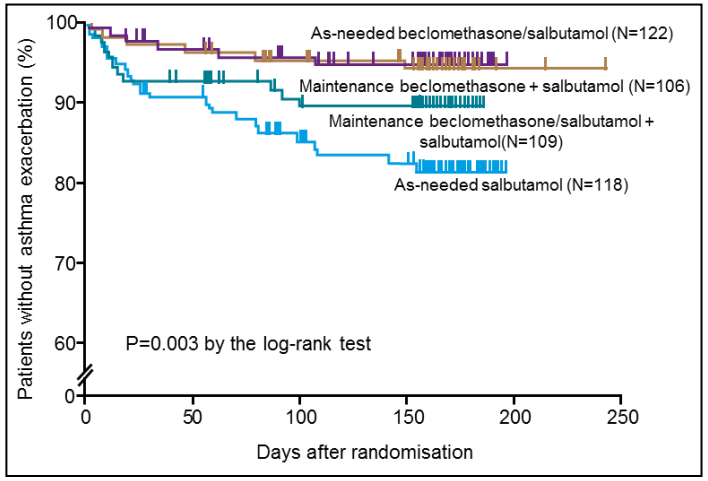
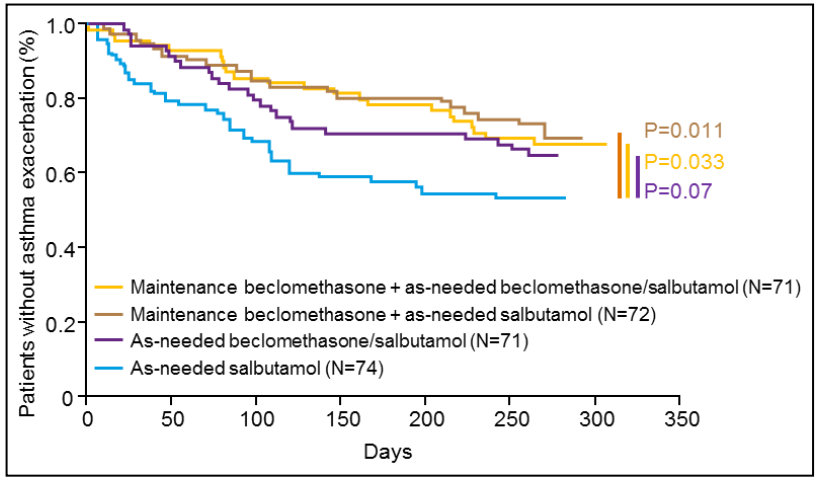
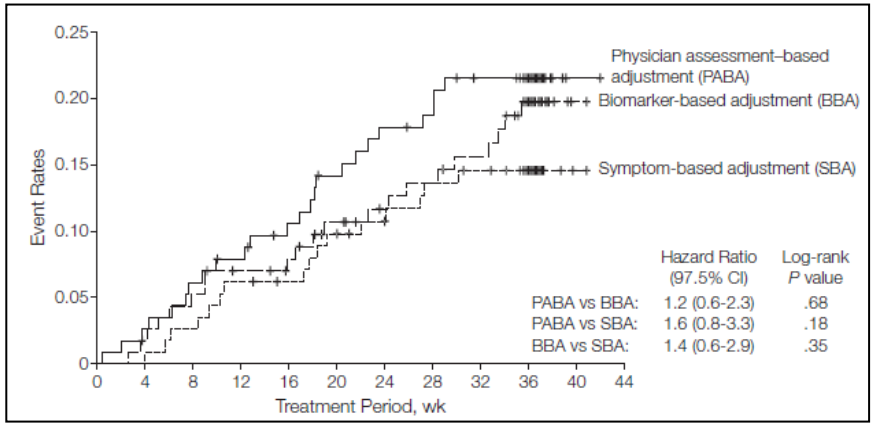
As-needed-only ICS-SABA in Steps 1–2



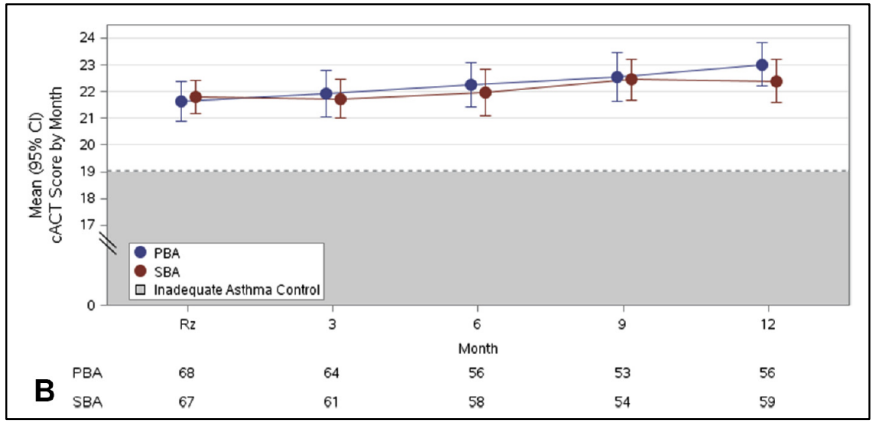
Papi et al, NEJM 2007
Beclometasone-albuterol combination
N=455, 18-65 yrs



Martinez, Lancet 2011
Separate BDP and albuterol
N=288, 5-18 yrs



Calhoun, JAMA 2012
Separate BDP and albuterol
N=342, adults



Sumino, JCAI IP 2019
Separate BDP and albuterol
N=206, 6-17 yrs

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Reliever-Triggered Inhaled Glucocorticoid in Black and Latinx Adults with Asthma

Israel E et al. DOI: 10.1056/NEJMoa2118813

CLINICAL PROBLEM

Black and Latinx adults are disproportionately affected by asthma, and attempts to address this disparity have been largely unsuccessful. Use of a single inhaler containing a glucocorticoid and a β_2-agonist for both maintenance and as-needed reliever therapy can reduce asthma exacerbations in patients with moderate-to-severe asthma but has not been well studied in Black and Latinx patients, who may face barriers to its use.

CLINICAL TRIAL

Design: A pragmatic, open-label, randomized trial enrolled 1201 Black and Latinx adults with moderate-to-severe asthma.

Intervention: Participants were assigned either to use a patient-activated, reliever-triggered inhaled glucocorticoid strategy plus usual care or to continue usual care. Participants in the intervention group received one-time instruction on using the glucocorticoid inhaler, which delivered a metered dose of 80 μg of beclomethasone dipropionate, each time they used their quick-reliever inhaler or nebulizer. The primary end point was the annualized rate of severe asthma exacerbations.

RESULTS

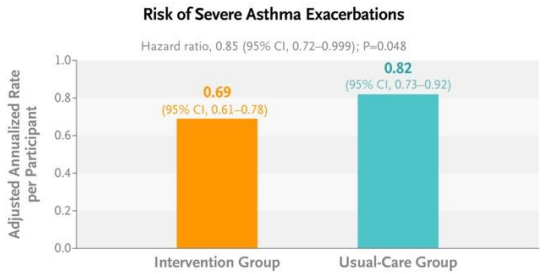
Efficacy: At a median follow-up of 15 months, the annualized rate of severe asthma exacerbations was significantly lower in the intervention group than in the control group.

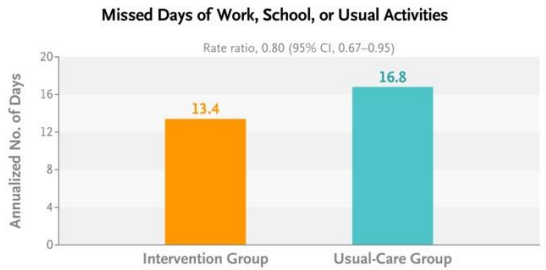
Safety: The incidence of serious adverse events was similar in the two groups.

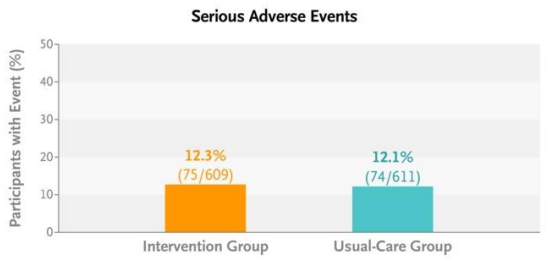
LIMITATIONS

- The trial was open-label, and inhaled glucocorticoids were provided at no cost, which could have affected the findings.
- Most of the trial participants were women, so the findings may not be as generalizable to men.
- Participants identified as Black or Latinx, but the trial included many different ethnic groups that may differ in asthma morbidity and in responsiveness to this treatment strategy.

Links: Full Article | NEJM Quick Take | Editorial





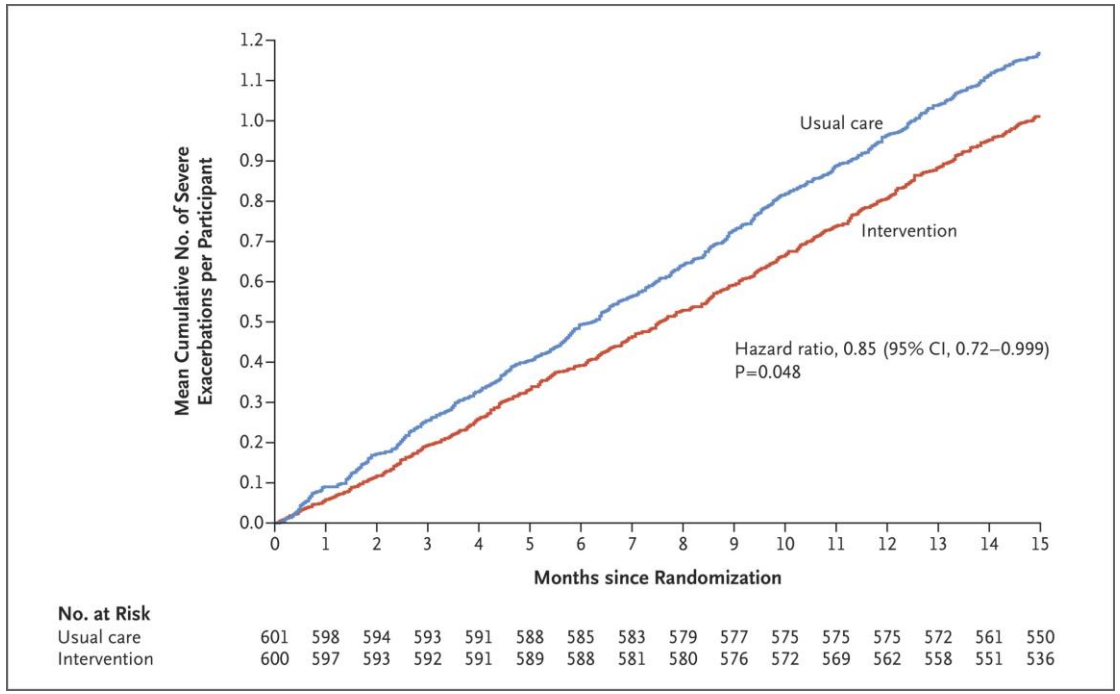


CONCLUSIONS

Adding inhaled glucocorticoids to as-needed reliever therapy led to a lower rate of severe asthma exacerbations among Black and Latinx adults with moderate-to-severe asthma.

PREPARE Trial

- Pragmatic, open-label trial
- 1201 Black and Latinx adults with **moderate-severe asthma**
- BDP-albuterol (separate inhalers or nebulized albuterol) as reliever vs usual care
- 15.4% reduction in risk of severe exacerbation
- Fewer days missed of work, school or usual activities
- 1.1 additional ICS inhaler needed/year



Israel E et al. N Engl J Med 2022;386:1505-1518

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Albuterol–Budesonide Fixed-Dose Combination Rescue Inhaler for Asthma

Papi A et al. DOI: 10.1056/NEJMoa2203163

MANDALA Trial

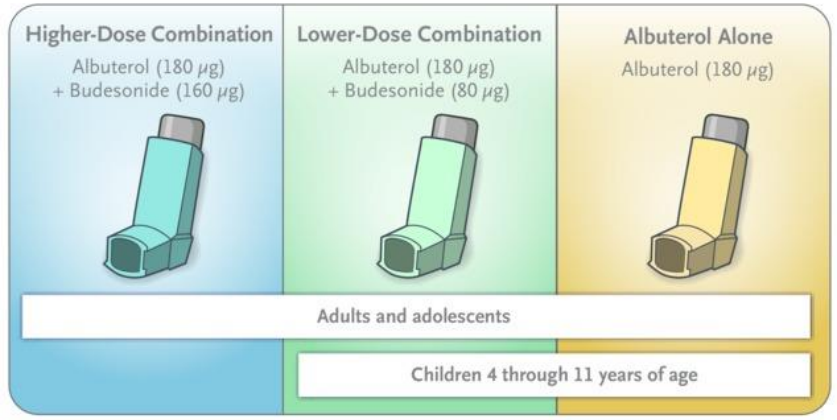
CLINICAL PROBLEM

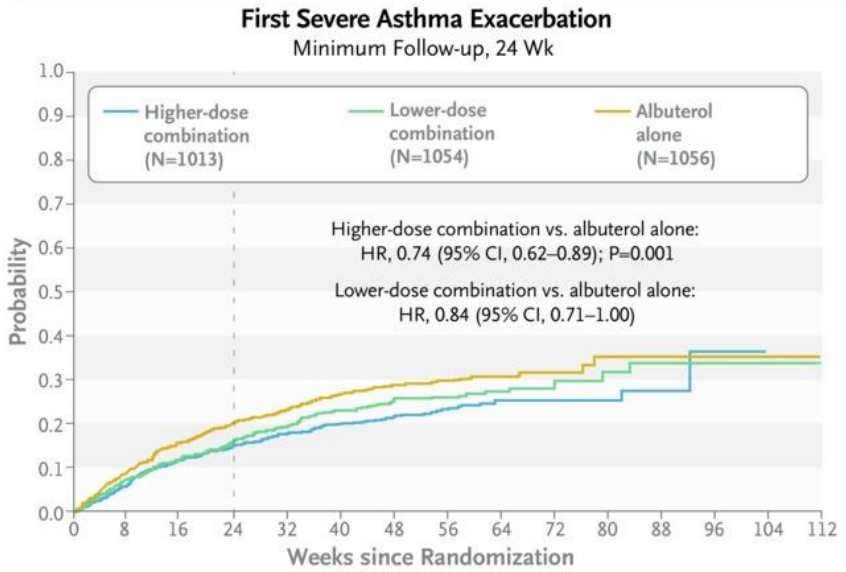
Patients typically treat acute asthma symptoms with short-acting β_2-agonist (SABA) rescue therapy. However, SABAs do not treat inflammation, leaving patients at risk for severe exacerbations. Whether rescue therapy with a fixed-dose combination of a SABA (albuterol) plus a glucocorticoid (budesonide) can improve outcomes is unknown.

CLINICAL TRIAL

Design: A multinational, phase 3, double-blind, randomized trial evaluated the safety and efficacy of as-needed use of a fixed-dose combination of albuterol and budesonide, as compared with albuterol alone, in patients with uncontrolled moderate-to-severe asthma receiving inhaled glucocorticoid-containing maintenance therapy.

Intervention: Adults and adolescents were randomly assigned to receive, on an as-needed basis, 180 μg of albuterol plus 160 μg of budesonide, 180 μg of albuterol plus 80 μg of budesonide, or 180 μg of albuterol; the treatments were delivered through a single metered-dose inhaler. Children 4 through 11 years of age were assigned only to the lower-dose combination group or the albuterol-alone group. Participants continued their baseline glucocorticoid-containing maintenance therapies. The primary efficacy end point was the first severe asthma exacerbation in a time-to-event analysis.





- Adolescents and adults with uncontrolled **moderate-severe asthma**
- 26% reduction in the risk of severe exacerbation in the higher dose combination group
- Lower systemic corticosteroid use (86.2+/- 262.9 mg in the higher-dose combination group and 129.3+/- 657.2 mg in the albuterol-alone group)
- Higher likelihood of significant improvement in ACQ-5 (OR 1.22 (95% CI, 1.02 to 1.47))
- Average daily as-needed use was similar in the three trial groups, 2.6 inhal/day in the higher-dose combination group, 2.7 inhal/day in the lower-dose combination group, and 2.8 inhal/day in the albuterol-alone group

Papi A et al. N Engl J Med 2022;386:2071-2083

Differences between NAEPP 2020 & GINA 2024 in Placement of ICS/SABA

	NAEPP 2020	GINA 2024
5-11 yrs (NAEPP), 6-11 yrs (GINA)	Not an option	Step 1 as monotherapy; Step 2 as an alternative to daily low dose ICS
12+ yrs	Preferred controller for Step 1; alternative at Step 2	Step 1 as monotherapy in Track 2, and as reliever in Steps 2^+ if using AIR without BUD/FORM

Strengths of ICS/SABA

- Evidence for superiority over SABA alone for rescue at all levels of severity
- Evidence for efficacy in populations at high risk/burden
- Can be used with all controller regimens
- FDA approved 18^{+} years

Limitations of ICS/SABA

- Still requires most patients to have/carry/use 2 separate inhalers (controller & reliever)
- Cost of 2 separate inhalers
- Not approved in children and adolescents

Potential Clinical Scenarios for ICS-SABA

- Step 1-2 (“mild asthma”) as an alternative to daily low dose ICS to reduce the risk of exacerbation
- Steps 2^{+} as reliever in place of SABA-alone (when MART is not available or appropriate)
- As a step up for patients with uncontrolled moderate-severe asthma prior to a trial of biologics
- OK and appropriate for use as pre-treatment for exercise

Unanswered Questions

- Children and adolescents
- Comparative effectiveness and safety with ICS/formoterol
- Role as AIR in Steps 1 and 2? Less evidence than for Steps 3^{+}

Options for “Annie”

- 18 years old with allergic, eosinophilic, T2 high asthma with 1-2 exacerbations/year
- At risk for exacerbations (AIRQ=2) but little impairment (ACT=22)
- Near normal lung function (slightly low FEV_1/FVC), and fully reversible with BD
- GINA 2024 suggests AIR as appropriate in this setting, either as ICS/formoterol PRN or ICS/albuterol PRN, or daily low dose ICS + SABA PRN if adherence to ICS is likely to be good

Conclusions

- Use of SABA-only reliever therapy is INFERIOR to an ICS-containing reliever in terms of risk of severe exacerbation
- 2 “options” for AIR – ICS/formoterol or ICS/SABA
  - Both are more effective in reducing exacerbation risk relative to SABA alone
  - “More” data available for ICS/formoterol in “mild” disease (i.e. used as AIR without a daily controller)
- Challenges in implementation and patient re-education, but these efforts are worthwhile given the improvement in asthma care they provide