Power Puff Inhaler Combo: Use of Combination ICS-LABA/SABA vs. SABA as a Reliever if on Scheduled ICS

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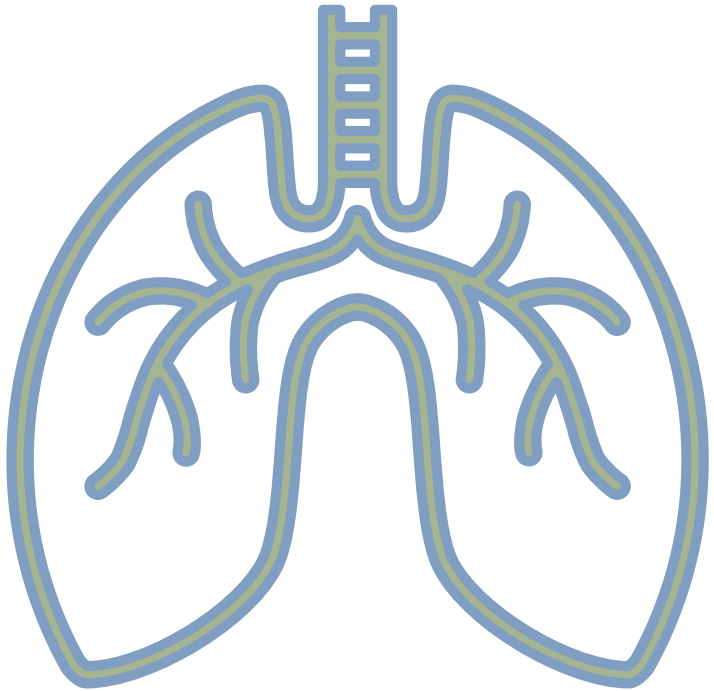
This speaker has no financial conflicts of interest to disclose

Learning Objectives for Pharmacists

1. Discuss the Global Initiative for Asthma (GINA) guideline and the National Asthma Education and Prevention Program (NAEPP) update on recommendations regarding the treatment of asthma in the outpatient setting
2. Interpret primary literature on the use of combination inhaled corticosteroid (ICS) and long-acting beta agonist (LABA) or short-acting beta agonist (SABA) as a rescue agent if currently on a scheduled ICS
3. Assess a patient with asthma to determine when the use of combination ICS and LABA/SABA is appropriate

Learning Objectives for Technicians

1. Identify appropriate maintenance and reliever inhalers for patients with asthma
2. List combination ICS-LABA/SABA rescue inhalers studied in primary literature for patients with asthma
3. Compare the risks and benefits of using combination ICS-LABA/SABA compared to SABA as a rescue agent for patients currently using a scheduled ICS



Overview of Asthma

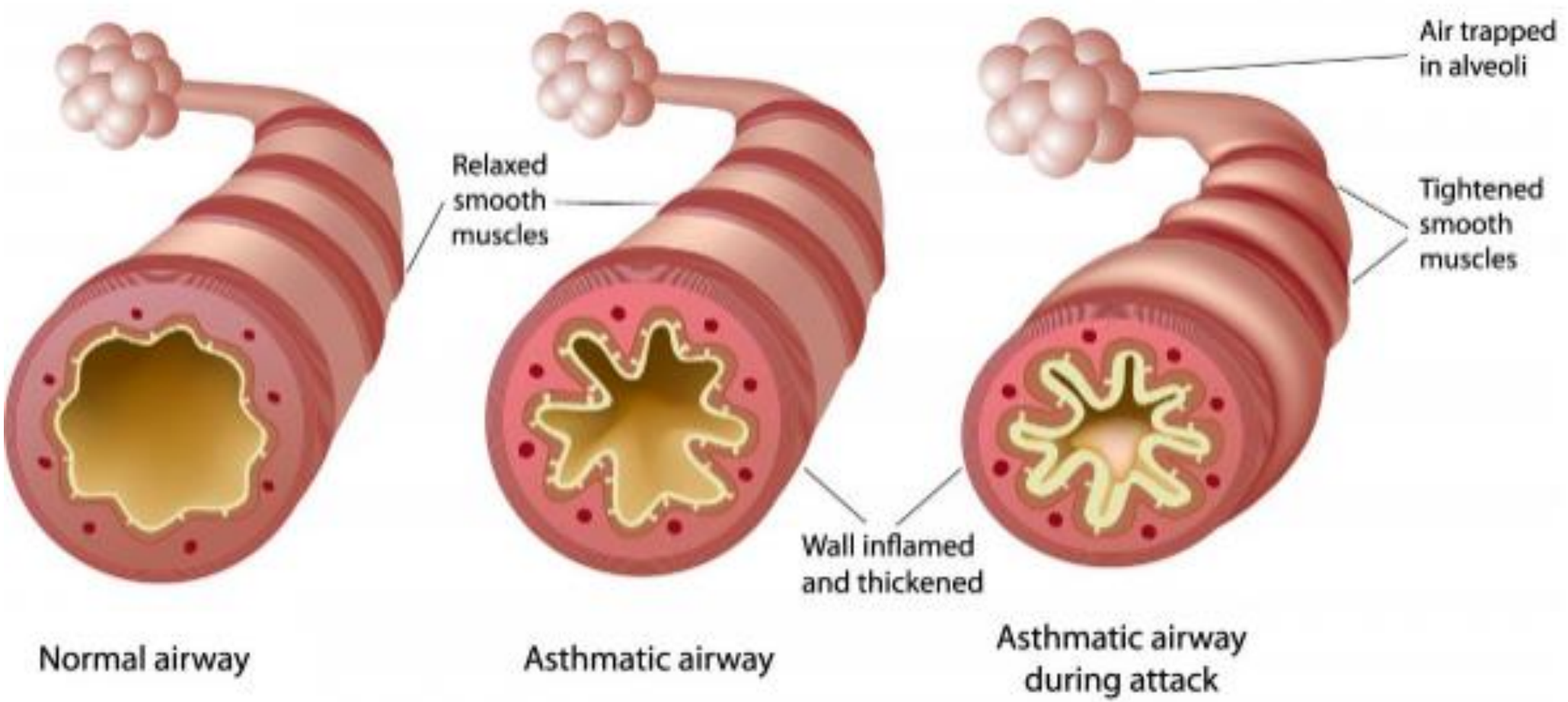
Asthma Epidemiology

16th leading cause of years lived with disability

300 million people worldwide

9.9% had an ED visit in past 12 months

Pathophysiology



Assessment of Asthma

Asthma severity based on ‘difficulty to treat’

Mild asthma – well controlled with low-intensity treatment

Moderate asthma – well controlled with low or medium dose of ICS-LABA

Severe asthma – remains uncontrolled despite optimized treatment with high-dose ICS-LABA or requires high dose ICS-LABA to prevent it from becoming uncontrolled

Assessment of Asthma

Exacerbations – change in symptoms and lung function from patient's usual status

- **Severe exacerbation:** dyspnea at rest, interferes with conversation, usually requires ED visit and likely hospitalization, partial relief from frequent inhaled SABA, oral systemic corticosteroids (some symptoms last for >3 days after treatment is begun), adjunctive therapies helpful

Asthma Control Test (ACT)

- Range: 5 to 25
- Score interpretation: not well controlled ≤ 19, well controlled ≥ 20

Asthma Control Questionnaire-5 (ACQ-5)

- Range: 0 to 6
- Score interpretation: uncontrolled ≥ 1.5, well controlled < 0.75

GINA. Global Strategy for Asthma Management and Prevention, 2023. Updated May 2023. Available from www.ginasthma.org

National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007 *J Allergy Clin Immunol*. 2007;120(5 Suppl):S94-S138.

Knowledge Check

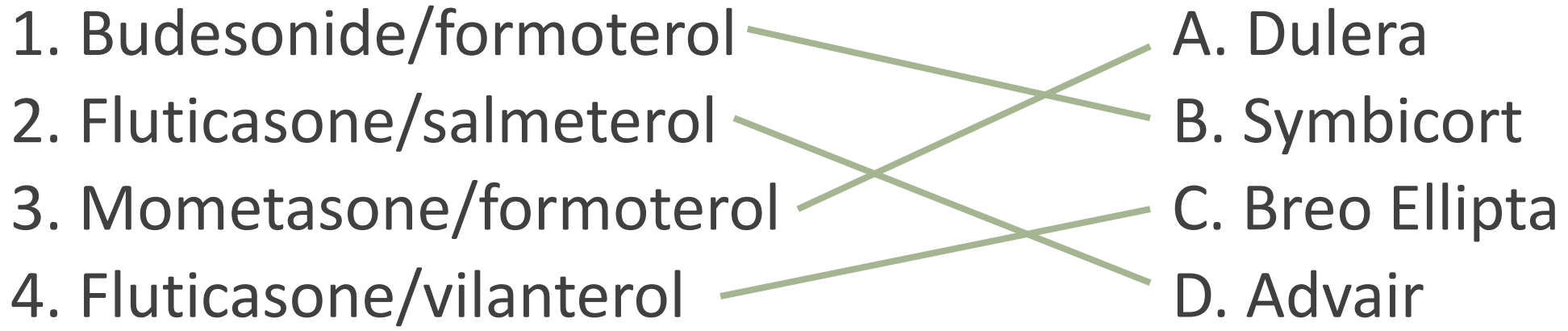
Match the following ICS-LABA combination inhalers with its brand name.

1. Budesonide/formoterol
2. Fluticasone/salmeterol
3. Mometasone/formoterol
4. Fluticasone/vilanterol

A. Dulera
B. Symbicort
C. Breo Ellipta
D. Advair

Knowledge Check

Match the following ICS-LABA combination inhalers with its brand name.



Combination Inhalers: ICS-LABA

Fluticasone furoate-vilanterol (Breo Ellipta)

Fluticasone propionate-salmeterol (Advair, Wixela)

Budesonide-formoterol (Symbicort)

Mometasone-formoterol (Dulera)

Fluticasone propionate-formoterol – Not available in US

Beclomethasone-formoterol – Not available in US

https://canadadrugstore.com/products/wixela-inhub
https://www.hematologyadvisor.com/drug/symbicort-160-4-5/
https://www.goodrx.com/breo-ellipta/what-is
https://pharmaserve.com/pharmacy_drugs/dulera/
https://nckpharma.com/gsks-advair-loe-and-mylans-wixela-inhub-generic-entry/

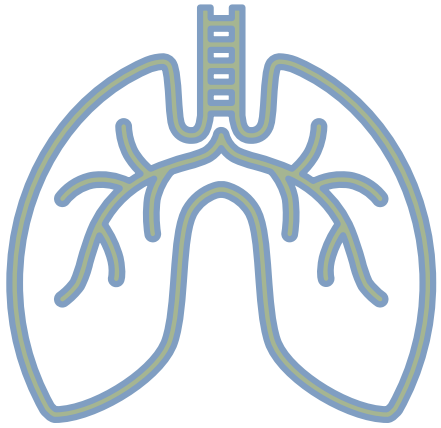
Combination Inhalers: ICS-SABA

Albuterol/budesonide (Airsupra)

- FDA approved January 2023
- In United States, will be commercially available first quarter of 2024
- Combination ICS-SABA included in GINA 2023 guidelines
  - Alternative to ICS-formoterol

ICS Inhalers: Dosing

ICS	Total Daily ICS Dose (mcg)		
	Low	Medium	High
Beclomethasone	100-200	>200-400	>400
Budesonide	200-400	>400-800	>800
Fluticasone furoate	100		200
Fluticasone propionate	100-250	>250-500	>500
Mometasone	200-400		>400



Adult Guideline Recommendations

Terminology

Maintenance: asthma treatment prescribed for use every day

Reliever: asthma inhaler taken as needed, for quick relief of asthma symptoms

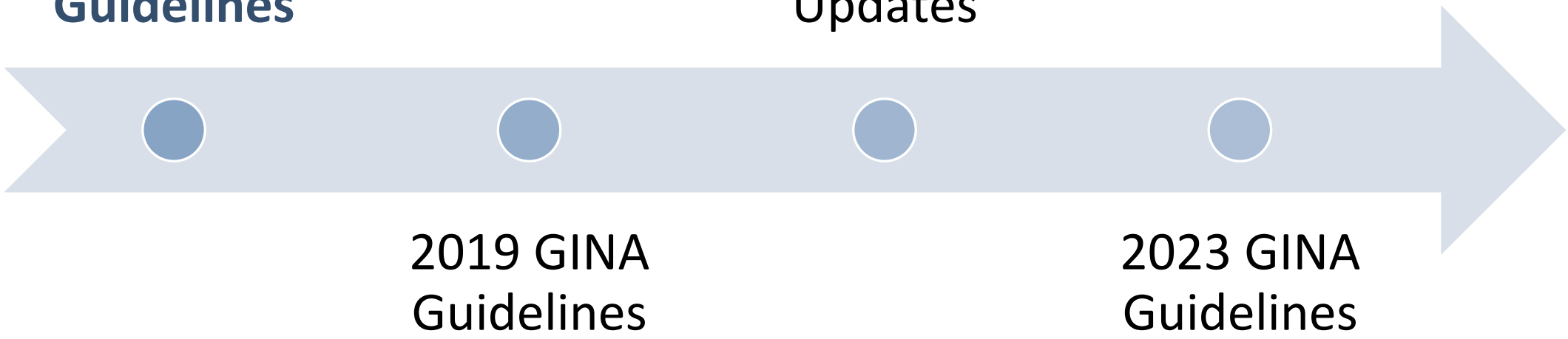
AIR: anti-**i**nflammatory **r**eliever, reliever inhaler contains both low-dose ICS and rapid-acting bronchodilator

SMART (AKA MART): single **m**aintenance **a**nd **r**eliever **t**herapy

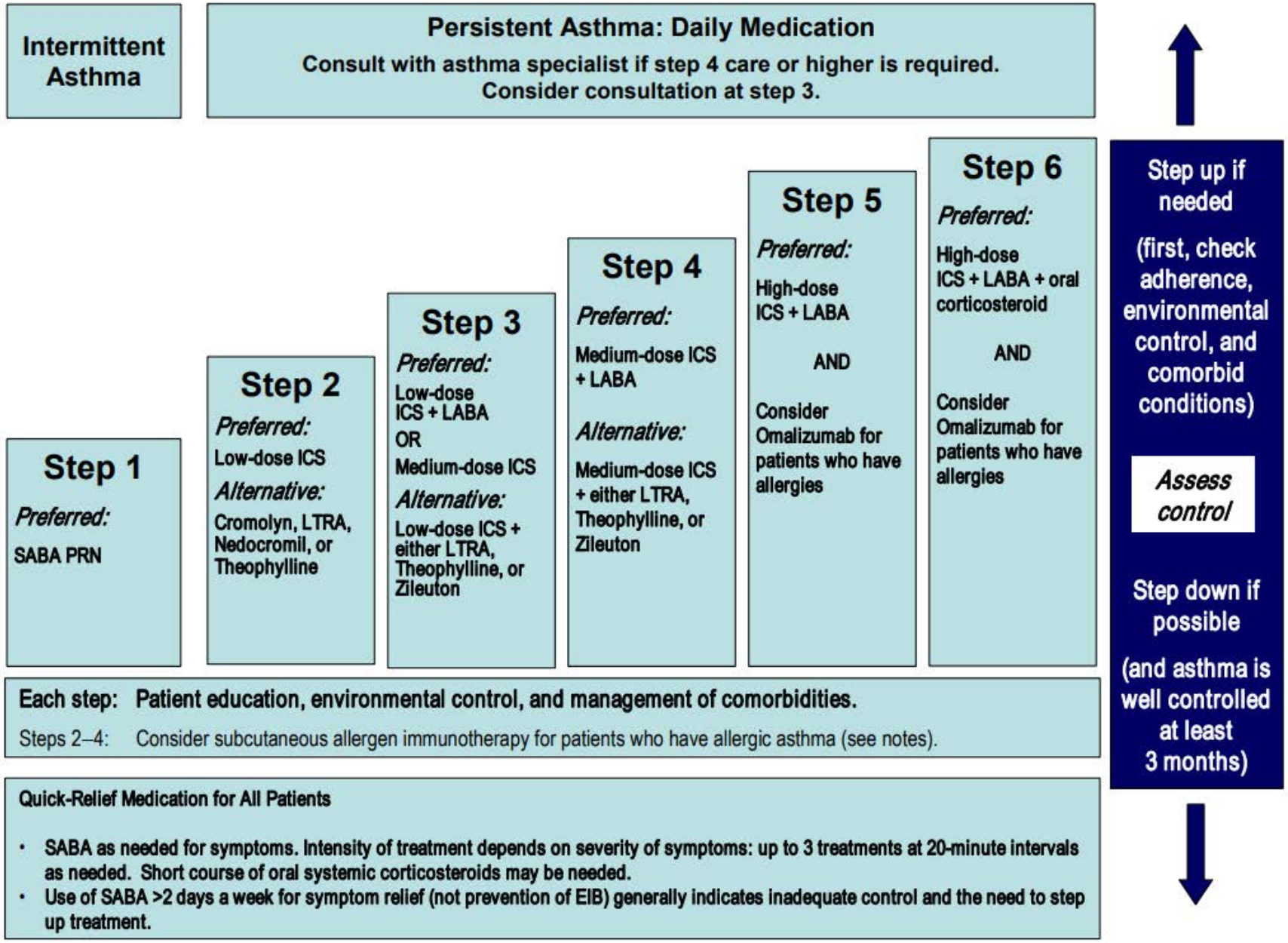
Literature on SABAs and Asthma Exacerbations

The Use of Beta-agonists and The Risk of Death and Near Death From Asthma			
Population	**Intervention**	**Outcome**	**Conclusion**
12,301 patients (5 to 54 years old) who were prescribed at least 10 asthma medications over 10-year period	Retrospective, matched case-control study	Near deaths or deaths from any inhaled β-agonist: (OR, 1.9; 95% CI 1.6 to 2.4)	Regular use of β2-agonist bronchodilators (fenoterol and albuterol) associated with increased risk of death from asthma

Asthma Recommendations

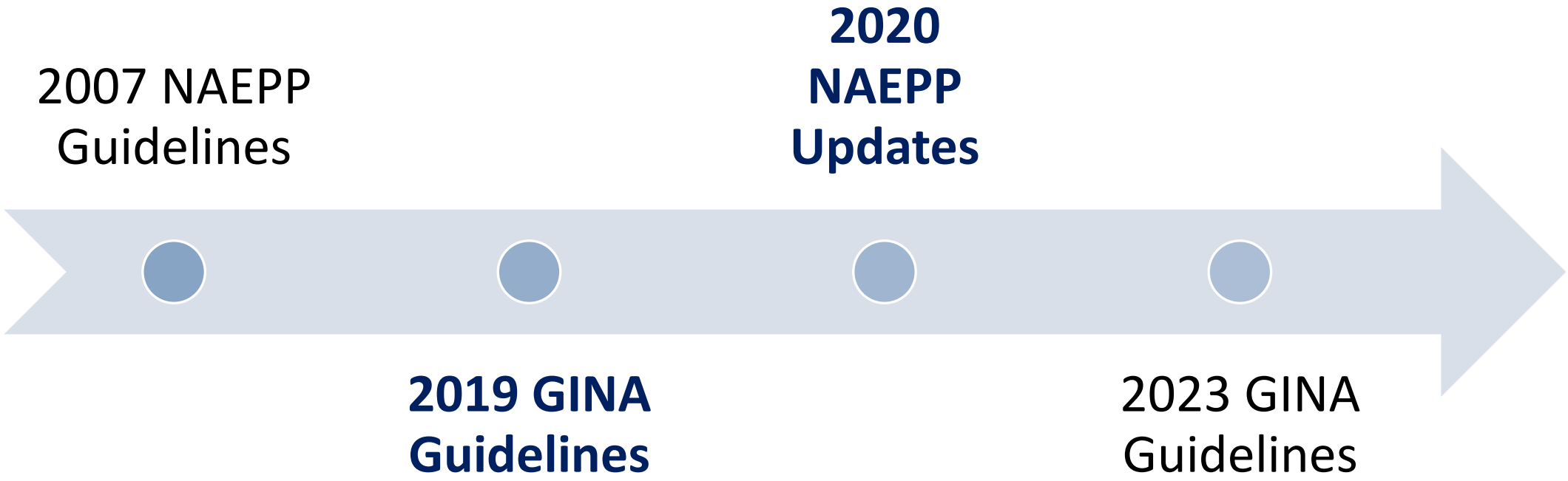


NAEPP 2007

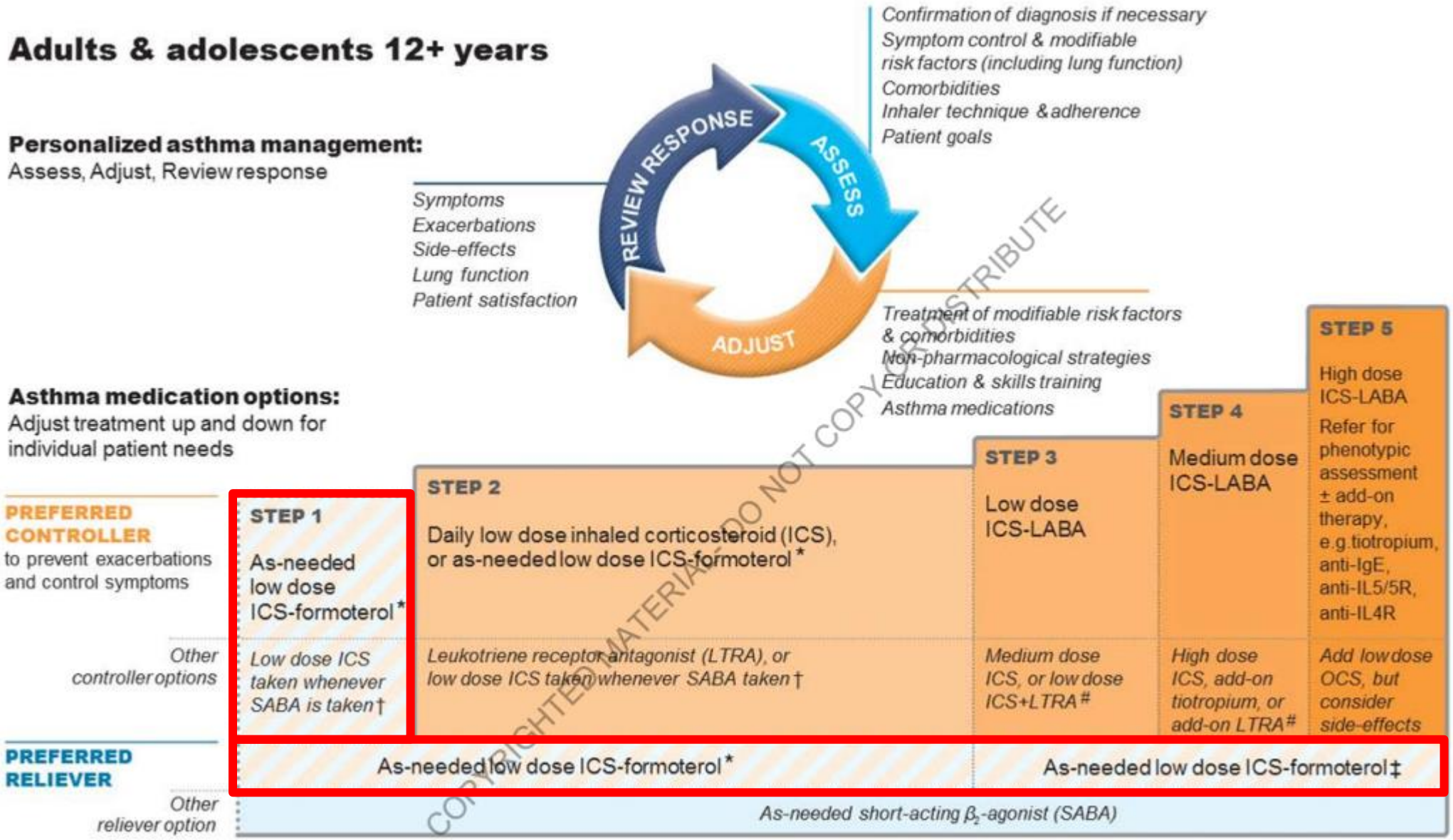


National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007 *J Allergy Clin Immunol*. 2007;120(5 Suppl):S94-S138.

Asthma Recommendations



Global Initiative for Asthma 2019 Guidelines



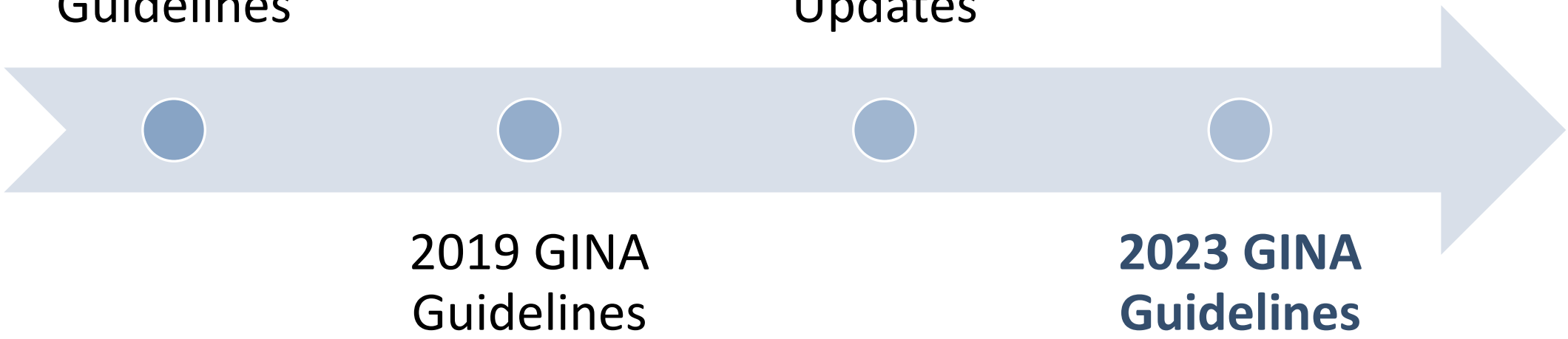
Mauer Y, Taliercio RM. Managing adult asthma: The 2019 GINA guidelines. *Cleve Clin J Med*. 2020;87(9):569-575.

NAEPP 2020 Updates

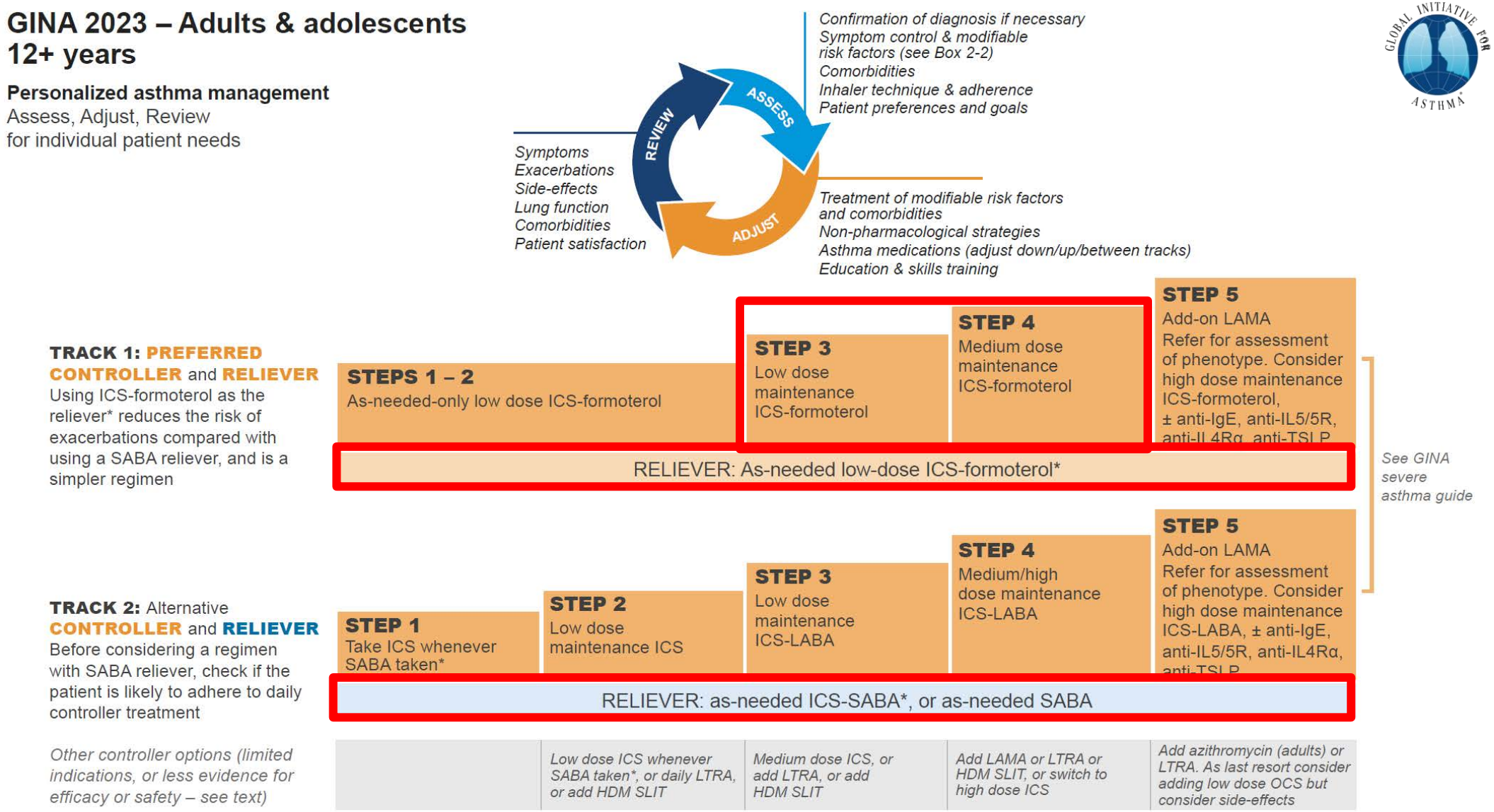
Treatment	Intermittent Asthma	Management of Persistent Asthma in Individuals Ages 12+ Years				
	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5	STEP 6 ■
Preferred	PRN SABA	Daily low-dose ICS and PRN SABA or PRN concomitant ICS and SABA▲	Daily and PRN combination low-dose ICS-formoterol▲	Daily and PRN combination medium-dose ICS-formoterol▲	Daily medium-high dose ICS-LABA + LAMA and PRN SABA▲	Daily high-dose ICS-LABA + oral systemic corticosteroids + PRN SABA
Alternative		Daily LTRA* and PRN SABA or Cromolyn,* or Nedocromil,* or Zileuton,* or Theophylline,* and PRN SABA	Daily medium-dose ICS and PRN SABA or Daily low-dose ICS-LABA, or daily low-dose ICS + LAMA,▲ or daily low-dose ICS + LTRA,* and PRN SABA or Daily low-dose ICS + Theophylline* or Zileuton,* and PRN SABA	Daily medium-dose ICS-LABA or daily medium-dose ICS + LAMA, and PRN SABA▲ or Daily medium-dose ICS + LTRA,* or daily medium-dose ICS + Theophylline,* or daily medium-dose ICS + Zileuton,* and PRN SABA	Daily medium-high dose ICS-LABA or daily high-dose ICS + LTRA,* and PRN SABA	

Expert Panel Working Group of the National Heart, Lung, and Blood Institute (NHLBI) administered and coordinated National Asthma Education and Prevention Program Coordinating Committee (NAEPPCC), Cloutier MM et al. *J Allergy Clin Immunol*. 2020;146(6):1217-1270.

Asthma Recommendations



Global Initiative for Asthma 2023 Guidelines



*Anti-inflammatory reliever (AIR)

Box 3-12

Literature Behind SMART Therapy

Combination Formoterol and budesonide as maintenance and reliever therapy versus current best practice (including inhaled steroid maintenance), for chronic asthma in adults and children

Methods

Objective	• To assess efficacy and safety of budesonide and formoterol in a single inhaler for maintenance and reliever therapy in asthma compared with maintenance with inhaled corticosteroids (ICS) (alone or as part of current best practice) and any reliever therapy	
Study Selection	• Utilized Cochrane Central, MEDLINE, EMBASE, CINAHL, AMED, and PsycINFO • Studies were included with the following parameters: – **Population:** Adults or children with chronic asthma – **Intervention:** combination of formoterol and budesonide as single inhaler therapy – **Comparator:** inhaled steroids and a separate reliever inhaler • 13 studies included, N=13,152	
Outcomes	**Primary** • Exacerbations requiring hospitalization • Exacerbations requiring oral corticosteroids • Serious adverse events (mortality and life-threatening events)	**Secondary** • Severe exacerbations (hospitalization/ER visit/oral steroid course) • Number of rescue medication puffs required per day

Cates CJ et al. *Cochrane Database Syst Rev*. 2013;2013(4):CD007313.

Results

Study	Country	Population Characteristics	Budesonide/formoterol Dose	Study Duration
DE-SOLO	Germany	N=1477; age ~46 yr; male ~41%; 60% low severity	160/4.5 µg, 1 inhalation BID plus PRN	26 weeks
MONO	Denmark, Finland, Norway	N=1835; age ~43 yr; male ~40%; mean ICS: 602 µg/day	160/4.5 µg, 1 inhalation BID plus PRN	26 weeks
PASSION	Turkey	N=430; age ~ 45 yr; male ~22%	160/4.5 µg, 1 inhalation BID plus PRN	26 weeks
Riemersma et al.	Netherlands	N=304; age ~40 yr; male ~20%; mean ICS: 538 µg/day mild asthma severity	80/4.5 µg, 2 inhalations BID plus PRN	12 months
SALTO	Belgium, Luxembourg	N=908; age ~43 yr; male ~44%; mean ICS: 580 µg/day	160/4.5 µg, 1 inhalation BID plus PRN	26 weeks
Scicchitano et al.	18 countries	N=1890; age ~43 yr; male ~42%; mean ICS: 746 µg/day, 83% severe asthma	160/4.5 µg, 2 inhalation daily plus PRN	12 months
SOLO	Canada	N=1538; age ~36 yr; male ~40%, mean ICS: 569 µg/day	160/4.5 µg, 1 inhalation BID	6 months
Sovani et al.	Nottinghamshire	N=71; age ~36 yr; male ~56%; mean ICS: 590 µg but only 278 µg taken	160/4.5 µg, 1 inhalation daily plus PRN	6 months
SPAIN	France, Lituania, Spain, UK	N=654; age ~44 yr; male ~36%	160/4.5 µg, 1 inhalation daily plus PRN	26 weeks
STAY-Adults	22 countries	N=2419; age ~35 yr; male ~45%; mean ICS: 660 µg/day	80/4.5 µg, 1 inhalation BID and PRN	12 months
STEAM	9 countries	N=696, age ~38 yr; male 18%; mean ICS: 348 µg/day	80/4.5 µg, 2 inhalations daily and PRN	6 months
STYLE	10 countries	N=1008, age ~45 yr; male ~36%; mean ICS: 243 µg/day	160/4.5 µg, 1 inhalation daily plus PRN	26 weeks
SYMPHONIE	France	N=1004, age ~45 yr; male ~41%; mean ICS: 792 µg/day	160/4.5 µg, 1 inhalation daily plus PRN	26 weeks

All studies funded by AstraZeneca

Cates CJ et al. *Cochrane Database Syst Rev*. 2013;2013(4):CD007313.

Results

	Population Characteristics	Budesonide/formoterol Dose	Study Duration
Multi-national • Europe • Asia • North America	**Sample Size:** N = 71-2419 **Age Range**: 12-80 years old **Male**: ~20-50% **Mean ICS dose**: 243-792 µg/day **Asthma severity**: mild to severe asthma	**Most common:** 160/4.5 µg 1 inhalation BID plus PRN	**Duration:** 26 weeks to 12 months

Cates CJ et al. *Cochrane Database Syst Rev*. 2013;2013(4):CD007313.

Study Outcomes

- **Exacerbations of asthma causing hospital admissions:**
  - 0.47% vs. 0.59% (OR 0.81; 95% CI 0.45 to 1.44)
- **Exacerbations of asthma treated with oral corticosteroids:**
  - 5.8% vs. 6.9% (OR 0.83; 95% CI 0.70 to 0.98)
- **Serious adverse events:**
  - Fatal events: 0.14% vs. 0.07% (OR 1.95; 95% CI 0.53 to 7.21)
  - Discontinuation due to adverse events: 2.1% vs. 0.74% (OR 2.85; 95% CI 1.89 to 4.3)

Conclusion:

- Single inhaler therapy reduces the number of exacerbations requiring oral steroids

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

Methods

Objective	• To conduct a systematic review and meta-analysis of the effects of SMART in patients with persistent asthma
Study Selection	• Utilized MEDLINE, EMBASE, Cochrane Central, and Cochrane Database • Studies were included with the following parameters: – **Population:** Adults or children with persistent asthma – **Intervention:** SMART – **Comparator:** either ICS alone or ICS/LABA as controller and SABA PRN • 16 studies included in analysis, N=22,748
Primary Outcome	• Asthma exacerbations

Sobieraj DM et al. *JAMA*. 2018;319(14):1485-1496.

Results

Study	Country	Population Characteristics	ICS/formoterol Dose	Duration
Scicchitano et al.	18 countries	N=1890; age ~43 yr; male ~42%; mean ICS: 746 µg/day, 83% severe asthma	160/4.5 µg, 2 inhalation daily plus PRN	12 months
Rabe et al.	20 countries	N=3394; age ~38 yr; male ~39%; mean ICS: 757 µg/day	80/4.5 µg, 2 inhalations daily plus PRN	6 months
Sovani et al.	Nottinghamshire	N=71; age ~36 yr; male ~56%; mean ICS: 590 µg but only 278 µg taken	160/4.5 µg, 1 inhalation daily plus PRN	6 months
STAY-Adults	22 countries	N=2419; age ~35 yr; male ~45%; mean ICS: 660 µg/day	80/4.5 µg, 1 inhalation BID and PRN	12 months
Vogelmeier et al.	Multinational	N=2143; age ~45 yr; male ~40%; mean ICS: 885 µg/day	160/4.5 µg, 2 inhalations BID plus PRN	12 months
Stallberg et al.	Sweden	N=1343; age ~44 yr; male ~40%; mean ICS: 645 µg/day	80/4.5 µg, 2 inhalations daily or 160/4.5 µg, 2 inhalations daily plus PRN	12 months
Atienza et al.	13 countries	N=2091; age ~45 yr; male ~32%; mean ICS: 660 µg/day	160/4.5 µg, 2 inhalations BID plus PRN	12 months
Papi et al.	14 European countries	N=1701; age ~48 yr; male ~30%; mean ICS: 1135 µg/day	Beclomethasone/formoterol: 84.6/5 µg BID + PRN	48 weeks
Patel et al.	New Zealand	N= 303; age ~42 yr; male ~31%; mean ICS: 807 µg/day	160/4.5 µg, 2 inhalations BID plus PRN	24 weeks
Hozawa et al.	Japan	N=30; age ~41 yr; male ~33%; mean ICS: 400-800 µg/day	160/4.5 µg, 2 inhalations BID plus PRN	8 weeks
Takeyma et al.	Japan	N=63; age ~40 yr; male ~37%; mean ICS: 592 µg/day	160/4.5 µg, 2 inhalations BID plus PRN	12 months
Lundborg et al.	Sweden	N=327; age ~39 yr; male ~45%; mean ICS: 715 µg/day	160/4.5 µg, 1 inhalation daily plus PRN	26 weeks
Bousquet et al.	17 countries	N=2309; age ~ 40 yr; males ~38%; mean ICS: 713 µg/day	160/4.5 µg, 2 inhalations BID plus PRN	6 months

All studies except 1-2 funded by AstraZeneca

Cates CJ et al. *Cochrane Database Syst Rev*. 2013;2013(4):CD007313.

Results

	Population Characteristics	ICS/formoterol Dose	Duration
Multi-national • Europe • Asia • North America	**Sample Size:** N = 30-3335 **Age Range**: 12-80 years old **Male**: ~30-55% **Mean ICS dose**: 592-1135 µg/day **Asthma severity**: moderate to severe asthma	**Most common:** 160/4.5 µg 1-2 inhalations BID plus PRN	**Duration:** 8 weeks to 12 months

Cates CJ et al. *Cochrane Database Syst Rev*. 2013;2013(4):CD007313.

Outcomes

SMART vs. ICS Controller	SMART associated with decreased risk of asthma exacerbations • Asthma exacerbations (same ICS dose): RR, 0.64 (95% CI, 0.53 to 0.78) • Asthma exacerbations (higher comparative ICS dose): RR, 0.59 (95% CI, 0.49 to 0.71)
SMART vs. ICS/LABA and SABA	SMART associated with lower risk of asthma exacerbations • Asthma exacerbations (same ICS dose): RR, 0.68 (95% CI, 0.58 to 0.80) • Asthma exacerbations (higher comparative ICS dose): RR, 0.77 (95% CI, 0.60 to 0.98)

Sobieraj DM et al. *JAMA*. 2018;319(14):1485-1496.

Strengths and Limitations of Both Meta-Analyses

Strengths

- Only included randomized controlled trials
- Multiple nationalities represented
- Large patient population
- Guideline references these meta-analyses to support recommendations

Limitations

- Open label trials included
  - 2013 review– 10 out of 13 trials
  - 2018 review– 6 out of 16 trials
- Limited to mostly European studies
- Different follow-up periods
- Funding bias in both meta-analyses (most studies funded by drug manufacturer)

Cates CJ et al. *Cochrane Database Syst Rev*. 2013;2013(4):CD007313.
Sobieraj DM et al. *JAMA*. 2018;319(14):1485-1496.

SMART Therapy Recommendations

- Budesonide/formoterol as maintenance therapy one to two puffs once or twice daily (depending on asthma severity)
- Maximum PRN recommended dose per day: 54 mcg formoterol (12 puffs)
- Rinsing mouth not needed after PRN use of low dose ICS-formoterol
  - No increase in risk of oral thrush

Knowledge Check

According to the GINA 2023 guidelines and the NAEPP 2020 updates, which of the following is the preferred inhaler to be used as a rescue medication for patients with asthma?

A. Symbicort (budesonide/formoterol)
B. ProAir HFA (albuterol)
C. Pulmicort (budesonide)
D. Spiriva (tiotropium)

Knowledge Check

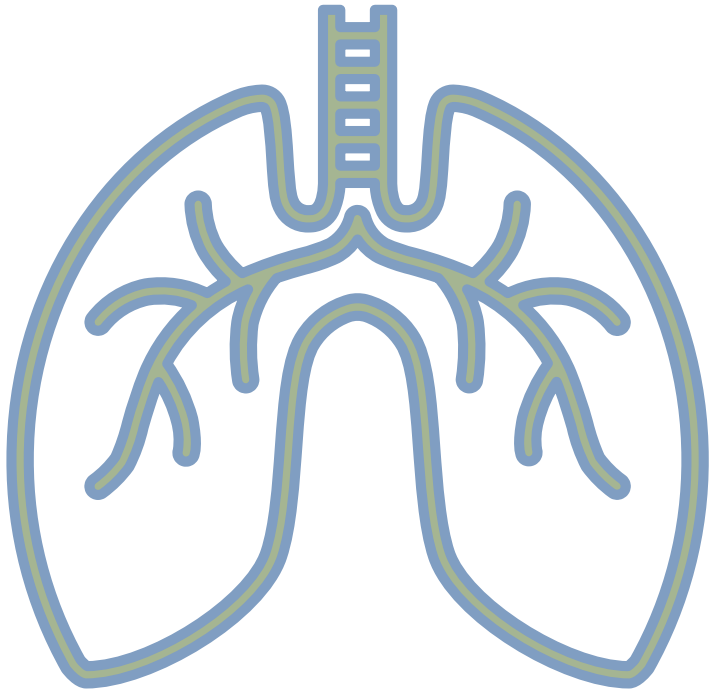
According to the GINA 2023 guidelines and the NAEPP 2020 updates, which of the following is the preferred inhaler to be used as a rescue medication for patients with asthma?

A. **Symbicort (budesonide/formoterol)**
B. ProAir HFA (albuterol)
C. Pulmicort (budesonide)
D. Spiriva (tiotropium)

SMART Implementation: Barriers

- Lack of FDA approval
- Inconsistent insurance coverage: financial barrier
  - Quantity Limits
    - Limit on amount of medication prescribed per month. SMART may require more medication use than typical 30-day
  - Prior authorization, age limits, step therapy
- Limited options of ICS-formoterol combination available

Which reliever agent is preferred to reduce exacerbations while on scheduled ICS, combination ICS-formoterol/SABA or SABA alone?



Literature Review

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

ISRAEL E, ET AL. N ENGL J MED. 2022;386(16):1505-1518

Study Objective

To assess if patient-guided, reliever-triggered ICS strategy could improve asthma outcomes in Black and Latinx patients with poorly controlled asthma

Methods

Design	• Randomized, open-label, pragmatic trial
Intervention	• 1:1 to either patient-activated reliever-trigger ICS (beclomethasone dipropionate) + usual care or to continue usual care • Intervention: one puff ICS for each puff of quick-reliever inhaler and five puffs ICS with each quick-reliever nebulization • Patient uses ICS each time a reliever medication such as SABA (e.g., albuterol) is used

Methods

INCLUSION

Adults 18-75 y.o. with asthma who self-identified as Black or Latinx

Prescribed daily inhaled glucocorticoids with or without LABA

Have uncontrolled asthma or at least one participant-reported asthma exacerbation leading to use of systemic glucocorticoids or overnight hospitalization in the previous year

EXCLUSION

Taking regular systemic glucocorticoids

Methods	
Primary Endpoint	• Annualized rate of severe asthma exacerbations (use of systemic glucocorticoids for ≥3 days or an asthma-related hospitalization)
Secondary Endpoints	• Monthly asthma control measured with ACT • Quality of life • Participant-reported days missed from work, school, or usual activities
Safety Endpoints	• Hospitalizations or death

Israel E, et al. N Engl J Med. 2022;386(16):1505-1518

Methods

Statistical Analysis	• Sample of **1200 participants** would provide the trial with **80% power** to detect a **23.5% difference** in exacerbation rate • **Study met power** • Analysis of timing and frequency of severe asthma exacerbation performed with **Cox proportional-hazards model** • **Hazard ratio** obtained to measure relative risk of severe asthma exacerbation event • Intention to treat analysis

Baseline Characteristics

	Patients, No. (%)	
Characteristic	Intervention (N=600)	Usual-Care (N=601)
Black - %	50.5	49.9
Latinx - %	49.5	50.1
Age – yr	48.3±13.5	47.0±13.9
Female - %	84.7	82.7
Obesity - %	35.2±9.1	35.1±9.5
Use of quick-reliever nebulizer - %	68.0	65.9
≥ 1 Asthma exacerbation in past year - %	73.3	71.0
Asthma Control Test (ACT) score	14.7±4.4	14.5±4.5

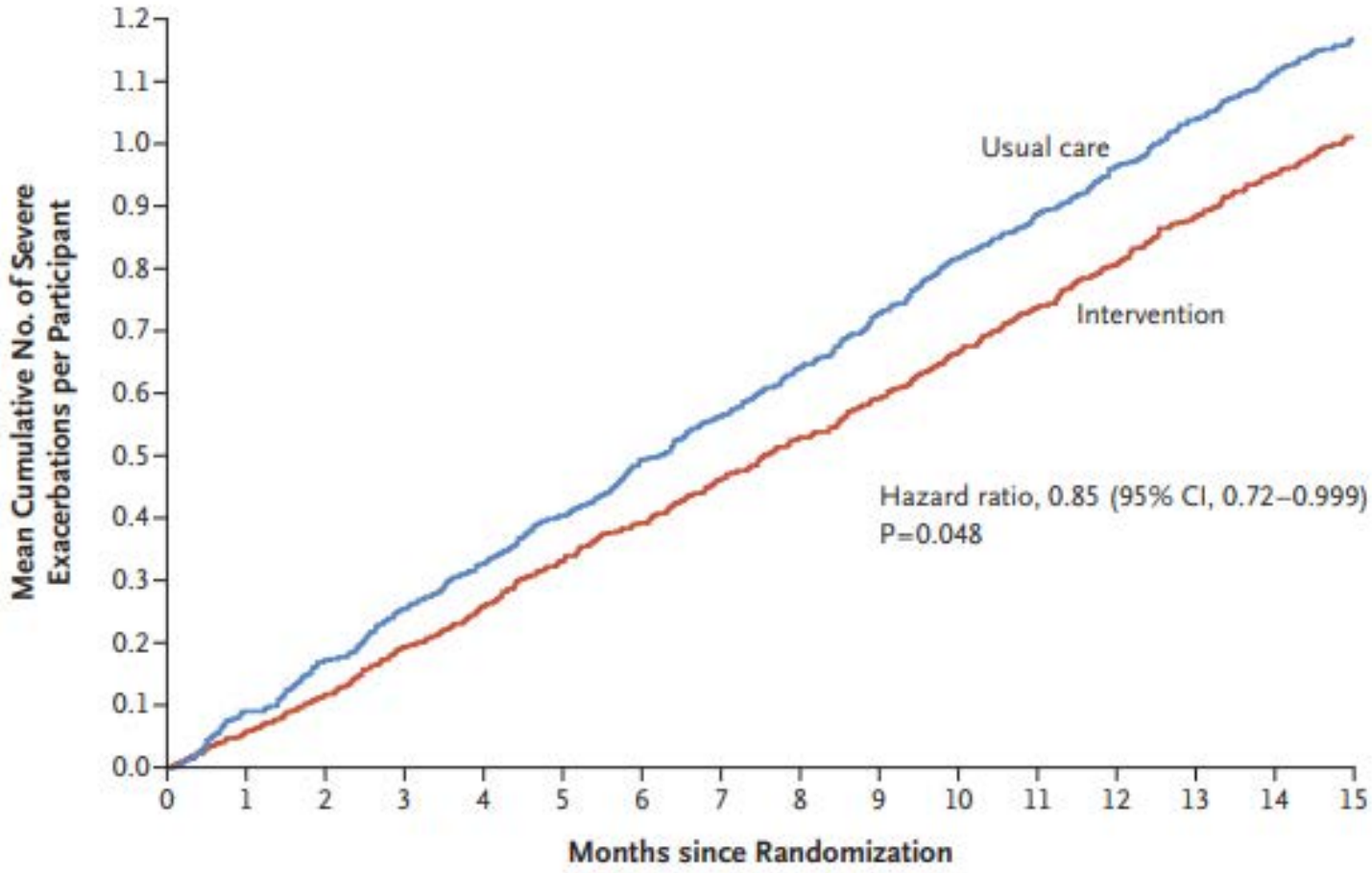
Israel E, et al. N Engl J Med. 2022;386(16):1505-1518

Maintenance Asthma Medications at Baseline

Maintenance Asthma Medications	Patients	
	Intervention (N=600)	Usual-Care (N=601)
ICS without LABA	28.5	28.1
ICS with LABA	71.3	71.7
LAMA	10.7	13.1
Leukotriene-receptor antagonist	51.3	48.3
Biologic agent	2.8	3.2

Israel E, et al. N Engl J Med. 2022;386(16):1505-1518

Primary Outcome



No. at Risk																
Usual care	601	598	594	593	591	588	585	583	579	577	575	575	575	572	561	550
Intervention	600	597	593	592	591	589	588	581	580	576	572	569	562	558	551	536

Israel E, et al. N Engl J Med. 2022;386(16):1505-1518

Outcomes

	Intervention (N=600)	Usual-Care (N=601)	Between-Group Comparison (95% CI)	P-value
Primary analysis: severe asthma exacerbation				
Total no. of exacerbations	585	680		
Adjusted annualized rate per participant (95% CI)	0.69 (0.61–0.78)	0.82 (0.73–0.92)	HR: 0.85 (0.72-0.999)	0.048
Secondary analyses				
Asthma Control Test				
Mean baseline score (95%)	14.7 (14.4–15.1)	14.5 (14.2–14.9)		
Least squares mean change from baseline (95% CI)	3.4 (3.1–3.6)	2.5 (2.3–2.8)	Difference: 0.9 (0.5–1.2)	
Annualized no. of days missed from work school, or usual activities (95% CI)	13.4 (11.9–15.2)	16.8 (14.9–18.9)	Rate ratio: 0.80 (0.67–0.95)	
Post hoc analysis				
Annualized no. of months with reported asthma-related ED or urgent care visit (95% CI)	0.75 (0.65–0.87)	0.90 (0.77–1.04)	Rate ratio: 0.84 (0.68–1.03)	

Israel E, et al. N Engl J Med. 2022;386(16):1505-1518

Safety Outcomes

	Patients, No. (%)	
	Intervention (n=609)	Usual Care (n=611)
Any serious adverse event	75 (12.3)	74 (12.1)
Infections and infestations	12 (2.0)	8 (1.3)
Cardiac events	8 (1.3)	10 (1.7)
Death	3 (0.5)	4 (0.7)
Hospitalization	72 (11.8)	70 (11.5)
Asthma-related hospitalization	45 (7.4)	44 (7.2)

Israel E, et al. N Engl J Med. 2022;386(16):1505-1518

Adherence

Self-reported adherence:

- 81% using ICS with quick-reliever MDI all or most of the time
- 75.7% using ICS with quick-reliever nebulization all or most of the time
- 50.4% using at least four of instructed five puffs of ICS per quick-reliever nebulization

Strengths

Pragmatic Inclusion/Exclusion Criteria

Increased external validity – results more generalizable to practice

No Funding Bias

Not funded by manufacturer

Adherence Check

Mean adherence: ~78%

~50% using at least four of instructed five puffs of ICS per quick-reliever nebulization

Minimize confounding factors

Intention-to-treat analysis and large sample size

Increased internal validity

Study Met Power

Increased internal validity

Israel E, et al. N Engl J Med. 2022;386(16):1505-1518

Limitations

Controller Medications

Not specify which ICS inhalers patients are using

Did not include how often rescue agent used

Self-reported Adherence

No way to validate adherence

Open-label

Possible bias

Key Takeaway

In black and Latinx patients with **uncontrolled moderate-to-severe asthma**, the risk of severe asthma exacerbation was significantly lower with the use of **beclomethasone dipropionate (ICS)** when quick-reliever therapy was used.

- **Recommend ICS + reliever therapy** in addition to maintenance therapy

Most patients (~71%) were using ICS + LABA as maintenance medication concomitantly

Albuterol-Budesonide Fixed-Dose Combination Rescue Inhaler for Asthma (MANDALA)

PAPI, ET AL. NEJM 2022; 386(22):2071-2083

Study Objective

To evaluate the efficacy and safety of as-needed use of albuterol-budesonide compared to as-needed use of albuterol alone in patients with **moderate-to-severe asthma**

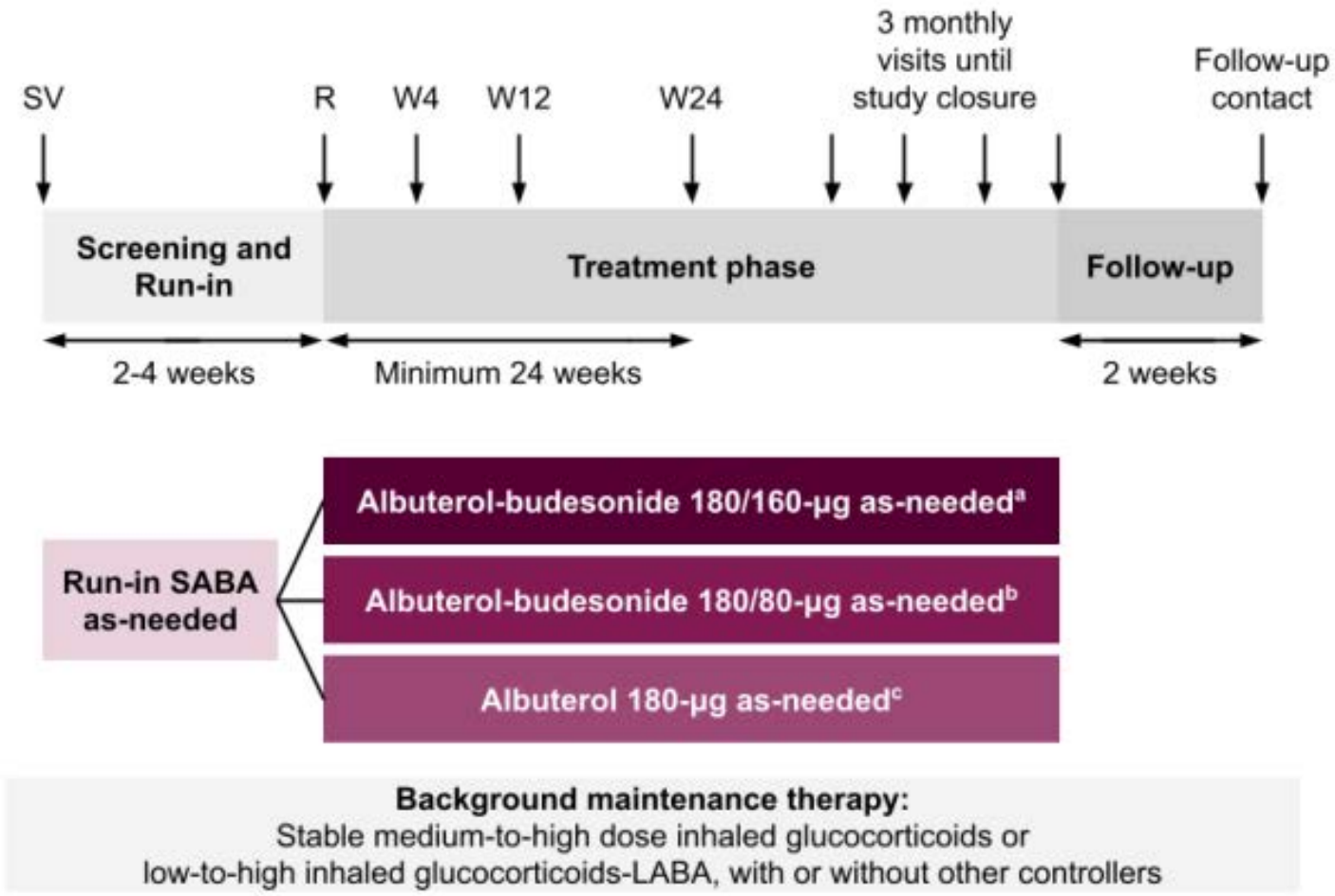
Methods

Design	• Multinational, phase 3, double-blind, randomized, parallel-group, event driven trial

Intervention	• 1:1:1 ratio to one of three **reliever** groups
	  • **Higher-dose combination**: fixed-dose combination of 180 µg of albuterol and 160 µg of budesonide
	  • **Lower-dose combination**: fixed-dose combination of 180 µg of albuterol and 80 µg of budesonide
	  • **Albuterol-alone**: 180 µg of albuterol
	• Pressurized metered-dose inhaler
	• 4 to 11 y.o. assigned to lower-dose combination or albuterol-alone group
	• Max: 6 doses of trial medication per day

Papi, et al. NEJM 2022; 386(22):2071-2083

Trial Design



Methods

INCLUSION

Symptomatic patients with asthma ≥ 4 yo and had at least one severe asthma exacerbation in the previous 12 months

Medium to high dose of ICS or low to high dose of ICS/LABA for ≥ 3 months, stable dose ≥ 4 weeks

FEV_1 of 40% - 90% of predicted normal value

FEV_1 reversibility of at least 12%

ACQ-5 of 1.5 or greater at visit 2

EXCLUSION

COPD or other notable lung disease

Use of systemic glucocorticoid within 3 months before screening

Use of biologic treatments within 3 months or for duration of 5 half-lives before screening

Methods	
Primary Endpoint	• First event of severe asthma exacerbation in a time-to-event analysis
Secondary Endpoints	• Annualized rate of severe asthma exacerbations • Total systemic glucocorticoid exposure for asthma during treatment period • Response at week 24 on ACQ-5
Safety Endpoints	• Incident of adverse events

Papi, et al. NEJM 2022; 386(22):2071-2083

Methods

Statistical Analysis	• Sample of **1000 adults and adolescents per trial group** and **570 first events** of severe asthma exacerbation would provide the trial with **87% power** to detect a **25% lower risk** of severe asthma exacerbation • **Study met power** • Analysis of primary endpoint performed with **Cox proportional-hazards regression model** • **Hazard ratio** obtained to measure relative risk of severe asthma exacerbation event • Intention to treat analysis

Papi, et al. NEJM 2022; 386(22):2071-2083

Baseline Characteristics

	Patients, No. (%)		
Characteristic	Albuterol (180 µg)–Budesonide (160 µg) (N=1013)	Albuterol (180 µg)–Budesonide (80 µg) (N=1054)	Albuterol (180 µg) (N=1056)
Mean age	50.6±15.1	48.5±16.7	49.1±17.2
White race/ethnicity	818 (80.8)	847 (80.4)	868 (82.2)
Hispanic or Latinx	233 (23.0)	260 (24.7)	315 (29.8)
Low-dose ICS-LABA or medium-dose ICS	314 (31.0)	334 (31.7)	308 (29.2)
Medium-dose ICS-LABA or high-dose ICS	385 (38.0)	435 (41.3)	441 (41.8)
High-dose ICS–LABA	295 (29.1)	267 (25.3)	285 (27.0)
Severe asthma exacerbations: 1	788 (77.8)	822 (78.0)	840 (79.5)
Severe asthma exacerbations: 2	185 (18.3)	185 (17.6)	164 (15.5)
Severe asthma exacerbations: 3	27 (2.7)	38 (3.6)	45 (4.3)
Severe asthma exacerbations: ≥ 4	13 (1.3)	9 (0.9)	7 (0.7)

Papi, et al. NEJM 2022; 386(22):2071-2083

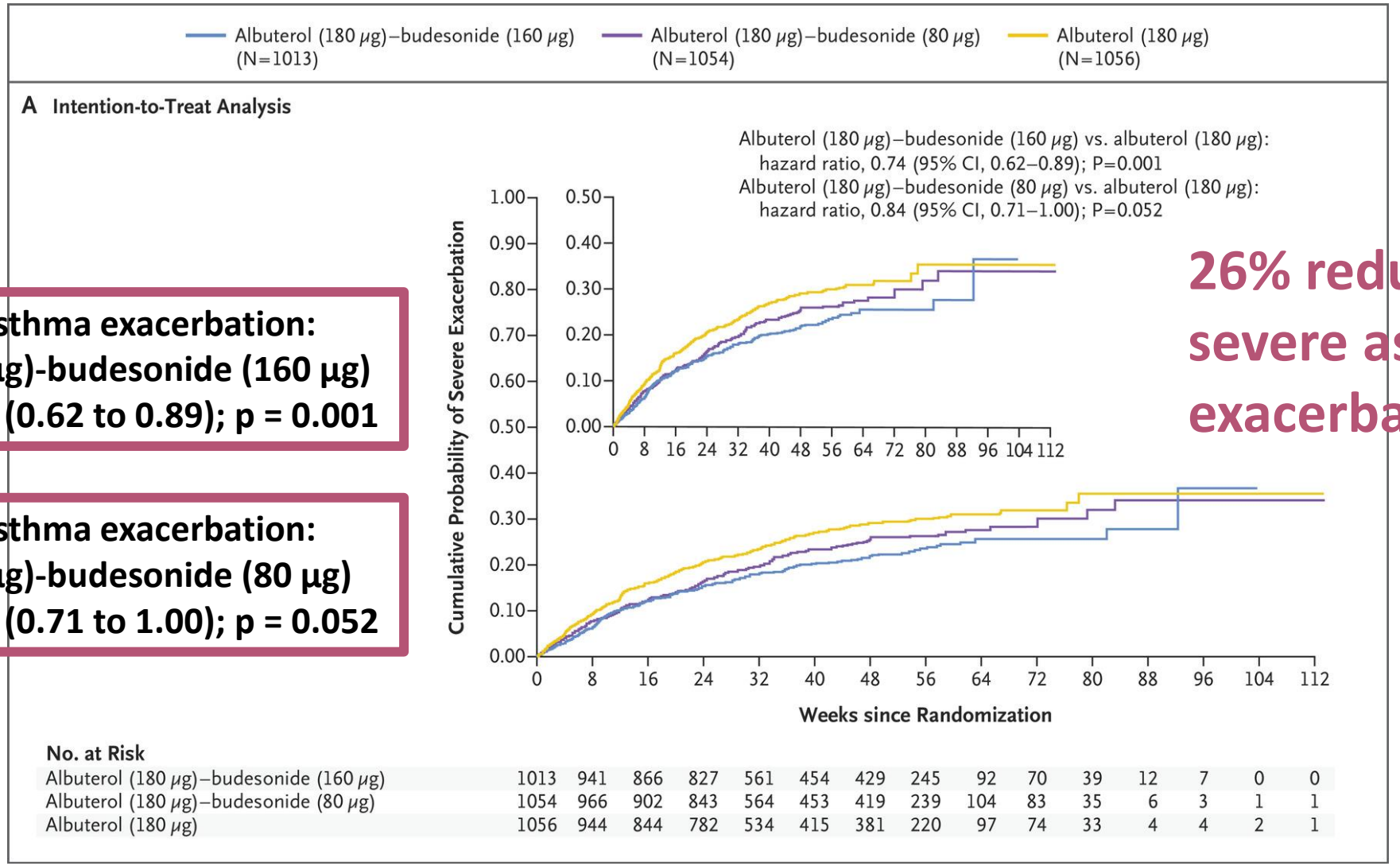
Maintenance ICS at Screening

	Patients		
ICS	Albuterol (180 µg)–Budesonide (160 µg) (N=1013)	Albuterol (180 µg)–Budesonide (80 µg) (N=1054)	Albuterol (180 µg) (N=1056)
Beclomethasone dipropionate	133	131	127
Budesonide	352	411	404
Fluticasone furoate	99	103	112
Fluticasone propionate	338	345	328
Mometasone furoate	6	3	7
Other	78	61	74

Primary Outcome Results

Risk of severe asthma exacerbation:
Albuterol (180 µg)-budesonide (160 µg)
HR 0.74; 95% CI (0.62 to 0.89); p = 0.001

Risk of severe asthma exacerbation:
Albuterol (180 µg)-budesonide (80 µg)
HR 0.84; 95% CI (0.71 to 1.00); p = 0.052



26% reduction of severe asthma exacerbation

Papi, et al. NEJM 2022; 386(22):2071-2083

Secondary Outcomes – Intention to Treat Analysis

	Adults and Adolescents	
	Albuterol (180 µg)–Budesonide (160 µg)	Albuterol (180 µg)
Annualized rate of severe asthma exacerbation		
Severe exacerbations – no.	345	427
Annualized rate (95% CI)	0.43 (0.33–0.58)	(0.44–0.77)
Rate ratio (95% CI)	0.75 (0.61–0.91)	Reference
Annualized total dose of systemic glucocorticoid		
Mean value – mg/yr	83.6±247.7	130.0±630.3
ACQ-5		
Patients with response – no. (%)	682 (67.3)	636 (62.7)
Odds ratio (95% CI)	1.22 (1.01–1.46)	Reference

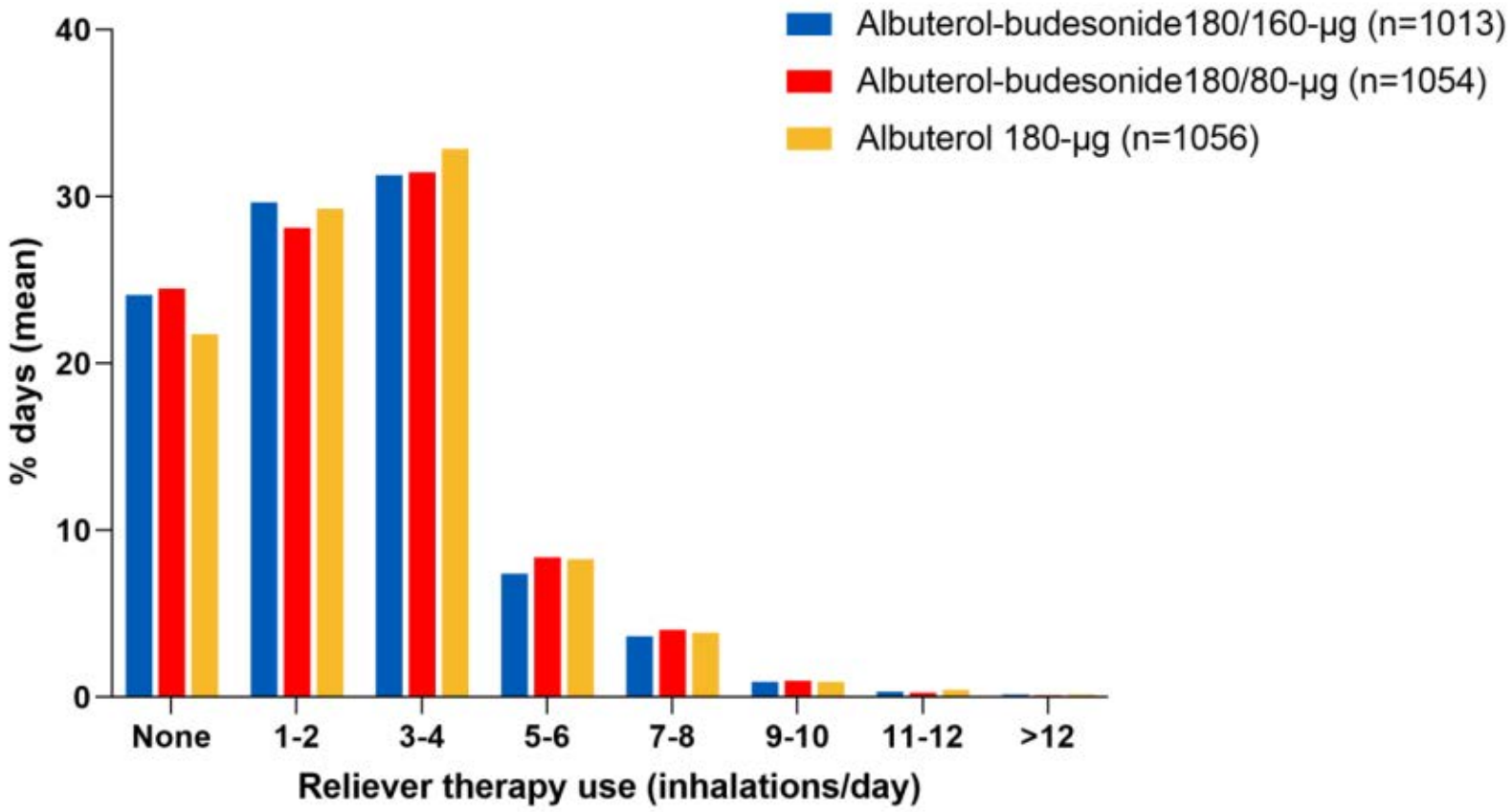
Papi, et al. NEJM 2022; 386(22):2071-2083

Safety Outcomes

	Patients, No. (%)		
	Albuterol (180 µg)–Budesonide (160 µg) (N=1015)	Albuterol (180 µg)–Budesonide (80 µg) (N=1055)	Albuterol (180 µg) (N=1057)
Any Adverse event	469 (46.2)	497 (47.1)	490 (46.4)
Nasopharyngitis	76 (7.5)	61 (5.8)	54 (5.1)
Headache	44 (4.3)	50 (4.7)	50 (4.7)
Upper respiratory tract infection	26 (2.6)	31 (2.9)	26 (2.5)
Oral candidiasis	10 (1.0)	9 (0.9)	5 (0.5)
Dysphonia	4 (0.4)	6 (0.6)	4 (0.4)
Any serious adverse event (including death)	53 (5.2)	40 (3.8)	48 (4.5)
Any AE leading to discontinuation of treatment	10 (1.0)	9 (0.9)	9 (0.9)

Papi, et al. NEJM 2022; 386(22):2071-2083

Percentage of Trial Days with Study Medication Use



Papi, et al. NEJM 2022; 386(22):2071-2083

Adherence

- Documented by patients or their guardians with use of an electronic diary and monitored by investigators and staff at trial site
- Similar adherence in the three trial groups
  - Median: 84.6%

Strengths

Multicenter

Increased external validity

Low Dropout Rate

- 7% dropout rate
- Low attrition bias

Adherence Check

Mean adherence: ~82%

Minimize confounding factors

Intention-to-treat analysis and large sample size

Increased internal validity

Study Met Power

Increased internal validity

Papi, et al. NEJM 2022; 386(22):2071-2083

Limitations

Controller Medications

Patients using different controller medications at baseline

Duration

- Not long enough to study long term effects

Comparator

Compared to PRN albuterol instead of guideline recommended ICS/formoterol

Funding Bias

Funded by Avillion

- Co-partnership: Avillion and AstraZeneca

Avillion coordinated data management and statistical analyses

AstraZeneca funded first draft of manuscript

Papi, et al. NEJM 2022; 386(22):2071-2083

Key Takeaway

In patients with **uncontrolled moderate-to-severe asthma**, the risk of severe asthma exacerbation was significantly lower with **fixed-dose combination of 180 µg of albuterol and 160 µg of budesonide** compared to as-needed use of albuterol alone.

Stable, scheduled dose of ICS

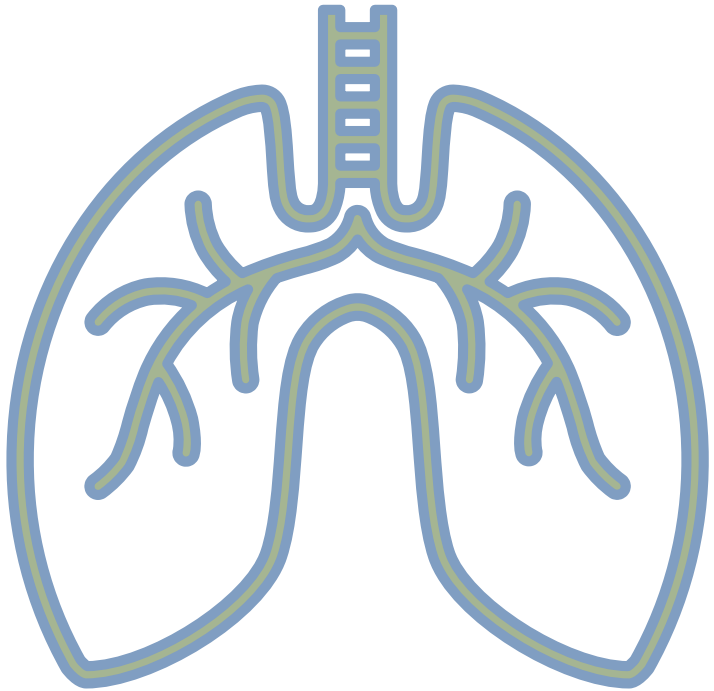
- Should be on scheduled medium to high dose ICS for at least 3 months with no dose changes for at least 4 weeks

PREPARE and MANDALA Takeaway

	PREPARE (2022)	MANDALA (2022)
Intervention	Reliever: ICS + reliever	Reliever: budesonide/albuterol
Results	Annualized rate of severe asthma exacerbations (**statistically significant**)	First event of severe asthma exacerbation (**statistically significant**)
Safety	No statistical difference	No statistical difference
Adherence	~78%	~82%
Funding	Patient-Centered Outcomes Research Institute	AstraZeneca

In patients with **uncontrolled moderate-to-severe asthma**, the risk of severe asthma exacerbation was significantly lower with the use of **ICS and LABA or SABA** as **reliever therapy** while on **ICS maintenance**

Israel E, et al. N Engl J Med. 2022;386(16):1505-1518
Papi, et al. NEJM 2022; 386(22):2071-2083



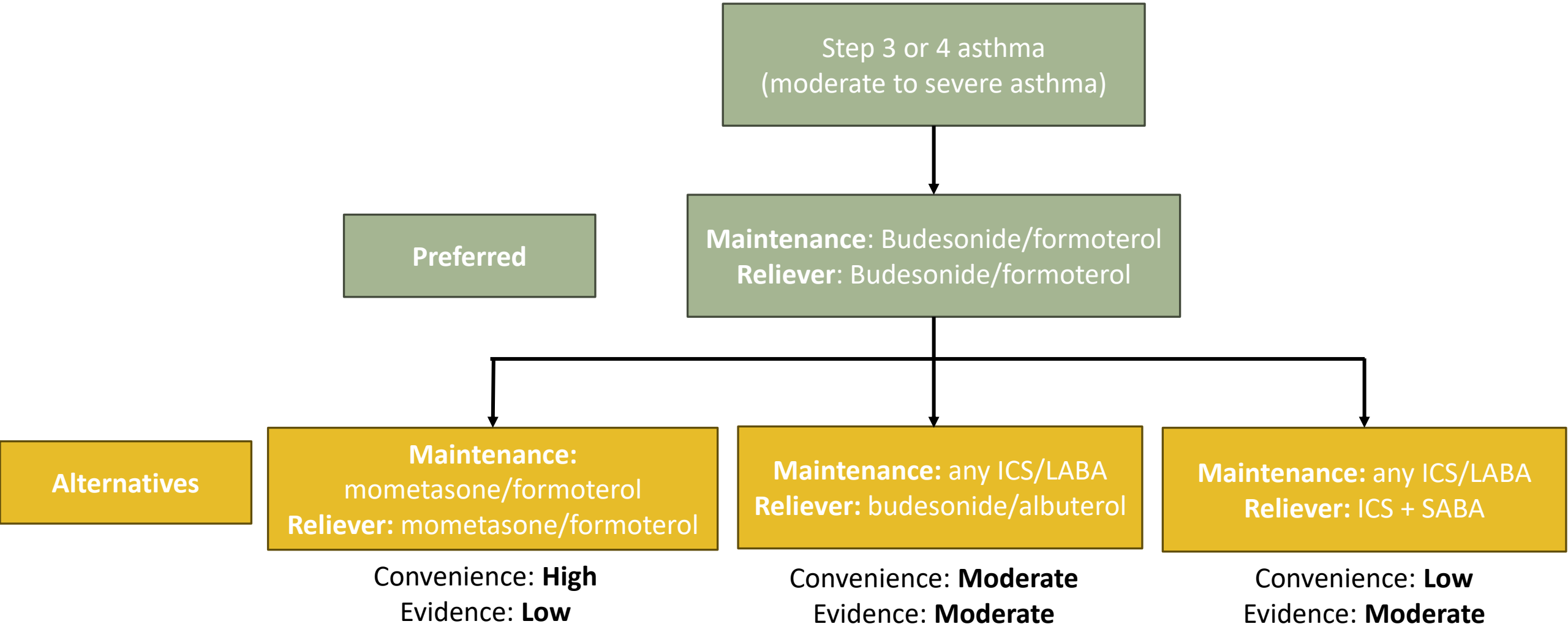
Summary and Conclusions

My Recommendation

- Who? Patients with moderate to severe asthma
- What? Combination ICS-formoterol or SABA should be preferred over SABA as a reliever when on scheduled ICS
  - Adding ICS to reliever therapy provides additional benefits by helping reduce severe asthma exacerbations
  - Does not necessarily have to be single inhaler or SMART therapy to provide additional benefits

❖ Remember: if asthma uncontrolled – need to increase ICS maintenance dose (step-up)

Reliever Algorithm

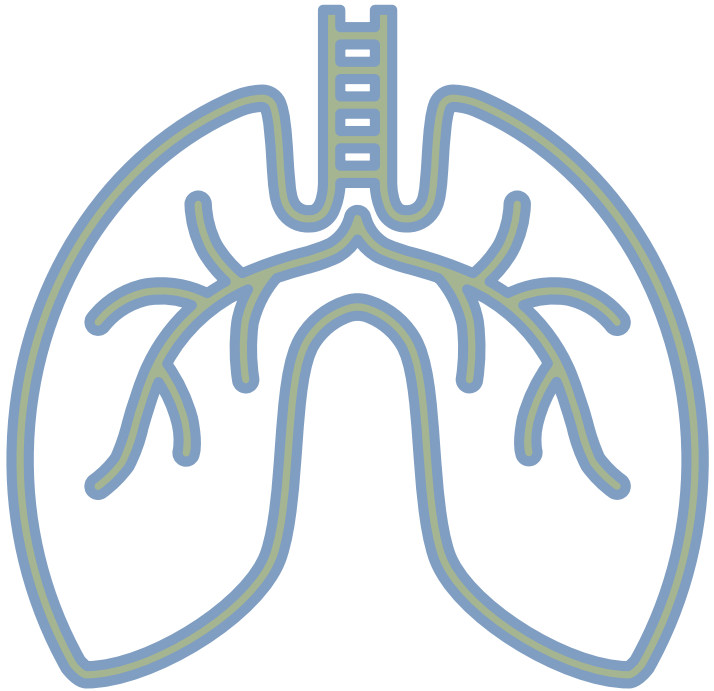


Additional Resources for Pharmacists

GINA. Global Strategy for Asthma Management and Prevention, 2023. Updated May 2023. Available from www.ginasthma.org

Expert Panel Working Group of the National Heart, Lung, and Blood Institute (NHLBI) administered and coordinated National Asthma Education and Prevention Program Coordinating Committee (NAEPPCC), Cloutier MM et al. J Allergy Clin Immunol. 2020;146(6):1217-1270.

Respiratory Inhalers-at-a-Glance and Other Posters in Our Online Store | Allergy & Asthma Network. allergyasthmanetwork.org. https://allergyasthmanetwork.org/news/inhalers-at-a-glance-posters-resources/



Post Test Questions

1. Which of the following statements regarding the 2023 GINA guideline recommendations for asthma is true?

A. The preferred rescue agent for patients with severe asthma is albuterol
B. Single maintenance and reliever therapy (SMART) can be used with any ICS-LABA inhalers such as budesonide-formoterol, fluticasone-salmeterol, or mometasone-formoterol
C. The recommended ICS-LABA when using SMART therapy is budesonide-formoterol
D. There is no max dose when using a rescue inhaler

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A. The preferred rescue agent for patients with severe asthma is albuterol
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C. **The recommended ICS-LABA when using SMART therapy is budesonide-formoterol**
D. There is no max dose when using a rescue inhaler

2. Which of the following is/are limitations of the MANDALA trial?

A. Possible funding bias from being funded by AstraZeneca
B. The comparator group consisted of PRN ICS/formoterol instead of standard of care albuterol
C. Low adherence rate
D. All of the above

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B. The comparator group consisted of PRN ICS/formoterol instead of standard of care albuterol
C. Low adherence rate
D. All of the above

3. AZ is a 25-year-old female with a past medical history of asthma. Her home medications include Symbicort (budesonide-formoterol) BID and Proair (albuterol) prn. Her asthma is not well controlled with a recent exacerbation that required hospitalization 3 months ago. She reports not regularly using her inhalers and gets confused on which inhaler is supposed to be used for maintenance and which one to use as a rescue agent. Which of the following recommendations is the best choice for AZ?

A. Increase the ICS maintenance dose of Symbicort BID and continue Proair prn
B. Start dexamethasone daily to help prevent exacerbations
C. Switch therapy to Symbicort as both maintenance (BID) and reliever therapy (prn)
D. Switch Symbicort to Breo (fluticasone-vilanterol) once daily maintenance and reliever therapy (prn)

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4. AT is a 55-year-old male with a PMH of asthma, type 2 diabetes, hypertension, and hyperlipidemia. His home medications include Wixela (fluticasone/salmeterol) 500/50 one inhalation po BID (ICS high dose), metformin 1000 mg po BID, losartan 25 mg po daily, and atorvastatin 20 mg po daily. AT has been on albuterol PRN for 40 years and experienced an asthma exacerbation requiring hospitalization 6 months ago. Which inhaler is the best rescue inhaler to prevent an asthma exacerbation?

A. Pulmicort (budesonide) PRN
B. Airsupra (budesonide/albuterol) PRN
C. Proair (albuterol) scheduled
D. Proair (albuterol) PRN

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C. Proair (albuterol) scheduled
D. Proair (albuterol) PRN

Special Thanks

- Kimberly Cauthon, PharmD, CGP, BC-ADM: Faculty Mentor
- Hansita Patel, PharmD, BCACP: Critique

Power Puff Inhaler Combo: Use of Combination ICS-LABA/SABA vs. SABA as a Reliever if on Scheduled ICS

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