Mass General Brigham
Brigham Research Institute

Clearing the Air:

Insights and Controversies in the Asthma Guidelines

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March 2024

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Disclosures

None

Outline

Redefining Reversibility
Updated criteria for bronchodilator response

Regulatory Roadblocks
GINA, Symbicort, and the FDA

Rapid Relief
Patient preferences for reliever therapies

Respiratory Responsibility
The global impact of treatment decisions

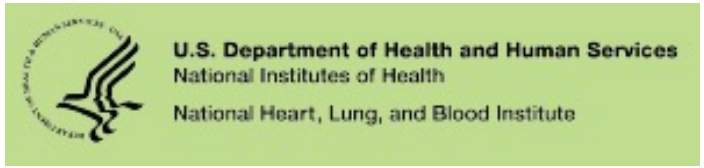
Summary and Questions

Guidelines and recommendations

GINA (annual)

ATS/ERS (2022)

NAEPP (2020)



BTS/SIGN (2019)

Redefining Reversibility

Updates to Bronchodilator Response

ATS/ERS lung function testing 2022

Topics Covered

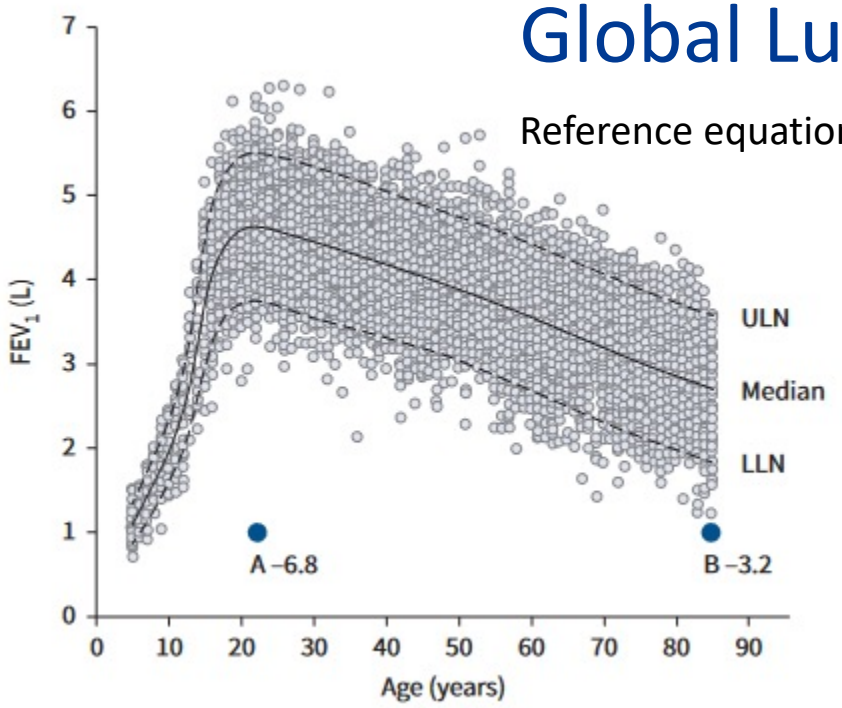
Reference equations

Normal range

Bronchodilator response

Severity

ERS/ATS technical standard on interpretive strategies for routine lung function tests



Global Lung Function Initiative

Reference equations for spirometry

Stanojevic 2022 *ERJ*

‘Bronchodilator response’
Significant change

2005 BD+

>= 12% & 200mL in FEV1 or FVC

Compares pre- & post- bronchodilator results

2022 BD+

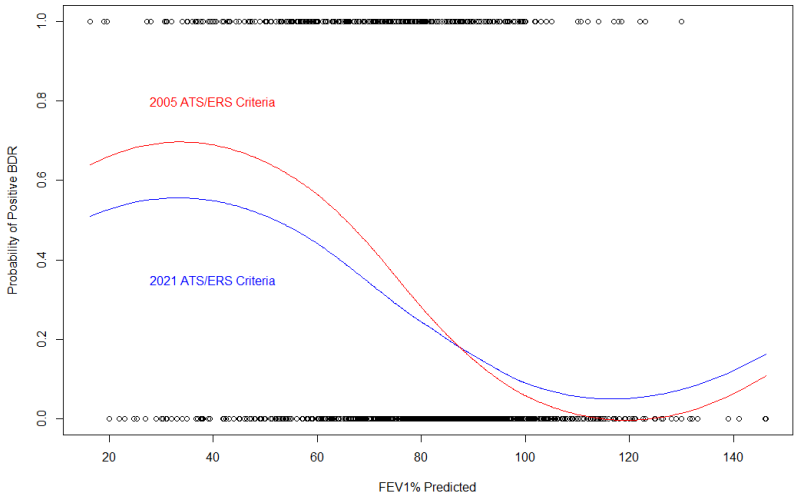
> 10% of predicted FEV1 or FVC

Minimizes sex and height difference in BDR

Spirometry		Pre Bronchodilator								Post Bronchodilator				
		FVC A FEV1 A	*Spirometry Grading*							FVC A FEV1 A				
		Actual	Pred	% Pred	Lower	Upper	Z-Score			Actual	Z-Score	% Pred	% Chg	BDR
FEV_1	L	1.98	4.47	44	3.54	5.36	-4.20	A	S	2.26	-3.76	51	14	6
FVC	L	5.08	5.60	91	4.45	6.76	-0.74	N		5.78	0.26	103	14	13
FEV_1 / FVC	%	39	80	49	70	89	-4.77	A	S	39	-4.77	49	0	--
FEF_{25-75} [ISO]	L/s	0.58	4.26	14	2.47	6.54	---			0.79	---	19	36	--
PEFR	L/s	6.51	10.62	61	8.16	13.08	---			7.51	---	71	15	--
FET	s	17.51	0.00	----	6.00	0.00	---			16.85	---	----	-4	--

Bronchodilator testing
Implications of changing definitions

Asthma



Unpublished
BWH Asthma Research Center
N = 2465

Asthma vs. COPD

BDR Definition	Asthma vs. COPD AUC (95% CI)	Asthma vs. COPD Sensitivity, Specificity
ΔFEV_1 or $\Delta FVC \geq 12\%$ and ≥ 200 ml	0.597 (0.572, 0.622)	0.55, 0.30
$\Delta FEV_1 \geq 12\%$ and ≥ 200 ml	0.659 (0.629, 0.690)	0.58, 0.21
$\Delta FVC \geq 12\%$ and ≥ 200 ml	0.592 (0.562, 0.622)	0.42, 0.43
$\Delta FEV_1 \geq 15\%$ and ≥ 400 ml	0.727 (0.652, 0.803)	0.80, 0.07
$\Delta FEV_1 > 10\%$ pred	0.571 (0.555, 0.586)	0.15, 0.92
$\Delta FVC > 10\%$ pred	0.578 (0.562, 0.593)	0.09, 0.86
ΔFEV_1 or $\Delta FVC > 10\%$ pred	0.505 (0.490, 0.521)	0.18, 0.82

Beasley et al., 2024 *AJRCCM*
NOVELTY Cohort
N = 6788

BDR alone fails to discriminate asthma vs. COPD

- Favor judgment for BDR interpretation in the context of clinical presentation
- BDR as a ‘treatable trait’ of small airway disease?

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10% of predicted

Regulatory Roadblocks
GINA, Symbicort, and the FDA

Rapid Relief
Patient preferences for reliever therapies

Respiratory Responsibility
The global impact of treatment decisions

Summary and Questions

Regulatory Roadblocks

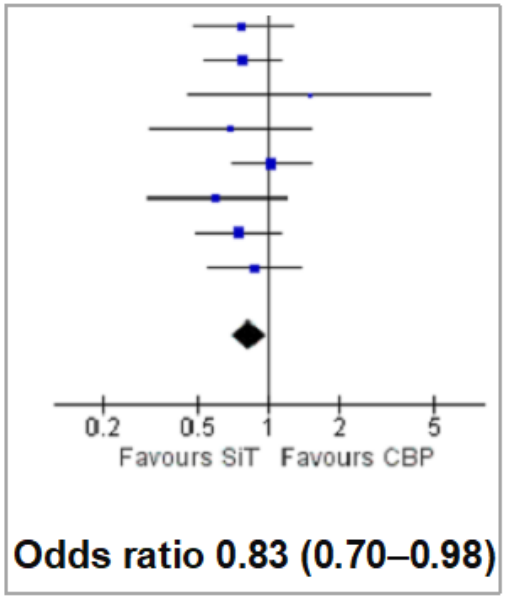
GINA, Symbicort, and the FDA

SMART reduces exacerbations

SMART therapy with ICS-formoterol reduces severe exacerbations.

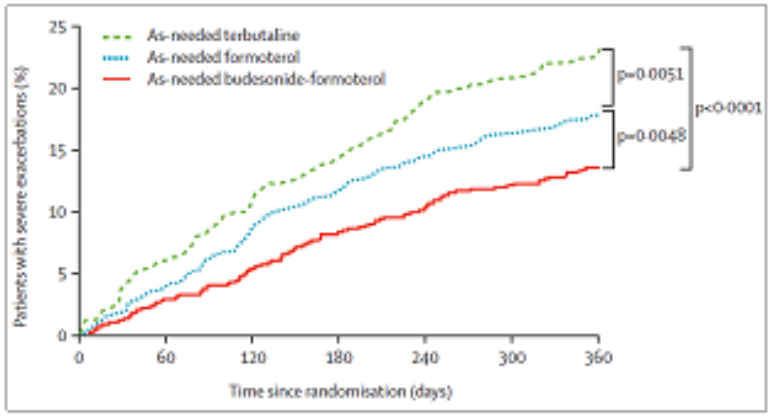
- Clinical trial and observational studies
- > 30k patients

Compared to Best Practice



Sobieraj 2018 *JAMA*

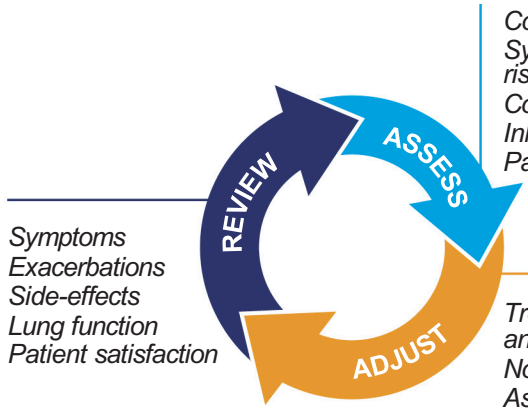
Compared to SABA or LABA



Rabe 2006 *Lancet*

Adults & adolescents 12+ years

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



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

Symptoms
Exacerbations
Side-effects
Lung function
Patient satisfaction

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

CONTROLLER and **PREFERRED RELIEVER**
(Track 1). Using ICS-formoterol as reliever reduces the risk of exacerbations compared with using a SABA reliever

STEPS 1 – 2	STEP 3	STEP 4	STEP 5
As-needed 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-IL4R, anti-TSLP
RELIEVER: As-needed low-dose ICS-formoterol			

See GINA severe asthma guide

CONTROLLER and **ALTERNATIVE RELIEVER**
(Track 2). Before considering a regimen with SABA reliever, check if the patient is likely to be adherent with daily controller

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-IL4R, anti-TSLP
RELIEVER: As-needed short-acting beta$_2$-agonist				

Other controller options for either track (limited indications, or less evidence for efficacy or safety)	*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*

GINA 2022, Box 3-5A

GINA summary

ICS-formoterol at all Steps

The management of asthma got easier:

- Step 1 – 2: Low-dose ICS-formoterol as needed
- Step 3: Low-dose ICS-formoterol
- Step 4: Medium-dose ICS-formoterol
- Step 5: Consider high-dose ICS-formoterol

ICS-formoterol

1. *Symbicort* = budesonide-formoterol
2. *Dulera* = mometasone-formoterol
3. (*Fostair* = beclomethasone-formoterol)

	Intermittent Asthma	Management of Persistent Asthma in Individuals Ages 12+ Years				
Treatment	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	
		Steps 2–4: Conditionally recommend the use of subcutaneous immunotherapy as an adjunct treatment to standard pharmacotherapy in individuals ≥ 5 years of age whose asthma is controlled at the initiation, build up, and maintenance phases of immunotherapy▲			Consider adding Asthma Biologics (e.g., anti-IgE, anti-IL5, anti-IL5R, anti-IL4/IL13)**	

Barriers to implementation

FDA/Regulatory

5.2 Deterioration of Disease and Acute Episodes

SYMBICORT should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of asthma or COPD. SYMBICORT has not been studied in patients with acutely deteriorating asthma or COPD. The initiation of SYMBICORT in this setting is not appropriate.

SYMBICORT should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. An inhaled, short-acting beta$_2$-agonist, not SYMBICORT, should be used to relieve acute symptoms such as shortness of breath. When prescribing SYMBICORT, the physician must also provide the patient with an inhaled, short-acting beta$_2$-agonist (e.g., albuterol) for treatment of acute symptoms, despite regular twice-daily (morning and evening) use of SYMBICORT.

Financial/Insurance Coverage

Out-of-pocket costs associated with Symbicort can be $200-400/month for some

Frequent ‘as-needed’ use can result in earlier refills, which is often not covered by insurance

Patient preference

Strong patient preference for inhaler devices, nebulizer devices

Outline

Redefining Reversibility
10% of predicted

Regulatory Roadblocks
Options for SMART are limited

Rapid Relief
Patient preferences for reliever therapies

Respiratory Responsibility
The global impact of treatment decisions

Summary and Questions

Rapid Relief

Patient Preferences for Reliever Therapy

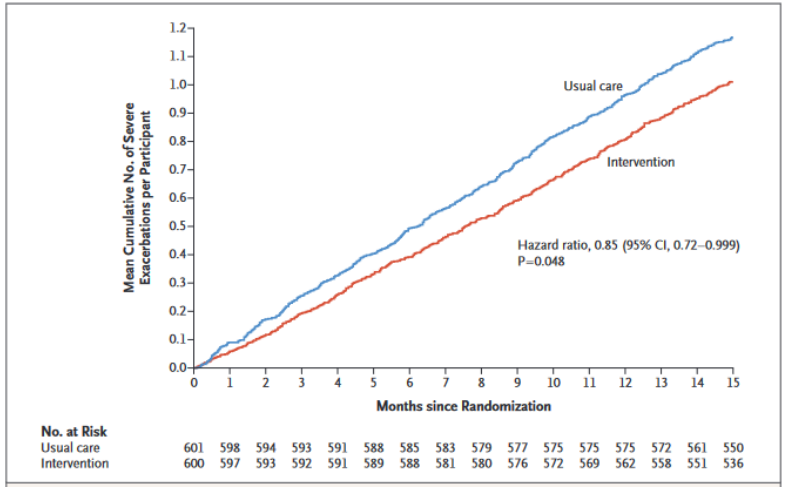
Patient-Activated Reliever-Triggered ICS (PARTICS)
Alternative reliever strategy for moderate-to-severe asthma

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

E. Israel, J.-C. Cardet, J.K. Carroll, A.L. Fuhlbrigge, L. She, F.W. Rockhold, N.E. Maher, M. Fagan, V.E. Forth, B.P. Yawn, P. Arias Hernandez, J.M. Kruse, B.K. Manning, J. Rodriguez-Louis, J.B. Shields, B. Ericson, A.D. Colon-Moya, S. Madison, T. Coyne-Beasley, G.M. Hammer, B.M. Kaplan, C.S. Rand, J. Robles, O. Thompson, M.E. Wechsler, J.P. Wisnivesky, M.D. McKee, S.P. Jariwala, E. Jerschow, P.J. Busse, D.C. Kaelber, S. Nazario, M.L. Hernandez, A.J. Apter, K.-L. Chang, V. Pinto-Plata, P.M. Stranges, L.P. Hurley, J. Trevor, T.B. Casale, G. Chupp, I.L. Riley, K. Shenoy, M. Pasarica, R.A. Calderon-Candelario, H. Tapp, A. Baydur, and W.D. Pace



Patient preference for nebulizers
Incompatible with GINA recommendations

PREPARE Cohort

- 67% of PREPARE participants reported using a nebulizer as a reliever device
- 45% report using nebulizer weekly
- Greater number of co-morbid conditions
- Utilize acute health care services (ED, hospitalization, exacerbation) more frequently (~50% vs. ~25%)

GINA

- ICS/LABA reliever for all asthma severity
- Specifically recommends against SABA in favor of LABA as bronchodilator
- Patient preference for nebulizer device is unaddressed

Apter 2022 *JACI-IP*

Nebulizer use is common
Significant associated risk

TriNetX Database

- 6M adults with asthma
- 25% nebulizer use overall
- 37% nebulizer use for medium/high dose ICS
- Propensity-matched cohort of 400k
- 4-year follow-up period

- All-Cause Mortality
  - HR 1.98 (95% CI 1.91 – 2.05)
- Severe Asthma Exacerbation
  - HR 1.29 (95% CI 1.28 – 1.29)

Salciccioli, unpublished

Formoterol superior to SABA for FEV1 change
At peak effect (~60min)

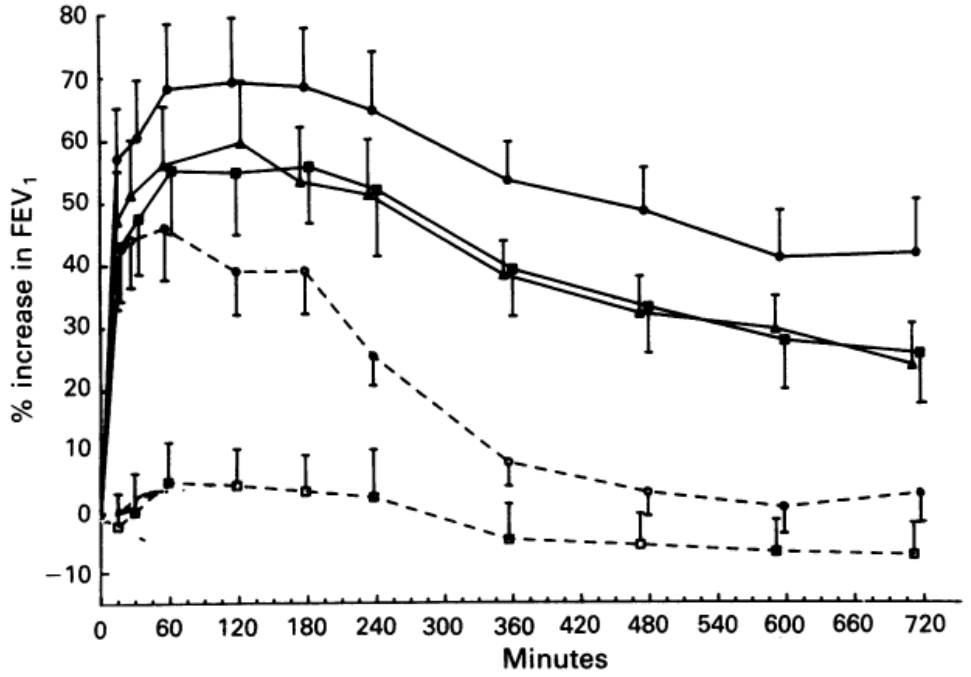


Figure 1 Time course of change in FEV_1 (mean (SE) in 14 patients) after inhalation of placebo (□— — —□), salbutamol (○— —○), 12 μg formoterol (■——■), 24 μg formoterol (▲——▲), and 48 μg formoterol (●——●).

Table 2 Mean (SE) baseline and maximum values of FEV_1 and sGaw with different treatments

	Placebo	Salbutamol 200 μg	Formoterol (μg) 12	24	48
			FEV_1 (l)		
Baseline	2·00 (0·20)	2·11 (0·24)	1·98 (0·24)	2·05 (0·24)	1·96 (0·20)
Maximum	2·36 (0·22)	3·03 (0·26)	3·05 (0·29)	3·16 (0·28)	3·22 (0·27)
			sGaw (cm H_2O.s)		
Baseline	0·031 (0·003)	0·041 (0·005)	0·041 (0·006)	0·038 (0·006)	0·035 (0·003)
Maximum	0·066 (0·008	0·130 (0·016)	0·133 (0·018)	0·151 (0·022)	0·167 (0·021)

Derom 1992 *Thorax*

Short-term effects favor SABA
FEV1 increase 100mL over 30min

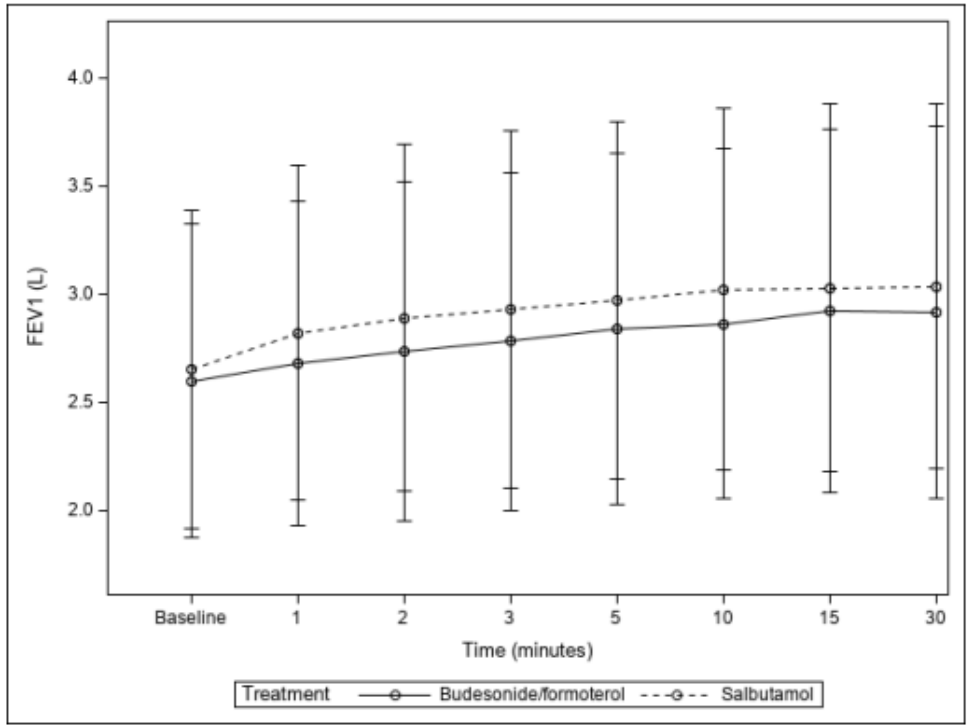


Figure 2 Time course of FEV_1 for budesonide/formoterol and salbutamol.

Table 2 Secondary analyses of FEV_1 comparison at all time points

Time (minutes)	Budesonide/formoterol minus Salbutamol Difference (95% CI)	P value (vs 0)
1	−0.11 (−0.16 to −0.05)	<0.001
2	−0.12 (−0.17 to −0.06)	<0.001
3	−0.11 (−0.17 to −0.05)	<0.001
5	−0.095 (−0.15 to −0.07)	0.001
10	−0.11 (−0.17 to −0.06)	<0.001
15	−0.07 (−0.12 to −0.01)	0.02
30	−0.08 (−0.14 to −0.03)	0.004
Averaged over all times	−0.10 (−0.12 to −0.08)	<0.001

Kearns 2023 *Thorax*

Combination ICS-SABA
'Anti-Inflammatory Reliever'


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

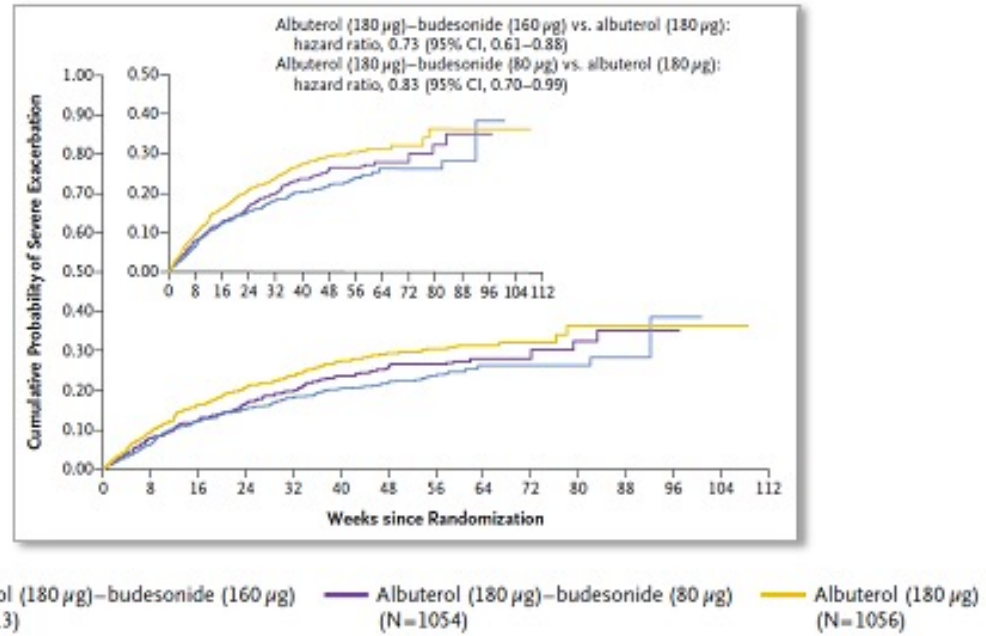
Albuterol–Budesonide Fixed-Dose Combination Rescue Inhaler for Asthma

Alberto Papi, M.D., Bradley E. Chipps, M.D., Richard Beasley, D.Sc., Reynold A. Panettieri, Jr., M.D., Elliot Israel, M.D., Mark Cooper, M.Sc., Lynn Dunsire, M.Sc., Allison Jeynes-Ellis, M.D., Eva Johnsson, M.D., Robert Rees, Ph.D., Christy Cappelletti, Pharm.D., and Frank C. Albers, M.D.

Papi et al, NEJMed 2022 (n=3,132)

In patients taking Step 3–5 maintenance treatment:

- Hazard ratio for probability of severe exacerbations was 0.73 (95% CI 0.61–0.88) with higher dose of as-needed albuterol-budesonide compared with as-needed albuterol
- Most benefit seen in Step 3



Selecting the optimal reliever therapy
‘Anti-Inflammatory Reliever’

- Anti-inflammatory (ICS-containing) reliever should be preferred over SABA-only therapy
- Add-on ICS with SABA effective in moderate-to-severe asthma (PARTICS)
- GINA 2022: *‘Providing access to anti-inflammatory relievers at affordable prices for all patients in all countries, whether MDI or DPI, is both important and urgent’*

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Anti-inflammatory reliever

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Respiratory Responsibility

Global impact of treatment decisions

Inhaler devices and the environment
Metered dose vs. dry powder

BTS/SIGN 2019

Poor asthma control (increased SABA use) is associated with GHG

- MDIs contribute ~3.5% of the carbon footprint of the National Health Service
  - Asthma in UK accounts for 750,000 tCO2/year

UK NICE: *'prescribers be aware of the global-warming potential of different inhalers and to use inhalers with lower global-warming potential where equally effective'*

wbur

Your inhaler saves lives, but its puffs hurt the planet

March 14, 2024 By Martha Bebinger

Inhaler selection
Weighing the environmental effect

Asthma Control
Poor asthma control is associated with increased SABA use and excess GHG.

>303K tCO2/yr

Wilkinson 2023 *Thorax*

Asthma Exacerbation
Exacerbations are associated with significant CO2 effects (regardless of MDI v. DPI).

185 tCO2/AEX

Kponee 2022 *JME*

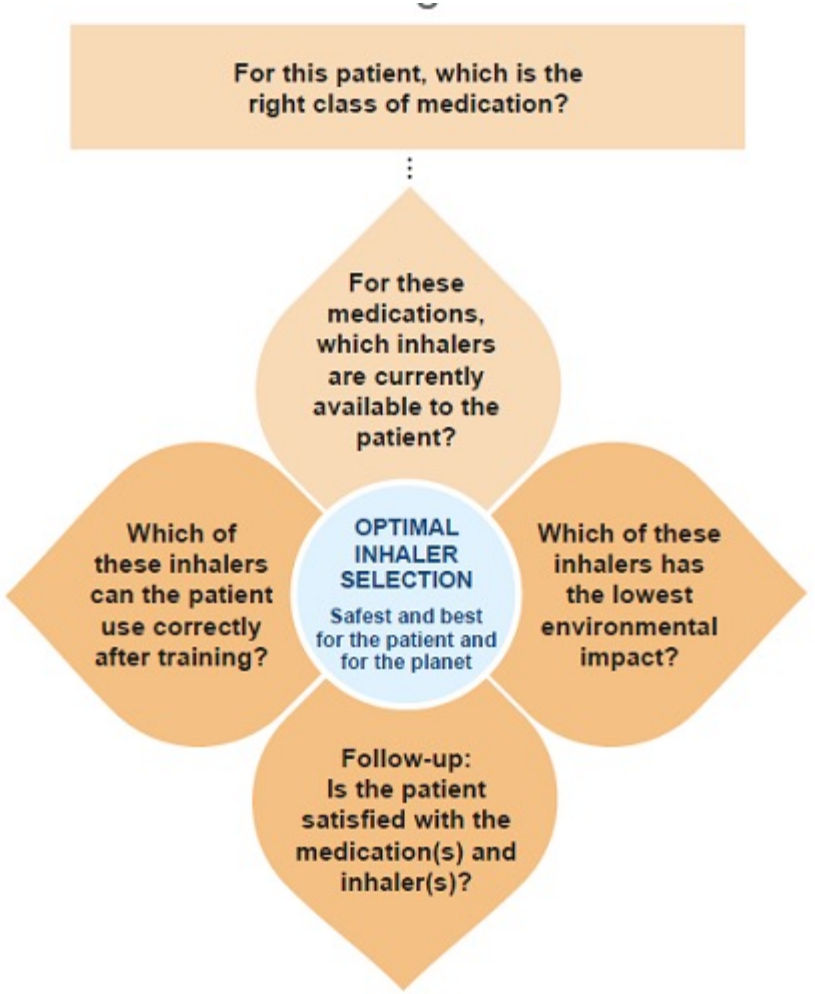
Inhaler Transitions
Non-medical transitions (insurance, generic, etc.) associated with loss of asthma control and exacerbation.

47% AEX rate

Gilbert 2021 *Pulm Ther*
McCarthy 2022 *J Pharm Prac*

Inhaler selection
On balance

- ‘Green Guilt’ may limit adherence
- Restricted production of MDI may adversely affect access to inhaler therapies in LMICs
- *Consider DPI for <u>initiation</u> of therapy*
- *<u>Transition</u> with caution*



Levy 2023 *Lancet*

Summary

Summary

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10% of predicted

Regulatory Roadblocks
Options for SMART are limited

Rapid Relief
Anti-inflammatory reliever

Respiratory Responsibility
Careful transitions

Summary and Questions

Questions?

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