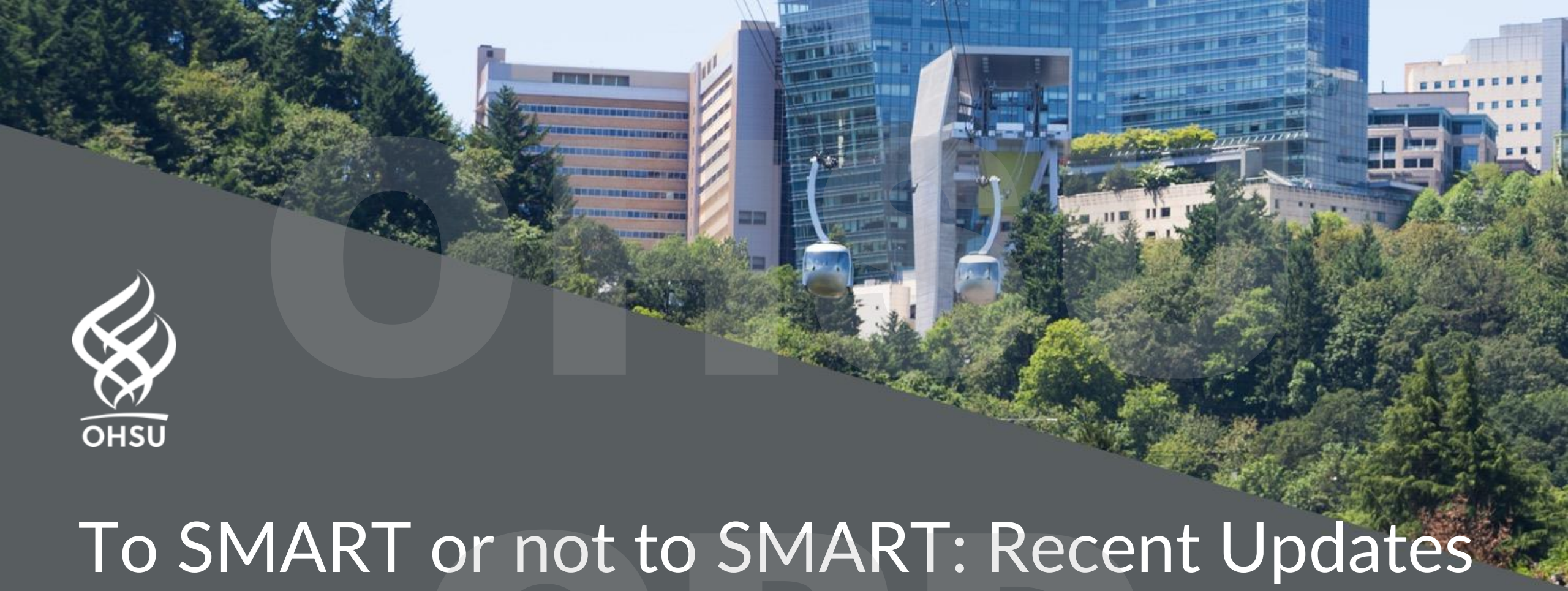

To SMART or not to SMART: Recent Updates in Asthma Guidelines and Therapies

Karen Anstey, MD
ASSISTANT PROFESSOR OF MEDICINE
SECTION OF ALLERGY AND IMMUNOLOGY

DATE: April 5th, 2024

Disclosures

I have no conflicts of interest in relation to this presentation.

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Objectives

- Understand the rationale behind SMART (ICS/LABA) therapy
- Develop a plan for which patients you would recommend SMART therapy
- Understand implementation concerns for SMART therapy

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Outline

1. Introduction
   - What is SMART therapy?
   - What is PARTICS therapy?

2. Data behind SMART therapy
   - In moderate-severe asthma
   - In mild asthma
   - Safety of SMART therapy

3. Data behind PARTICS therapy

4. Asthma guidelines
   - GINA
   - NAEPP

5. Implementation concerns for SMART therapy



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Case Consideration

A 45 year old male with moderate asthma is following up with you due to poorly controlled asthma in the last 6 months. He notes using albuterol about 3 times a week and waking up 1-2 times a week due to asthma. He is currently on a medium dose ICS inhaler as his therapy (and you confirm he takes this medication as directed). What do you recommend as far as therapy?

a) Low to medium dose ICS/LABA daily and albuterol PRN
b) Low dose ICS/formoterol daily and PRN
c) Low to medium dose ICS/LABA daily and ICS/SABA PRN

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Case Consideration

A 45 year old male with moderate asthma is following up with you due to poorly controlled asthma in the last 6 months. He notes using albuterol about 3 times a week and waking up 1-2 times a week due to asthma. He is currently on a medium dose ICS inhaler as his therapy (and you confirm he takes this medication as directed). What do you recommend as far as therapy?

a) Low to medium dose ICS/LABA daily and albuterol PRN

b) Low dose ICS/formoterol daily and PRN -> SMART

c) Low to medium dose ICS/LABA daily and ICS/SABA PRN -> PARTICS

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COPD

A little more about SMART

- SMART = **S**ingle **M**aintenance **A**nd **R**eliever **T**herapy
- Inhaled corticosteroid (ICS) with long acting beta agonist (LABA)
  - Budesonide
  - Formoterol (Onset of action < 5 minutes!)
    The onset of action of formoterol is as rapid as albuterol, but it has the added advantage of a longer duration of action
- Rationale is to provide additional anti-inflammatory treatment during the window when asthma and airway inflammation are worsening

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A little more about PARTICS

- PARTICS = **P**atient **A**ctivated **R**eliever **T**riggered **ICS**

- Inhaled corticosteroid (ICS) with short acting beta agonist (SABA)



Albuterol

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SMART Therapy Data

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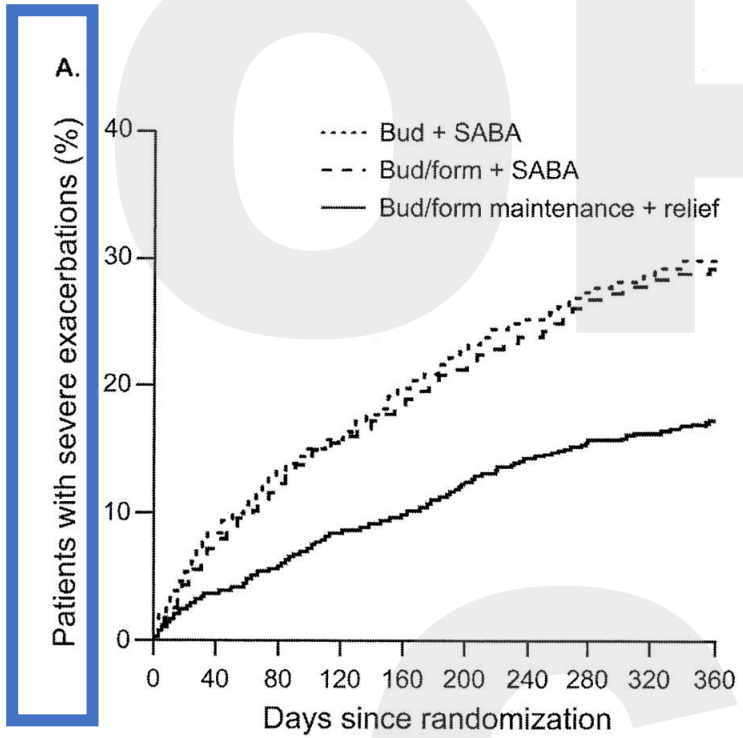
SMART Therapy Data in Mod-Severe Asthma



Low dose ICS/LABA + SABA: SABA with bud/form 80/4.5 microg twice a day (bud/form + SABA)

High dose ICS + SABA: Bud 320 microg twice a day (bud + SABA)

SMART: Bud/form 80/4.5 microg twice a day with 80/4.5 microg as-needed (bud/form maintenance + relief)

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O'Byrne PM, et al. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. Am J Respir Crit Care Med. 2005

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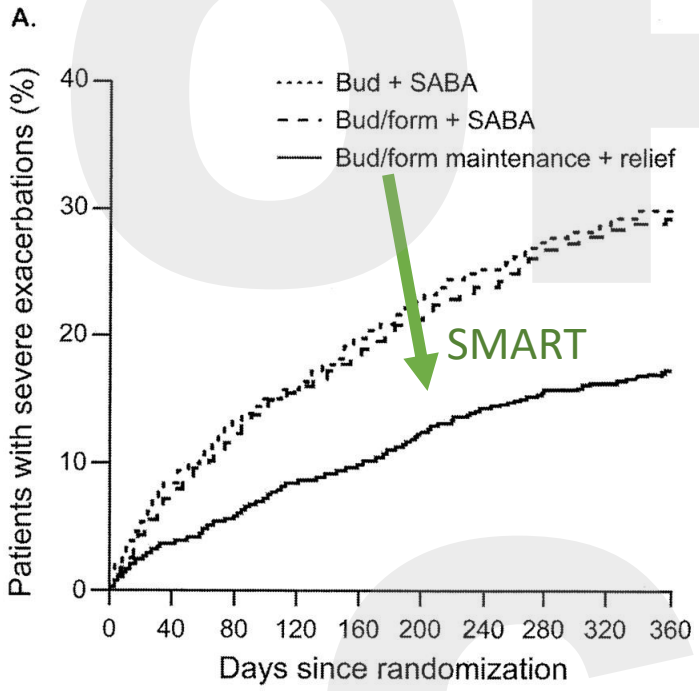
SMART Therapy Data in Mod-Severe Asthma



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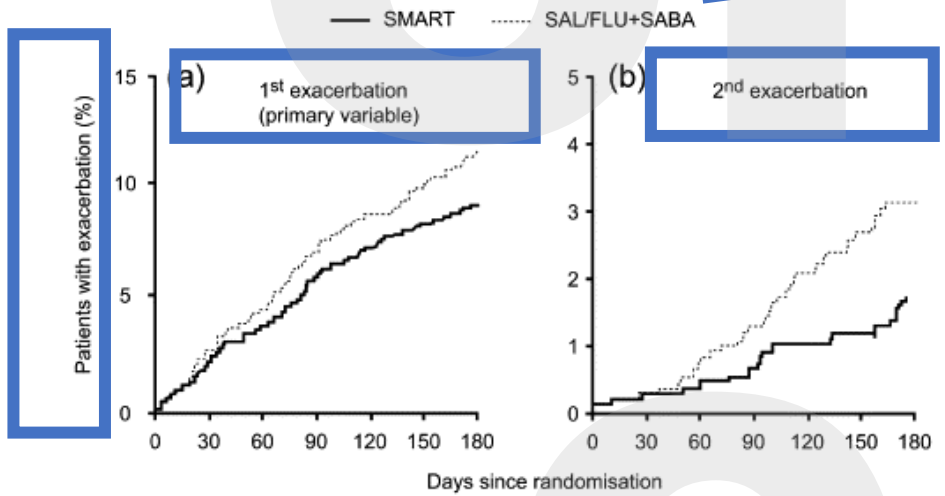
SMART Therapy in Mod-Severe Asthma



Budesonide/formoterol 160/4.5 microg two inhalations twice daily and PRN

Salmeterol/fluticasone 50/500 microg twice daily (Same dose as bud/form above) plus SABA PRN

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Bousquet J, et al. Budesonide/formoterol for maintenance and relief in uncontrolled asthma vs. high-dose salmeterol/fluticasone. Respir Med. 2007

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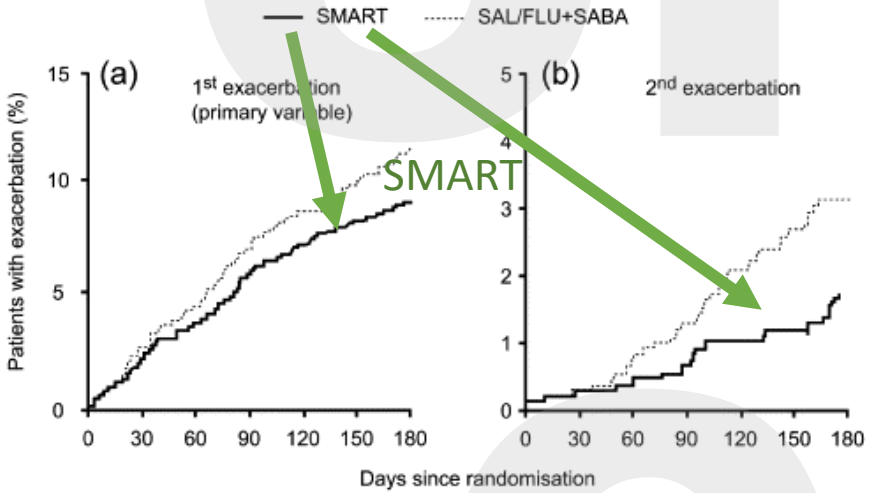
SMART Therapy in Mod-Severe Asthma



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Bousquet J, et al. Budesonide/formoterol for maintenance and relief in uncontrolled asthma vs. high-dose salmeterol/fluticasone. Respir Med. 2007

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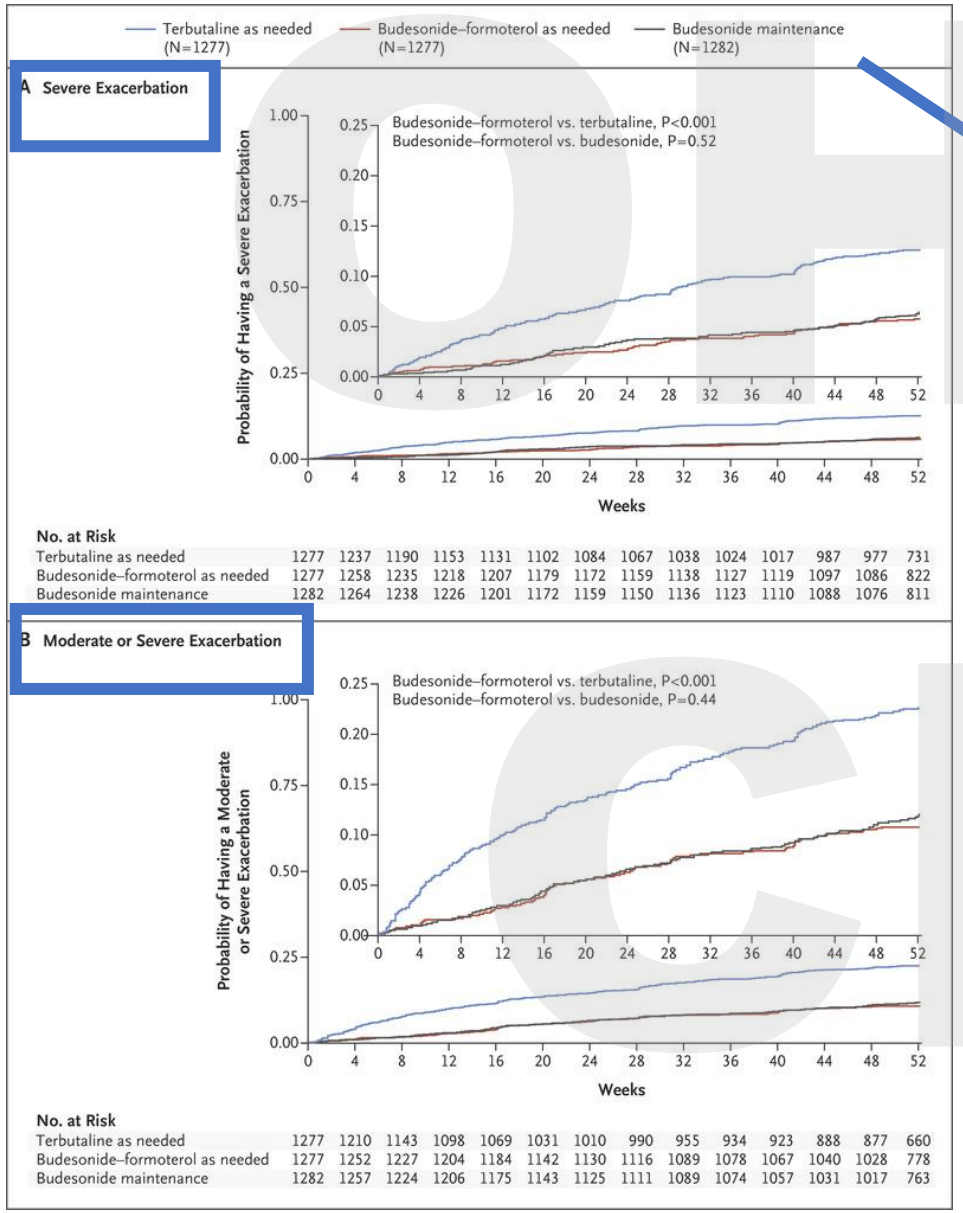
SMART Therapy Data in Mild Asthma



Twice-daily placebo plus SABA (0.5 mg) used as needed (terbutaline group, SABA PRN)

Twice-daily placebo plus budesonide-formoterol (200 µg of budesonide and 6 µg of formoterol) used as needed (budesonide-formoterol group, SMART)

Twice-daily budesonide (200 µg) plus terbutaline used as needed (budesonide maintenance group, ICS + SABA PRN)

O'Byrne PM, et al. Inhaled Combined Budesonide-Formoterol as Needed in Mild Asthma. N Engl J Med. 2018

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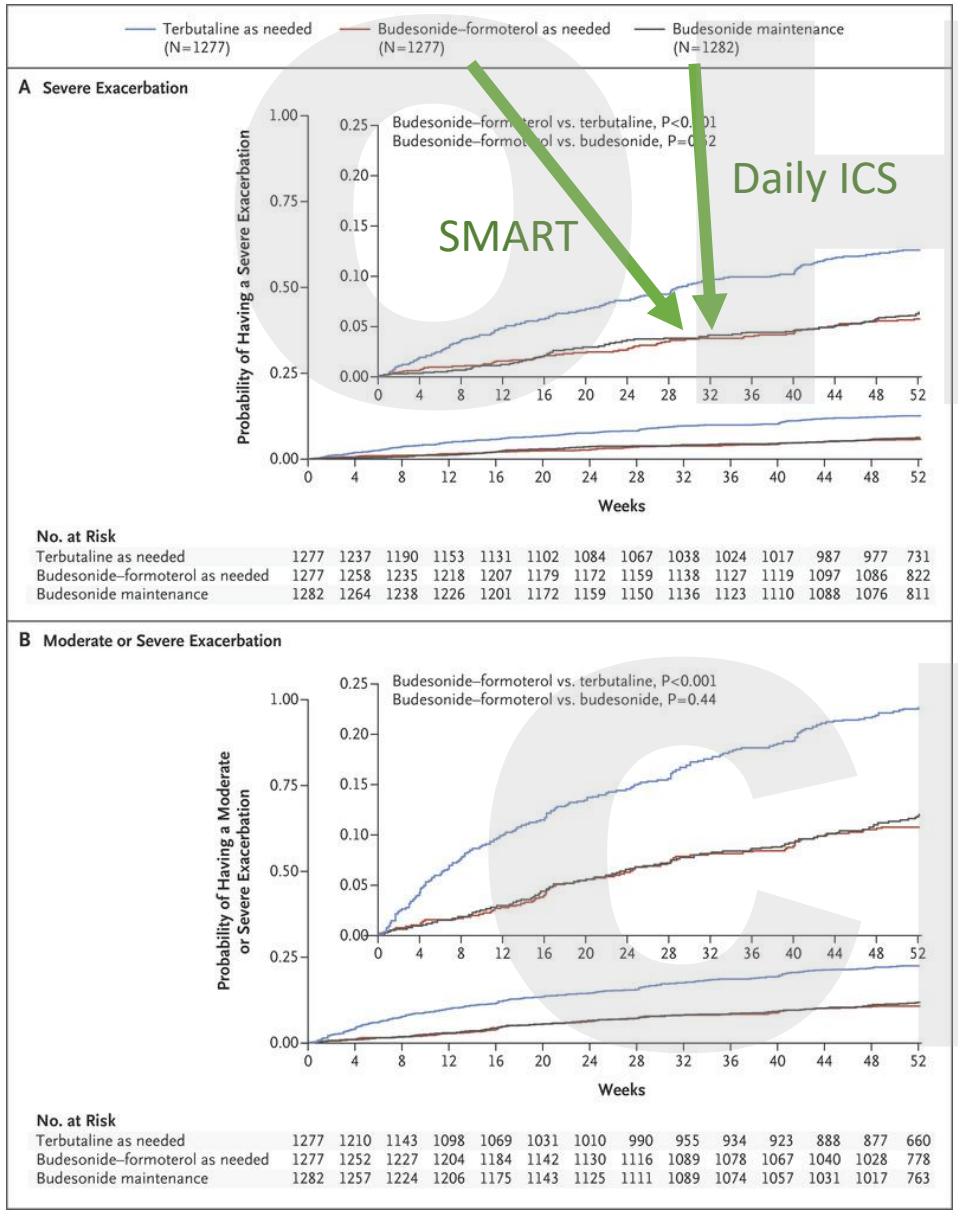
SMART Therapy Data in Mild Asthma



Twice-daily placebo plus SABA (0.5 mg) used as needed (terbutaline group)

Twice-daily placebo plus budesonide-formoterol (200 µg of budesonide and 6 µg of formoterol) used as needed (budesonide-formoterol group)

Twice-daily budesonide (200 µg) plus terbutaline used as needed (budesonide maintenance group)

O'Byrne PM, et al. Inhaled Combined Budesonide-Formoterol as Needed in Mild Asthma. N Engl J Med. 2018

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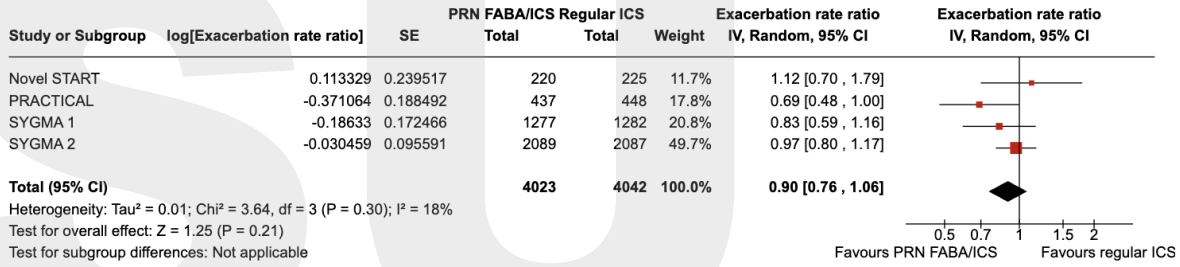
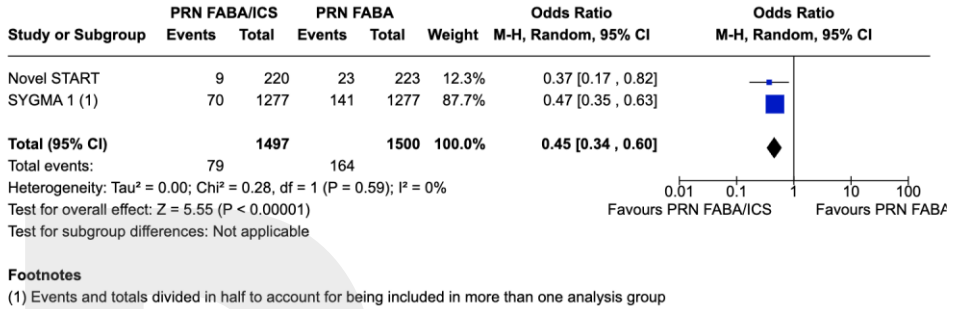
Systematic Reviews on SMART Therapy

- Mild asthma
  - No difference between SMART and ICS daily
  - Odds ratio = 0.45 for SMART vs SABA PRN





Kew KM, et al. Combination formoterol and budesonide as maintenance and reliever therapy versus combination inhaler maintenance for chronic asthma in adults and children. Cochrane Database Syst Rev. 2013

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Systematic Reviews on SMART Therapy

- Mild asthma
  - No difference between SMART and ICS daily
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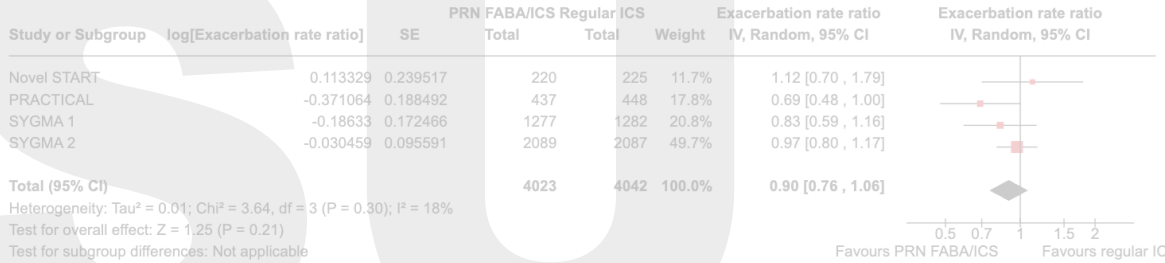
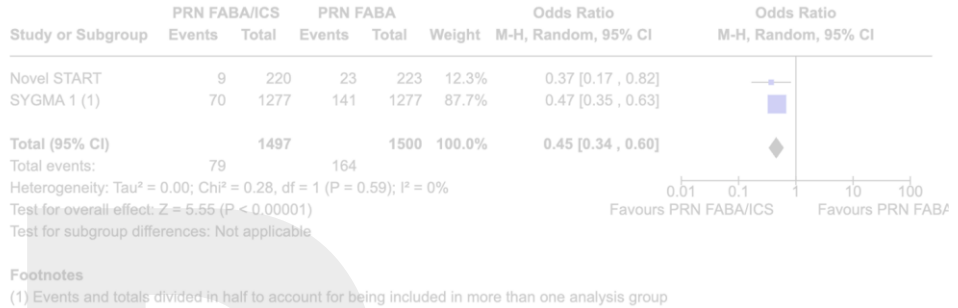
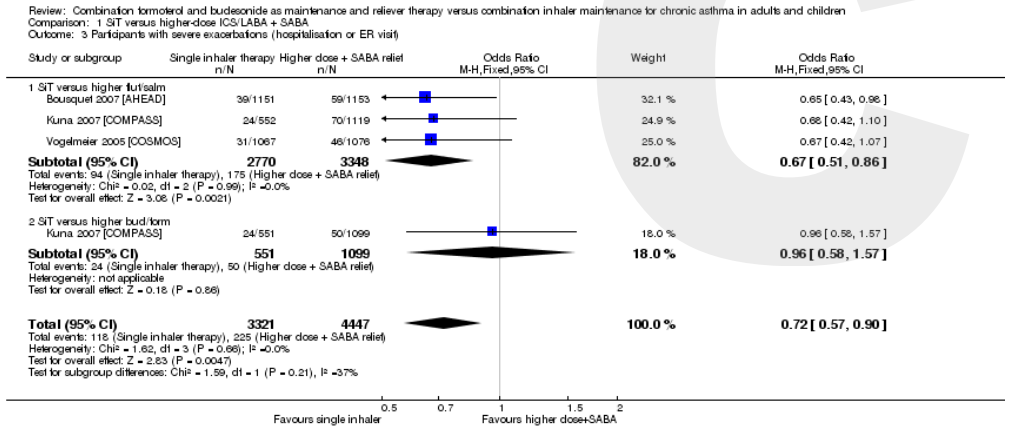


- Mod-Severe asthma
  - Odds ratio for exacerbations = 0.72 for SMART vs ICS/LABA+SABA





Kew KM, et al. Combination formoterol and budesonide as maintenance and reliever therapy versus combination inhaler maintenance for chronic asthma in adults and children. Cochrane Database Syst Rev. 2013

Crossingham I, et al. Combination fixed-dose beta agonist and steroid inhaler as required for adults or children with mild asthma. Cochrane Database Syst Rev. 2021

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Conclusion on SMART Data

- SMART reduces exacerbations in mild to moderate-severe persistent asthma
  - However, for mild persistent asthma, no difference between SMART and ICS daily

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SMART Safety

- No increased risk of cardiac-related serious adverse events and/or death with SMART therapy

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O'Byrne PM, et al. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. Am J Respir Crit Care Med. 2005

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PARTICS Therapy Data

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A little more about PARTICS

- PARTICS = **P**atient **A**ctivated **R**eliever **T**riggered **ICS**

- Inhaled corticosteroid (ICS) with short acting beta agonist (SABA)



Albuterol

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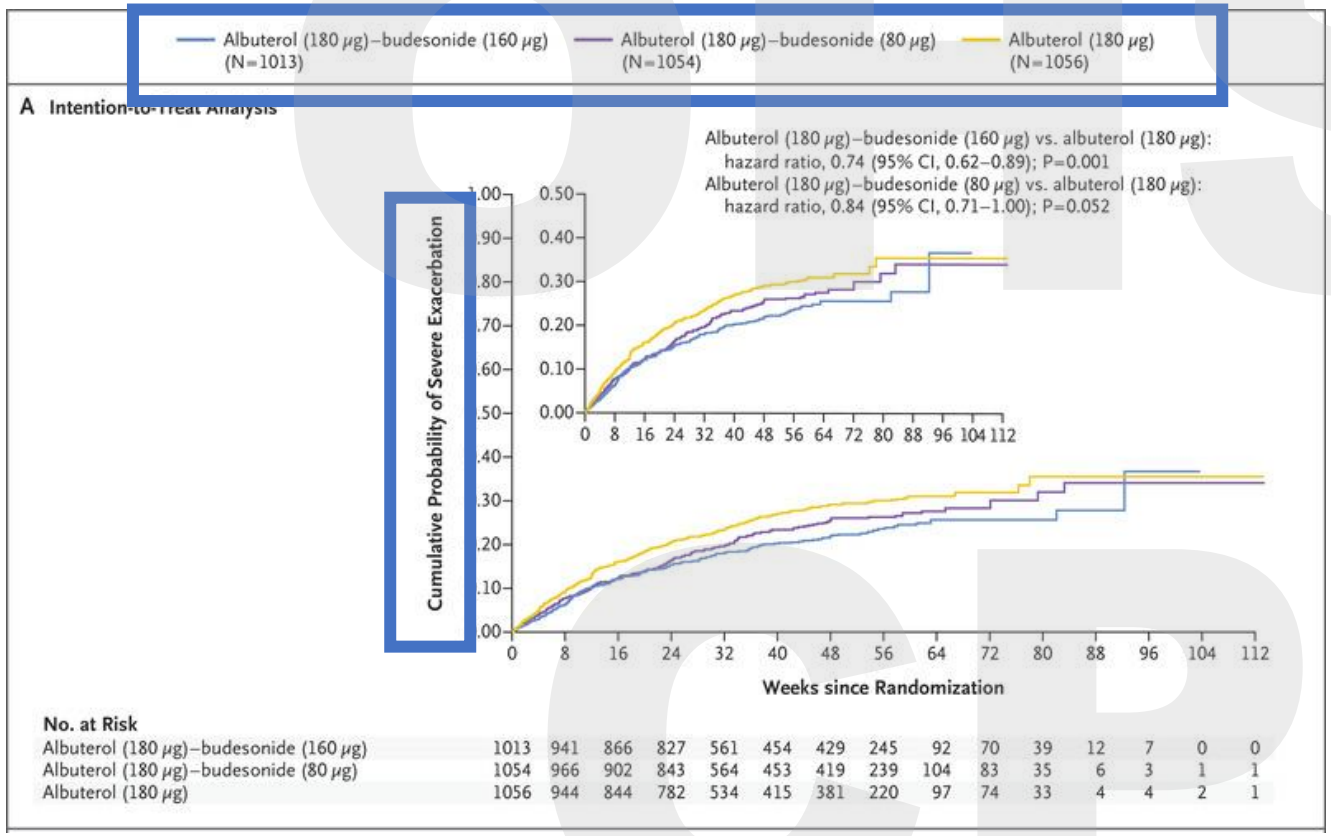
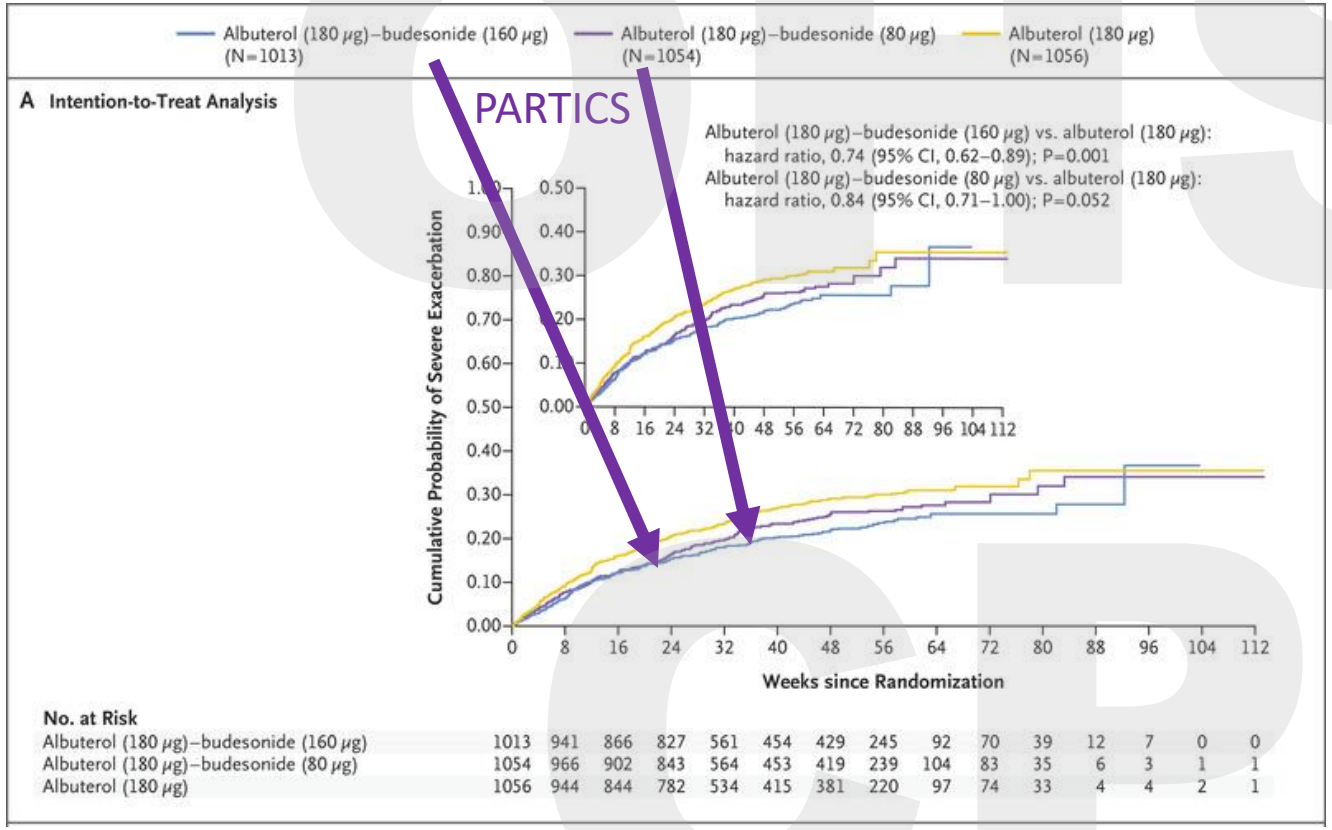
PARTICS Data in Mild Asthma



Papi A, et al. Albuterol-Budesonide Fixed-Dose Combination Rescue Inhaler for Asthma. N Engl J Med. 2022

PARTICS Data in Mild Asthma



Papi A, et al. Albuterol-Budesonide Fixed-Dose Combination Rescue Inhaler for Asthma. N Engl J Med. 2022

PARTICS Safety

- No increased risk of cardiac-related side serious adverse events and/or death but increase in oral candidiasis

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O'Byrne PM, et al. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. Am J Respir Crit Care Med. 2005

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Guidelines

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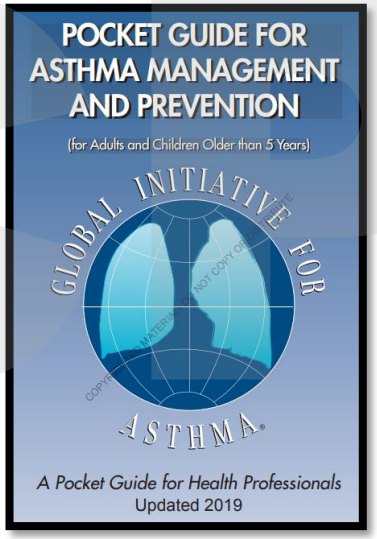
Guidelines Methodologies

GINA

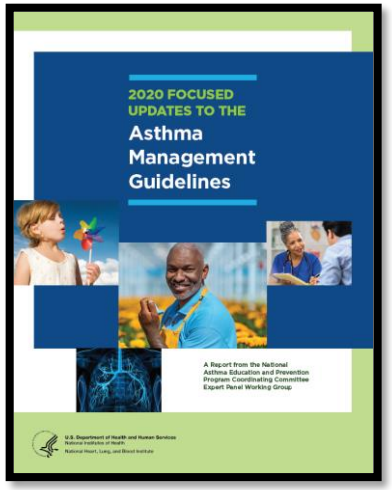
- International Committee
- Annually updated
- Evidence categories
- Includes 3 components:

  -Evaluation of the relevance and quality of the publication
  -Decision about inclusion in the report
  -Discussion about related changes to recommendations in the report



NAEPP

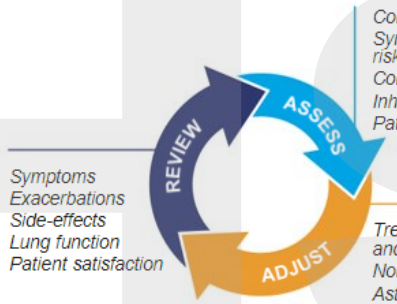
- US based committee
- Focused update in 2020
- Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Methodology
  - Evidence profiles for each pre identified question/outcome
  - Evidence to decision tables for recommendations



POCKET GUIDE FOR ASTHMA MANAGEMENT AND PREVENTION
(for Adults and Children Older than 5 Years)
A Pocket Guide for Health Professionals
Updated 2019

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
As-needed low dose ICS-formoterol

SMART

STEP 3
Low dose maintenance ICS-formoterol

STEP 4
Medium dose maintenance ICS-formoterol

STEP 5
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 SMART

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

PARTICS

STEP 1
Take ICS whenever SABA taken

STEP 2
Low dose maintenance ICS

STEP 3
Low dose maintenance ICS-LABA

STEP 4
Medium/high dose maintenance ICS-LABA

STEP 5
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

Box 3-5A

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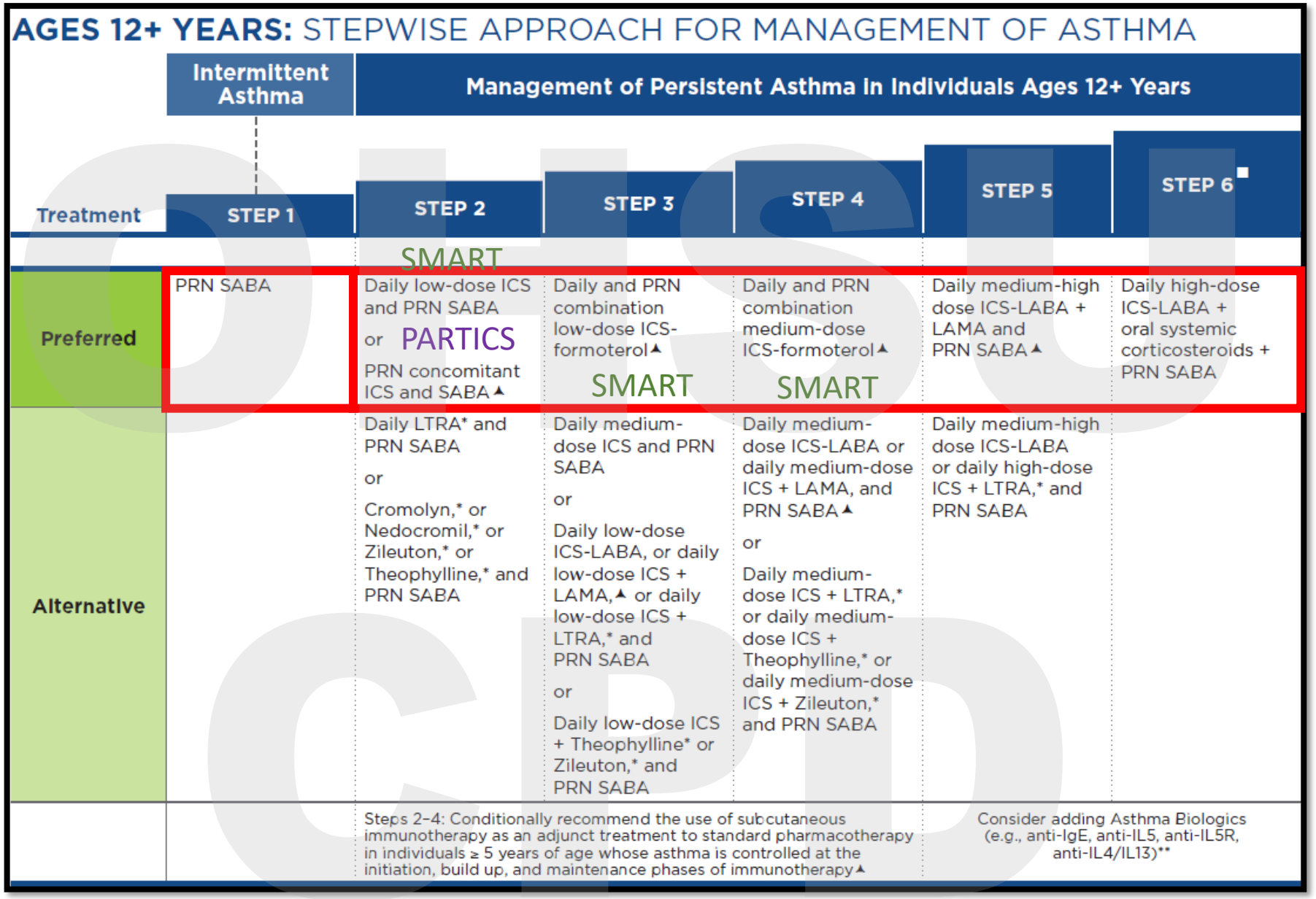
National Asthma Education and Prevention Program (NAEPP)



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Implementation Issues

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Common Practical Questions

- If formoterol is the LABA used in SMART therapy, can I prescribe mometasone-formoterol instead for SMART therapy?
  - No studies with this medication
  - Guidelines suggest against extrapolating data to other ICS-formoterol

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Reddel HK, et al. A Practical Guide to Implementing SMART in Asthma Management. J Allergy Clin Immunol Pract. 2022

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Common Practical Questions

- If formoterol is the LABA used in SMART therapy, can I prescribe mometasone-formoterol instead for SMART therapy?
  - No studies with this medication
  - Guidelines suggest against extrapolating data to other ICS-formoterol
- How much additional PRN budesonide-formoterol can a patient take?
  - Typically recommended to take 1 puff PRN with additional 1 puff PRN if symptoms persist in a few minutes
  - Typically maximum of 12 inhalations per day of ICS/LABA (Usual maintenance dosing is maximum of 2 puffs BID)

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Reddel HK, et al. A Practical Guide to Implementing SMART in Asthma Management. J Allergy Clin Immunol Pract. 2022

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Common Practical Questions

- If a patient is on ICS/salmeterol, can you still prescribe ICS/formoterol for reliever therapy?
  - This combination is not recommended

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Reddel HK, et al. A Practical Guide to Implementing SMART in Asthma Management. J Allergy Clin Immunol Pract. 2022

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Common Practical Questions

- If a patient is on ICS/salmeterol, can you still prescribe ICS/formoterol for reliever therapy?
  - This combination is not recommended
- Will SMART inhaler therapy reduce adherence to maintenance dosing?
  - No, not according to two studies. If anything, improved it!

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Reddel HK, et al. A Practical Guide to Implementing SMART in Asthma Management. J Allergy Clin Immunol Pract. 2022

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Common Practical Questions

- Does SMART therapy improve day-to-day symptom control?
  - This is important to consider! Significant data for exacerbations but no significant or clinically important difference measured by ACQ (Asthma Control Questionnaire)

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Reddel HK, et al. A Practical Guide to Implementing SMART in Asthma Management. J Allergy Clin Immunol Pract. 2022

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Common Practical Questions

- Does SMART therapy improve day-to-day symptom control?
  - This is important to consider! Significant data for exacerbations but no significant or clinically important difference measured by ACQ (Asthma Control Questionnaire)
- For patients on SMART therapy who have exercise induced asthma too, do you still need albuterol prior to exercise?
  - No, recommended to use SMART inhaler PRN instead of albuterol PRN for this instance

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Reddel HK, et al. A Practical Guide to Implementing SMART in Asthma Management. J Allergy Clin Immunol Pract. 2022

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Common Practical Questions

- How would this change an asthma action plan?

(Example of action plan template for budesonide/formoterol.
A similar action plan could be constructed for other ICS/formoterol formulations, e.g. mometasone/formoterol)

My Asthma Action Plan

For Single Inhaler Maintenance and Reliever Therapy (SMART) with budesonide/formoterol

Name: _____ Action plan provided by: _____

Date: _____ Doctor: _____

Usual best PEF: _____ L/min (If used) Doctor's phone: _____

Normal mode

My SMART Asthma Treatment is:

- ☐ budesonide/formoterol 160/4.5 (12 years or over)
- ☐ budesonide/formoterol 80/4.5 (4-11 years)

My Regular Treatment Every Day:

(Write in or circle the number of doses prescribed for this patient)

Take [1, 2] inhalation(s) in the morning

and [0, 1, 2] inhalation(s) in the evening, every day

Reliever

Use 1 inhalation of budesonide/formoterol whenever needed for relief of my asthma symptoms

I should always carry my budesonide/formoterol inhaler

My asthma is stable if:

- I can take part in normal physical activity without asthma symptoms

AND

- I do not wake up at night or in the morning because of asthma

Other Instructions

_____

_____

Asthma Flare-up

If over a Period of 2-3 Days:

- My asthma symptoms are getting worse **OR NOT** improving **OR**
- I am using more than 6 budesonide/formoterol reliever inhalations a day (if aged 12 years and older) or more than 4 inhalations a day (if 4–11 years)

I should:

- ☑ Continue to use my regular everyday treatment **PLUS** 1 inhalation budesonide/formoterol whenever needed to relieve symptoms
- ☐ Start a course of prednisolone
- ☐ Contact my doctor

Course of Prednisolone Tablets:

Take _____ mg prednisolone tablets per day for _____ days **OR**

_____

_____

If I need more than **12 budesonide/formoterol inhalations (total)** in any day, (or more than 8 inhalations for children 4-11 years) I **MUST** see my doctor or go to the hospital the same day

Asthma Emergency

Signs of an Asthma Emergency:

- Symptoms getting worse quickly
- Extreme difficulty breathing or speaking
- Little or no improvement from my budesonide/formoterol reliever inhalations.

If I have any of the above danger signs, I should dial ___ for an ambulance and say I am having a severe asthma attack.

While I am waiting for the ambulance start my asthma first aid plan:

- Sit upright and stay calm
- Take 1 inhalation of budesonide/formoterol. Wait 1-3 minutes. If there is no improvement take another inhalation of budesonide/formoterol (up to a maximum of 6 inhalations on a single occasion)
- If only albuterol is available, take 4 puffs as often as needed until help arrives
- Start a course of prednisolone tablets (as directed) while waiting for the ambulance
- Even if my symptoms appear to settle quickly, I should see my doctor immediately after a serious attack

Modified from Australian action plan with permission from National Asthma Council Australia and AstraZeneca Australia

Reddel HK, et al. A Practical Guide to Implementing SMART in Asthma Management. J Allergy Clin Immunol Pract. 2022

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Implementation issues

- Frequent barriers include
  - Budesonide-formoterol is not currently approved by the FDA for use in SMART therapy and package insert recommends against use of more than 4 puffs per day
    - Of note, as of Jan 2023, FDA did approve combination inhaler with budesonide and albuterol for PRN treatment (PARTICS)
  - Many insurances won't cover the cost of more than a usual 30 days supply for maintenance medication (ie more than 4 puffs of budesonide-formoterol per day)
  - Increased cost compared to albuterol for reliever therapy

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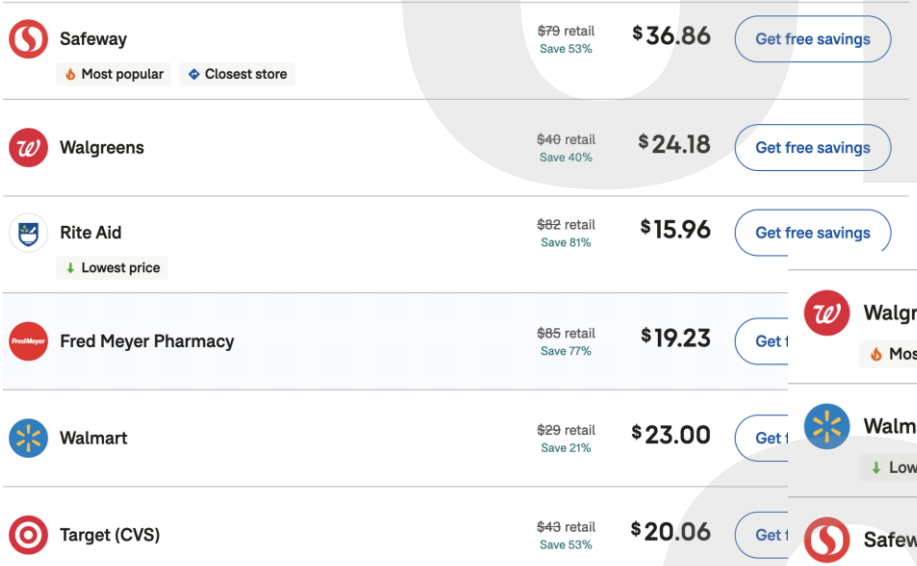
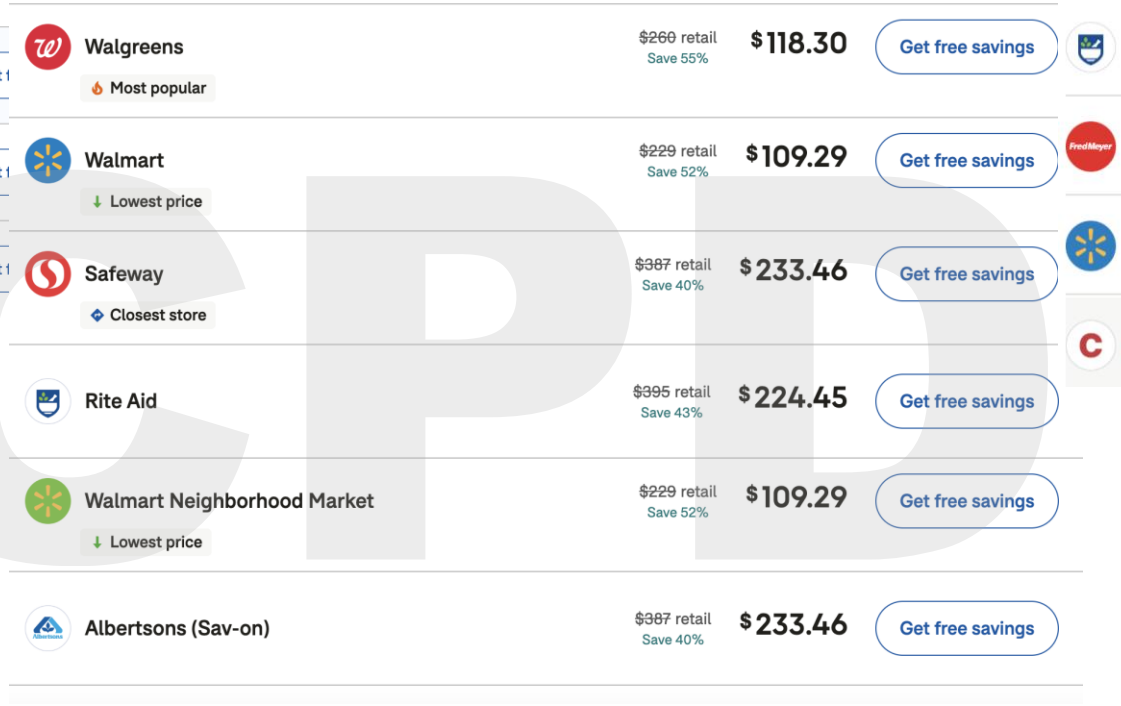
Costs

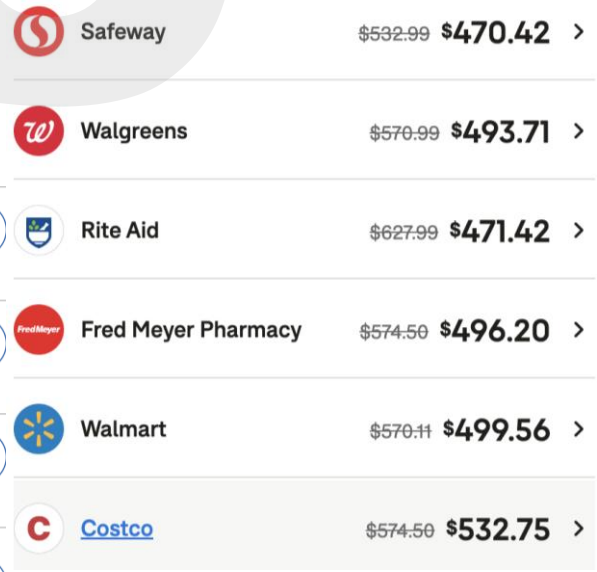
Albuterol



Budesonide-Formoterol SMART



Albuterol-Budesonide PARTICS



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Oregon Medicaid Coverage of SMART Therapy

- As of a recent check, budesonide/formoterol is currently on the preferred list on the Oregon Medicaid formulary
  - Despite this, Oregon Medicaid typically doesn't cover more than budesonide/formoterol 2 puffs BID
  - Formulary changes regularly and sometimes only will cover inhalers with alternative LABAs (Not to be used with SMART therapy)

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Conclusions

- SMART = **S**ingle **M**aintenance **A**nd **R**eliever **T**herapy = Inhaled corticosteroid (ICS, budesonide) with formoterol (long acting beta agonist/LABA)
  - Not FDA approved
  - Supportive data in mild and mod-severe asthma
- PARTICS = **P**atient **A**ctivated **R**eliever **T**riggered **ICS** = Inhaled corticosteroid (ICS) with short acting beta agonist (SABA)
  - Albuterol-Budesonide inhaler is FDA approved
  - Supportive data in mild asthma
- Putting together all of the data, consider SMART therapy in those with mild persistent to mod-severe persistent asthma
  - Can also consider SMART therapy in those with mild intermittent asthma
  - Can also consider PARTICS therapy in those with mild intermittent and mild persistent asthma
  - Likely less added benefit in those whose symptoms are well controlled with no exacerbations in the recent past and no risk factors for severe exacerbations
- Keep in mind implementation issues with changes including potential for increased cost and insurance coverage issues

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Thank you!

Allergy and Clinical Immunology



Dr. Shyam Joshi



Dr. Colleen Sabella



Dr. Haley Peterson Hostetler



Dr. Karen Anstey

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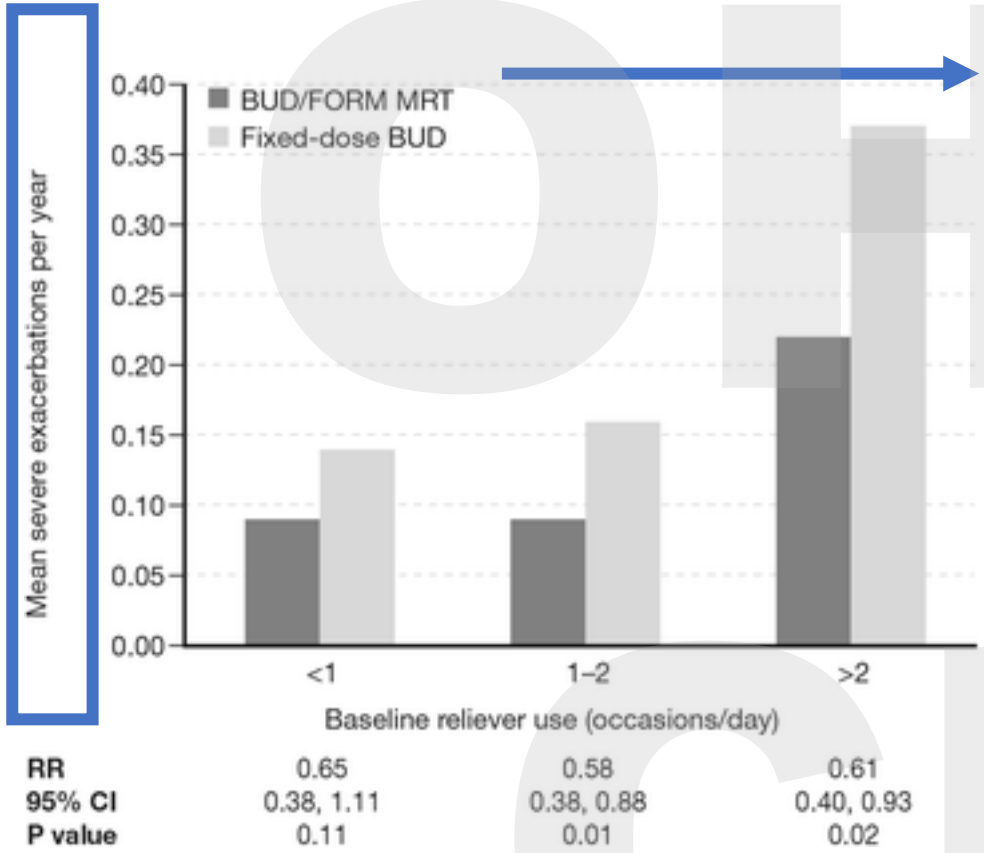
SMART Therapy Data in Mild Asthma



Budesonide/formoterol maintenance and reliever therapy (SMART)

Higher, fixed-dose budesonide plus SABA

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Jenkins CR, et al. Efficacy of budesonide/formoterol maintenance and reliever therapy compared with higher-dose budesonide as step-up from low-dose inhaled corticosteroid treatment. BMC Pulm Med. 2017

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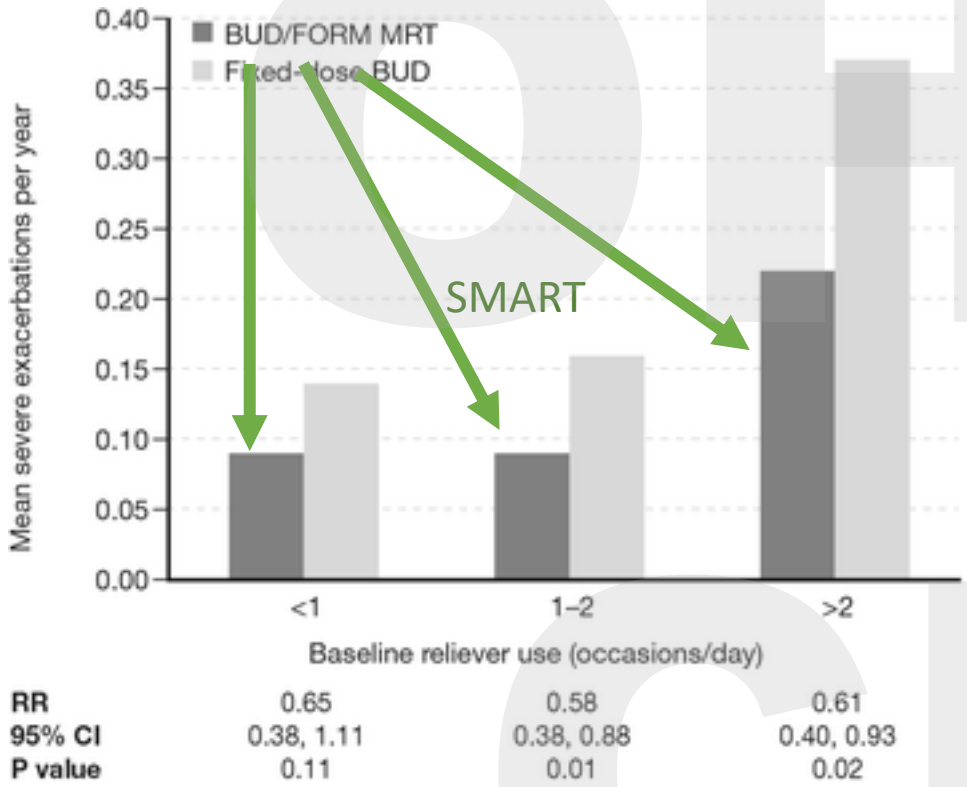
SMART Therapy Data in Mild Asthma



Budesonide/formoterol maintenance and reliever therapy (MRT)

Higher, fixed-dose budesonide plus SABA

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Jenkins CR, et al. Efficacy of budesonide/formoterol maintenance and reliever therapy compared with higher-dose budesonide as step-up from low-dose inhaled corticosteroid treatment. BMC Pulm Med. 2017

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