

Anti- Inflammatory Rescue: Options and Challenges

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Disclosures

- Author, UpToDate chapters on asthma



Abbreviations

- **ICS:** inhaled corticosteroids
- **SABA:** short-acting beta agonist
 - albuterol, terbutaline, salbutamol
- **LABA:** long-acting beta agonist
 - formoterol, salmeterol, vilanterol
- **FABA:** FAST-acting beta agonist
 - Any SABA or formoterol
- **(S)MART:** (Single) Maintenance and Reliever Therapy
- **AIR:** Anti-Inflammatory Rescue/Reliever



Outline

Why AIR has potential to be one of the most impactful advances in asthma care in the last 2+ decades...but still very limited in implementation

- SABA as rescue
- (S)MART and other AIR options reduce exacerbations
- Additional benefits of AIR/SMART
- Barriers to implementation



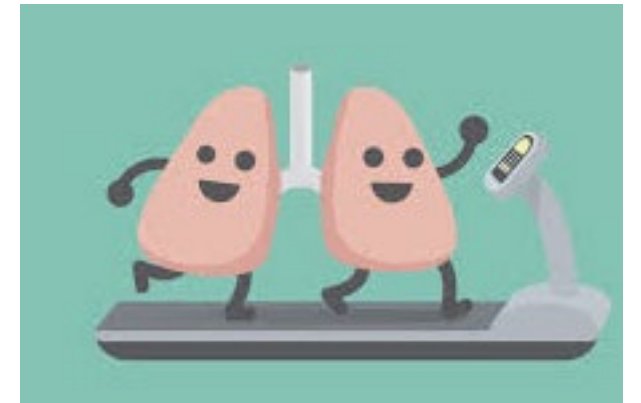
Asthma Burden

- Over 260 million worldwide
 - In US Adults: 20 million; 8.7% (2022)
 - In US Children: 5.1 million; 6.2%
- Health care utilization
 - 5.8 million physician office visits
 - 1.2 million emergency department visits
 - 40% with asthma report asthma “attack” in last year
- Deaths
 - >400,000 worldwide; in US >4,000 (2020)
 - 1.3 per 100,000 population



Goals of asthma treatment

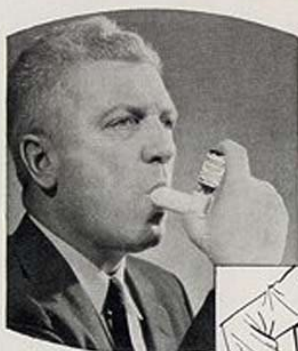
- Reduce mortality
- Reduce exacerbations
 - hospitalizations / ED / UC / systemic steroids
- Reduce symptoms, interference with normal life / activity
 - Improve quality of life
- Minimize side effects of treatment (including cost)



At Last...
UNIFORM DOSAGE NEBULIZATION
in Asthma

MEDIHALER™

with Your Favorite
Bronchodilator*



Medihaler Oral Adapter is nonbreakable. Vial of Medihaler medication is leakproof, spillproof, provides 200 applications. Economical.



- NO RUBBER BULBS TO DETERIORATE
- NO BREAKAGE OF COSTLY GLASS NEBULIZERS
- NO SPILLING OF SOLUTION IN POCKET OR PURSE

True nebulization—80% of particles from 1/2 to 4 microns radius. Amount of medication released does not depend on pressure applied—dosage always the same. One application usually sufficient for most patients.

Notably safe for use with children. One application usually aborts attack.



* **MEDIHALER-EPI™**
0.5% solution of epinephrine
HCl U.S.P.

* **MEDIHALER-ISO™**
0.25% solution of isoproterenol
HCl U.S.P.

On your prescription be sure to write "Medihaler-Iso (or Medihaler-Epi) AND Medihaler Oral Adapter," since medication cannot be used without Adapter. For refills write for medication only.

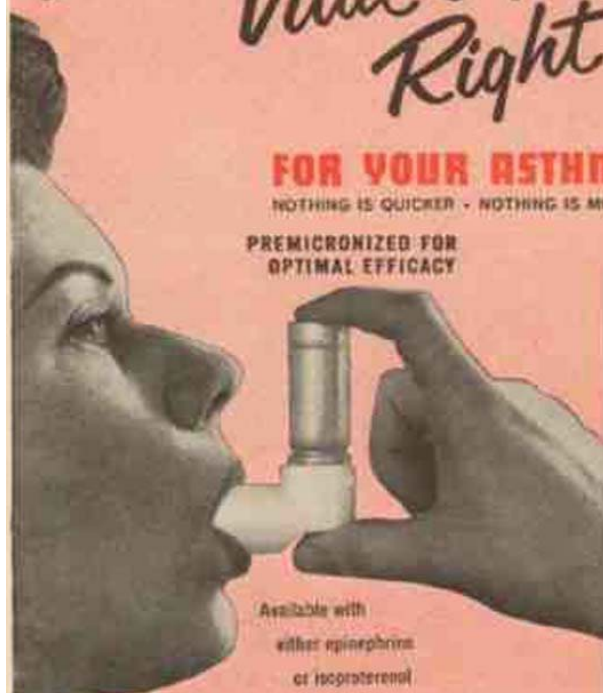


22½% More
Vital Capacity
Right Now

FOR YOUR ASTHMATICS

NOTHING IS QUICKER • NOTHING IS MORE EFFECTIVE

PREMICRONIZED FOR
OPTIMAL EFFICACY



Available with
either epinephrine
or isoproterenol

Medihaler-EPI™

Epinephrine bitartrate, 2.0 mg. per cc., suspended in inert, nontoxic aerosol vehicle. Contains no alcohol. Each measured dose contains 0.15 mg. epinephrine.

Medihaler-ISO™

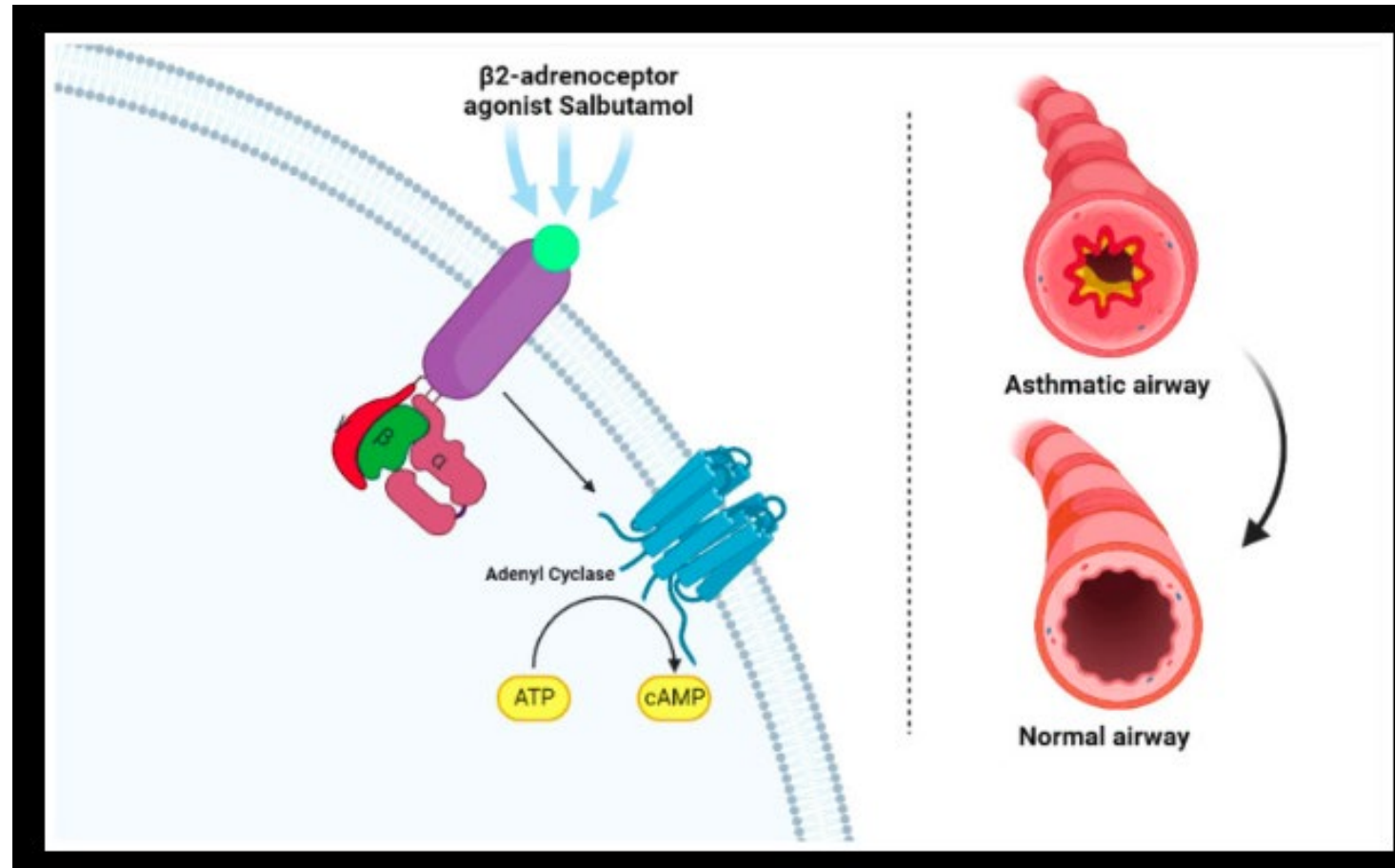
Isoproterenol sulfate, 2.0 mg. per cc., suspended in inert, nontoxic aerosol vehicle. Contains no alcohol. Each measured dose contains 0.06 mg. isoproterenol.



SUITABLE FOR CHILDREN, TOO.

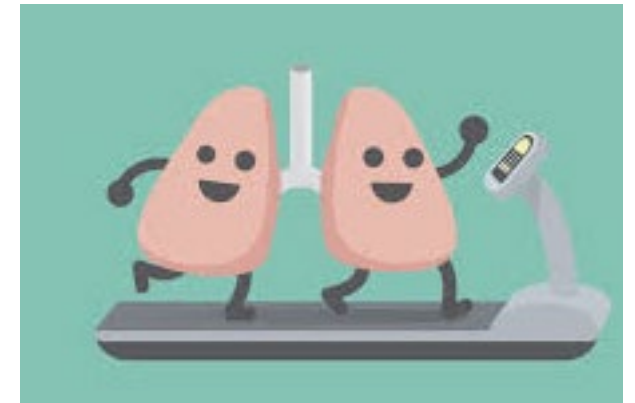
MEDIHALER™
automatically measured-dose aerosol medication.
Epinephrine • Isoproterenol • Sulfate • Bitartrate • Leukaphor

Beta agonist: mechanism of action



Goals of asthma treatment

- Reduce mortality
- Reduce exacerbations
 - hospitalizations / ED / UC / systemic steroids
- **Reduce symptoms** interference with normal life / activity
 - Improve quality of life
- Minimize side effects of treatment (including cost)



Disadvantages of SABA

- **Physiology**

- Tolerance / tachyphylaxis
- Rebound bronchoconstriction
- Increased airway hyperresponsiveness
- Increased eosinophilic inflammation

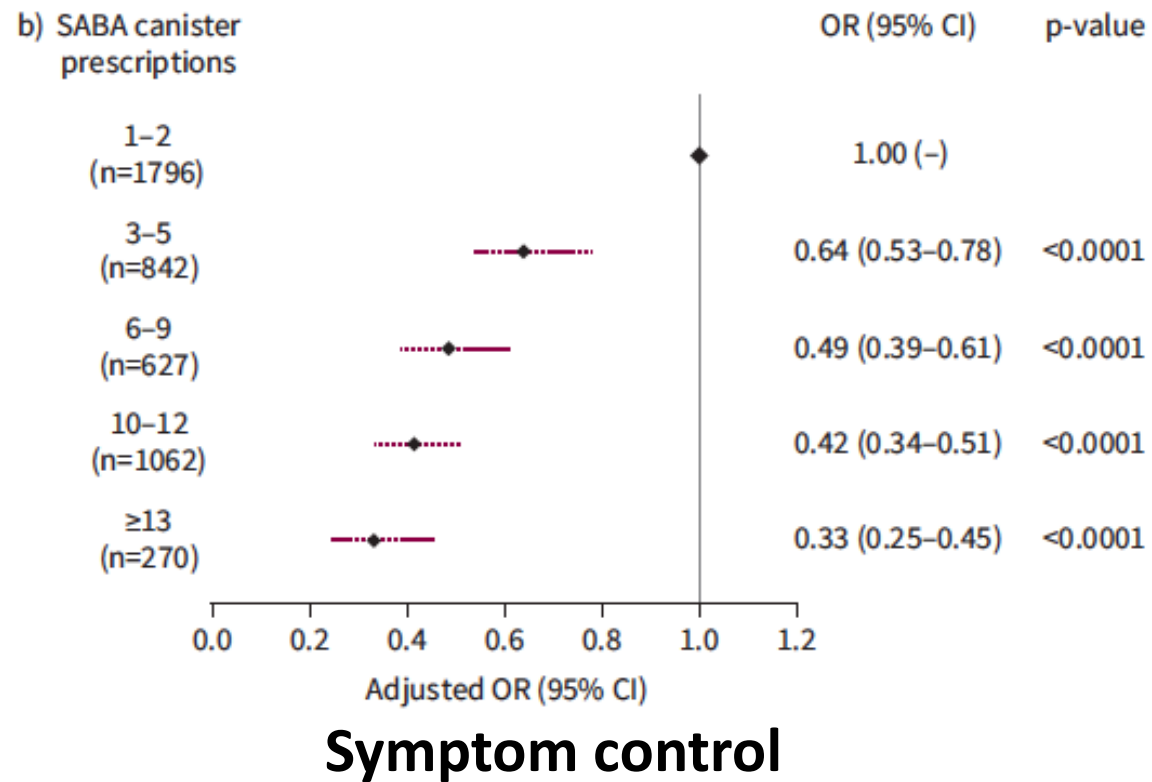
- **Epidemiology**

- Exacerbations
- Death

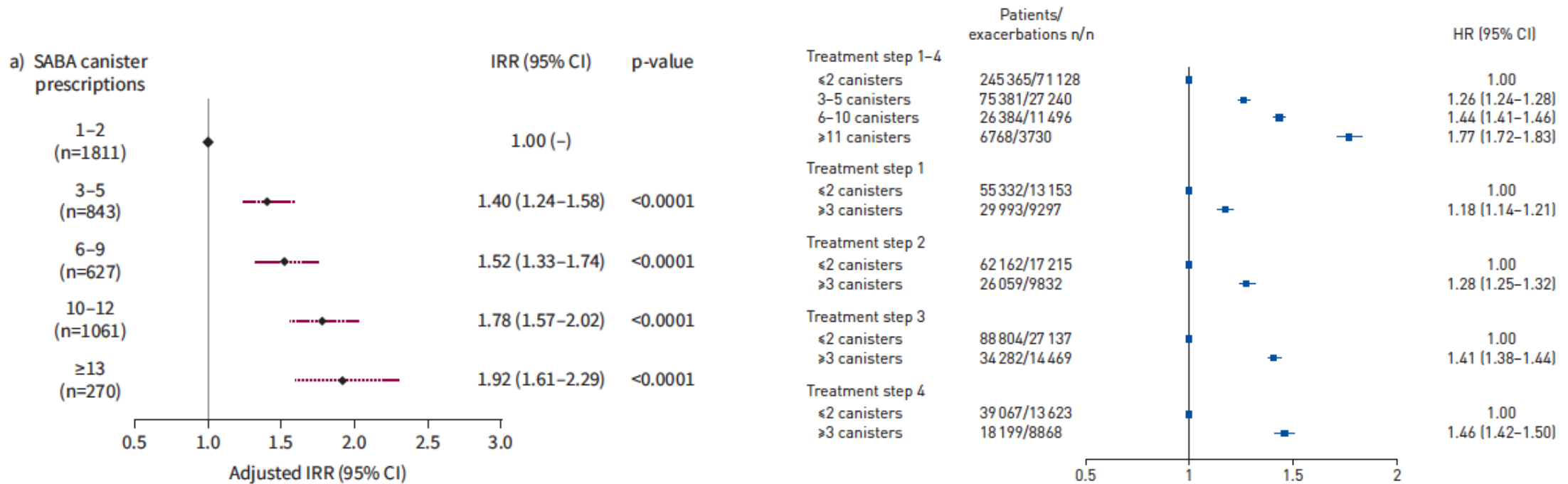


SABA overuse: symptom control

Overuse: 10-38% prevalence

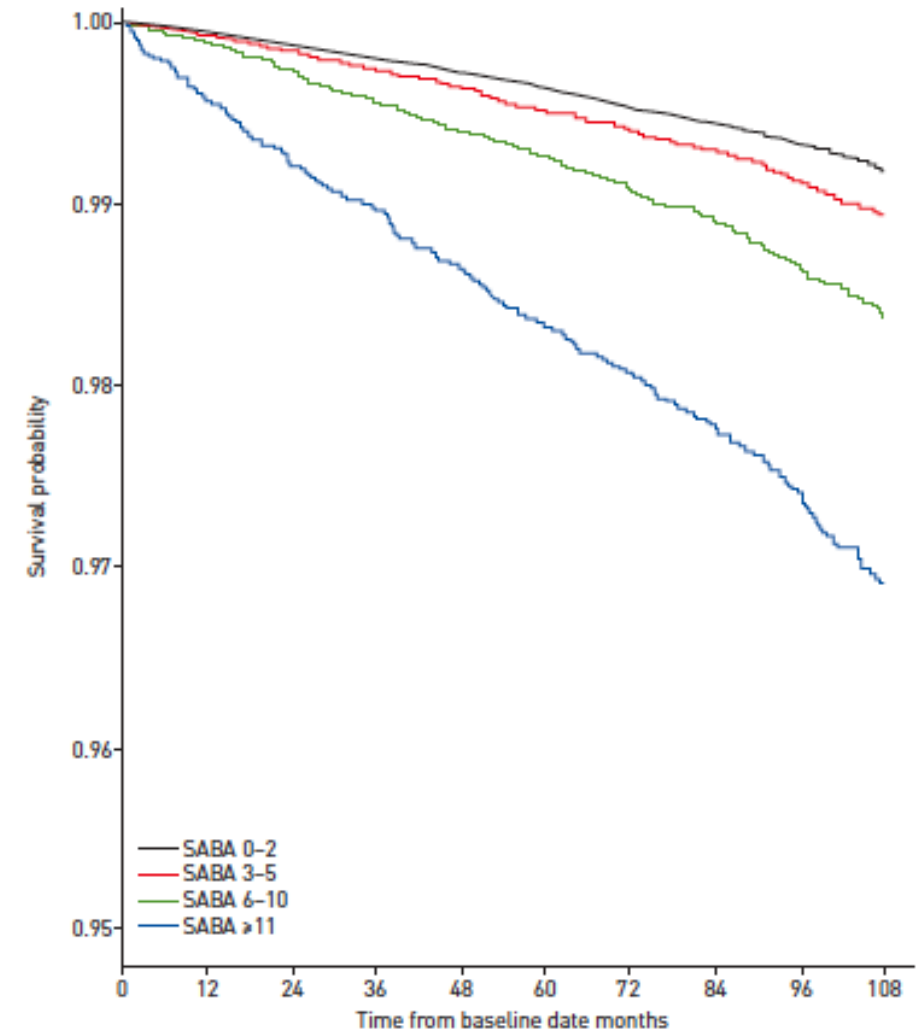


SABA overuse and exacerbations



SABA overuse and mortality

- ↑mortality
- OVERALL and asthma-related



| At risk n | 0 | 12 | 24 | 36 | 48 | 60 | 72 | 84 | 96 | 108 |
|-----------|---------|---------|---------|---------|---------|---------|---------|---------|--------|--------|
| SABA 0-2 | 254 500 | 254 367 | 230 860 | 210 403 | 187 331 | 165 549 | 142 973 | 118 674 | 91 999 | 54 765 |
| SABA 3-5 | 76 619 | 76 563 | 71 316 | 66 801 | 61 790 | 56 015 | 49 939 | 43 024 | 34 937 | 22 584 |
| SABA 6-10 | 27 065 | 27 034 | 25 769 | 24 552 | 23 280 | 21 836 | 20 212 | 18 503 | 16 436 | 13 034 |
| SABA ≥11 | 7 140 | 7 190 | 6 912 | 6 729 | 6 539 | 6 321 | 6 078 | 5 820 | 5 500 | 4 994 |

FIGURE 4 Kaplan-Meier plot of overall survival by baseline short-acting β_2 -agonist (SABA) use.



“Regardless of whether there is a **causal** effect of SABA use and these adverse effects, or if they are mainly a **marker for more severe asthma** and/or a **reflection of the frailty of the patients**, **increased use of SABA should alert clinicians to monitor these patients more closely**”

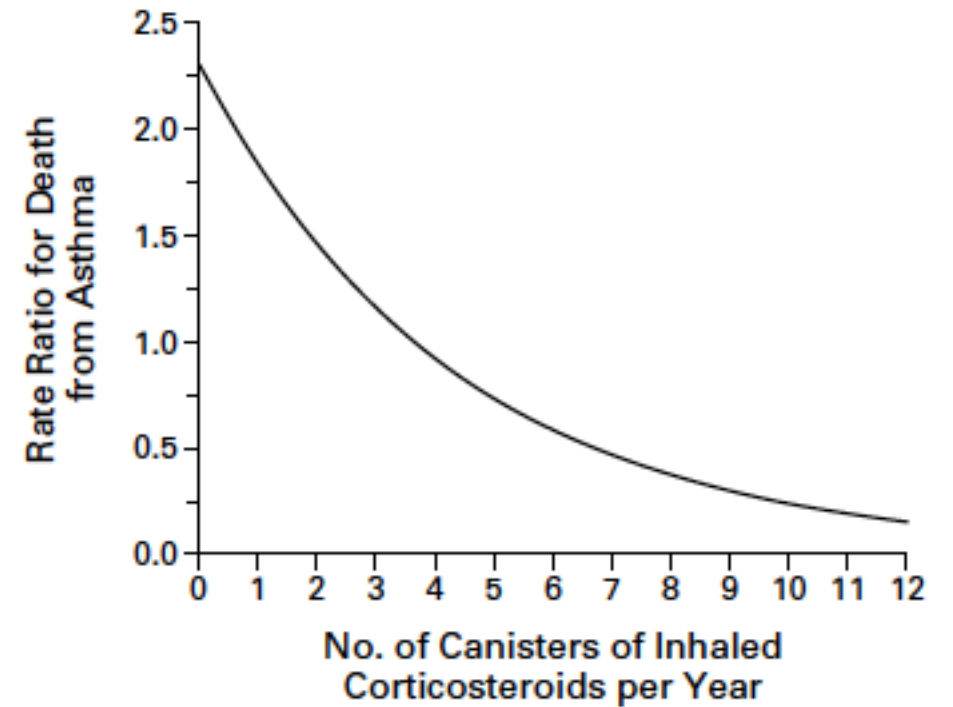
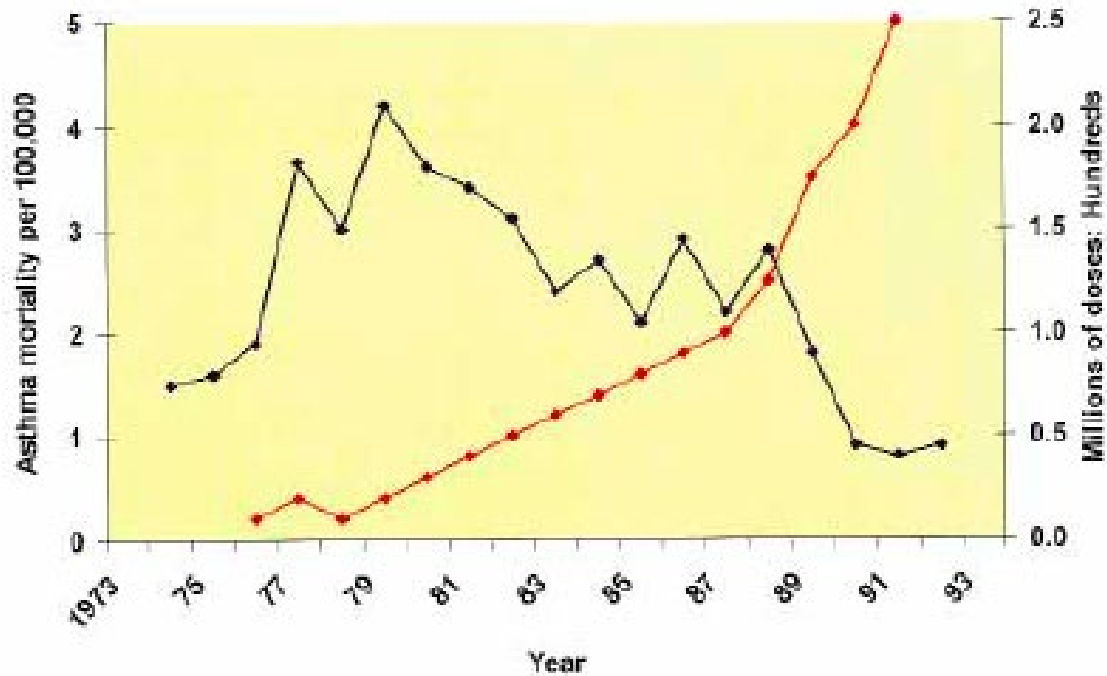
...but this may be a missed opportunity for PREVENTION





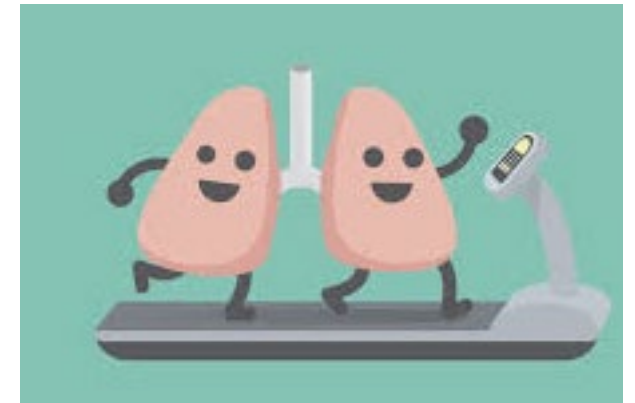
What about **AIR**

ICS and asthma mortality



Goals of asthma treatment

- Reduce mortality
- Reduce exacerbations
 - hospitalizations / ED / UC / systemic steroids
- Reduce symptoms, interference with normal life / activity
 - Improve quality of life
- Minimize side effects of treatment (including cost)



Adherence

ECRHS ASTHMA TREATMENT COMPLIANCE RESULTS

40%

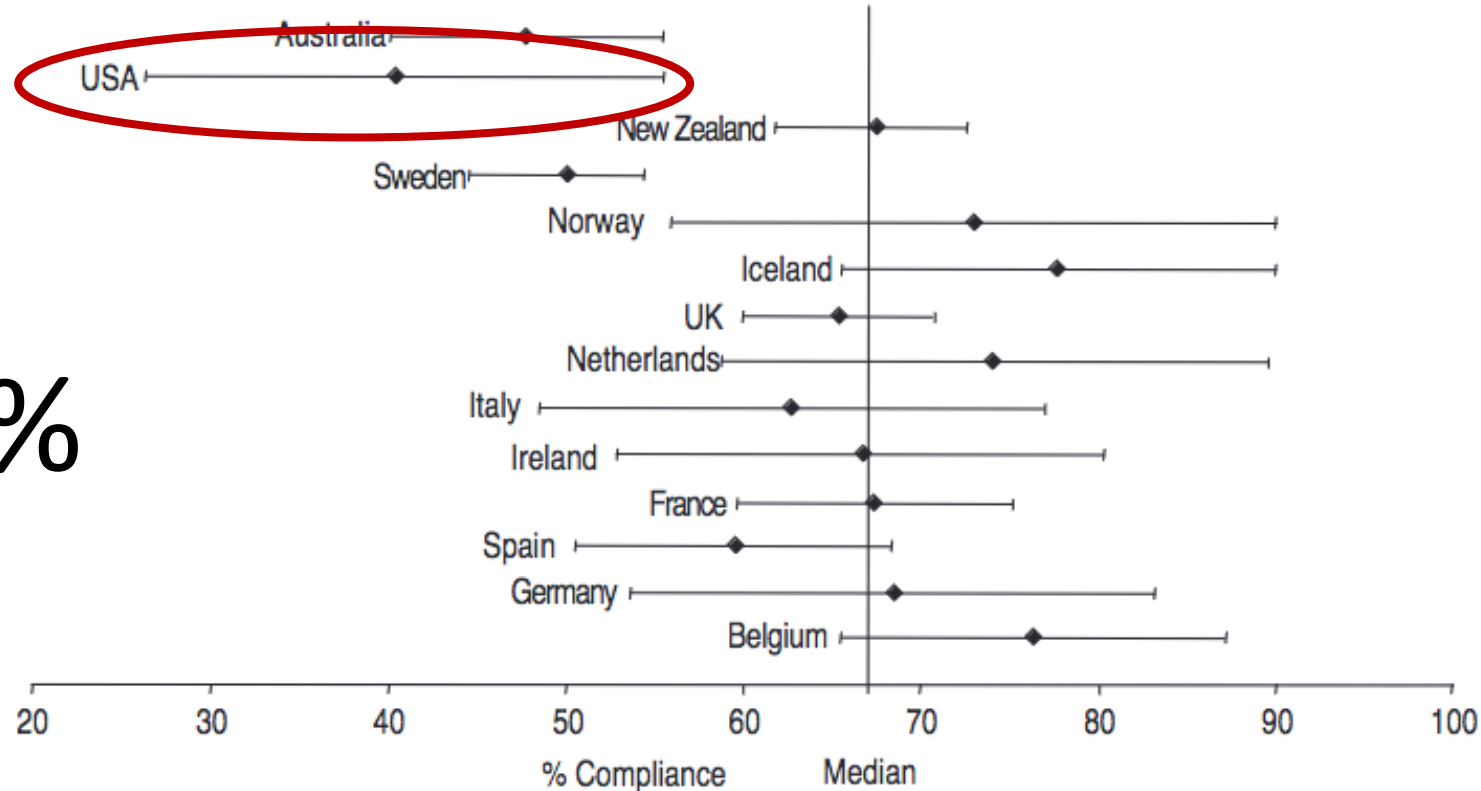
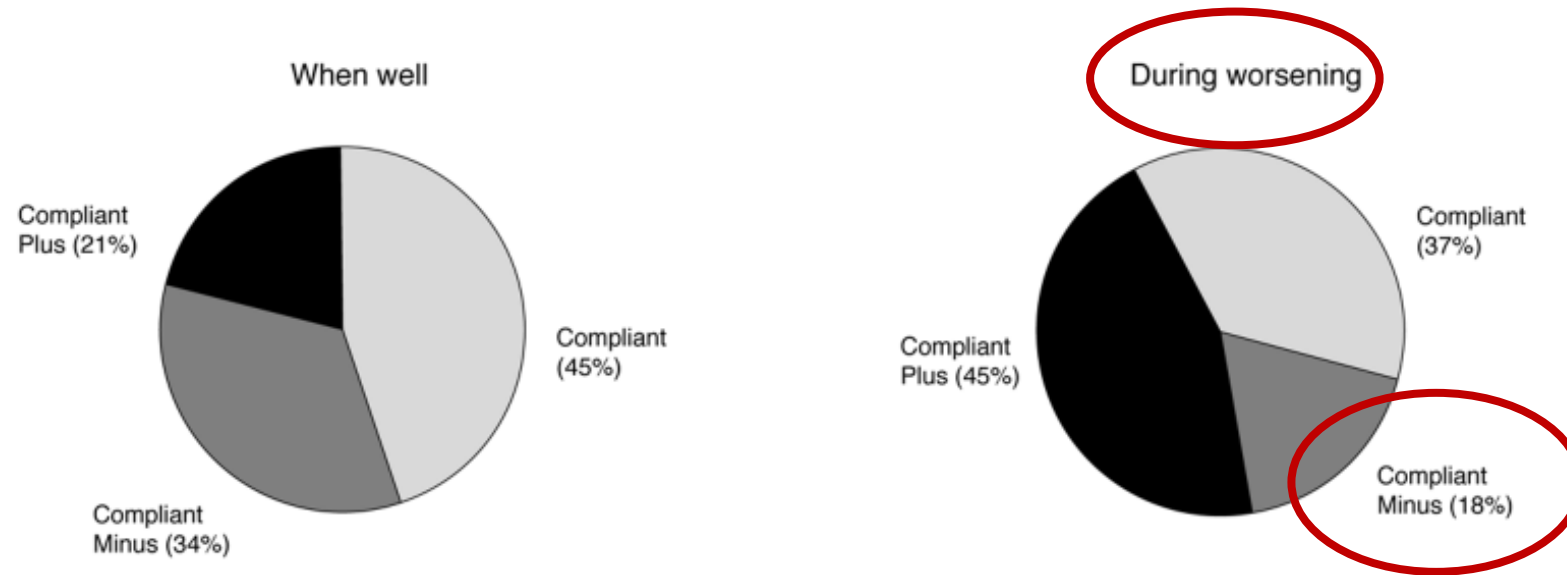


Fig. 2. – Prevalence (%) (◆) (95% confidence intervals (CI)) (—) of compliance between subjects with indications for treatment by country. A prevalence significantly different from the median is present when the 95% CI does not fit the vertical line of the median value.



Patient behavior: adherence to maintenance medication



n=3415

Figure 4

Patient compliance with their regular maintenance medication when feeling well and during asthma worsenings. Definitions were as follows: Compliant Minus: using less maintenance medication than prescribed; Compliant: using maintenance medication as prescribed; Compliant Plus: using more maintenance medication than prescribed.

Asthma: intermittent

- Triggers are unpredictable

- Viruses
- Pollens
- Pollution



- Oral steroids: ~ 4–5 lifetime courses ↑ risk:

- Osteoporosis/fracture
- Weight gain
- Diabetes
- Cataract

Summary so far:

- ICS addresses asthma treatment goals
BUT
- Patients don't use their maintenance therapy as prescribed
YET
- Patients DO use their rescue therapy (SABA), A LOT
 - This is not preventing exacerbations or deathTHUS....
- SMART / AIR approach



An analogy



ICS



FABA

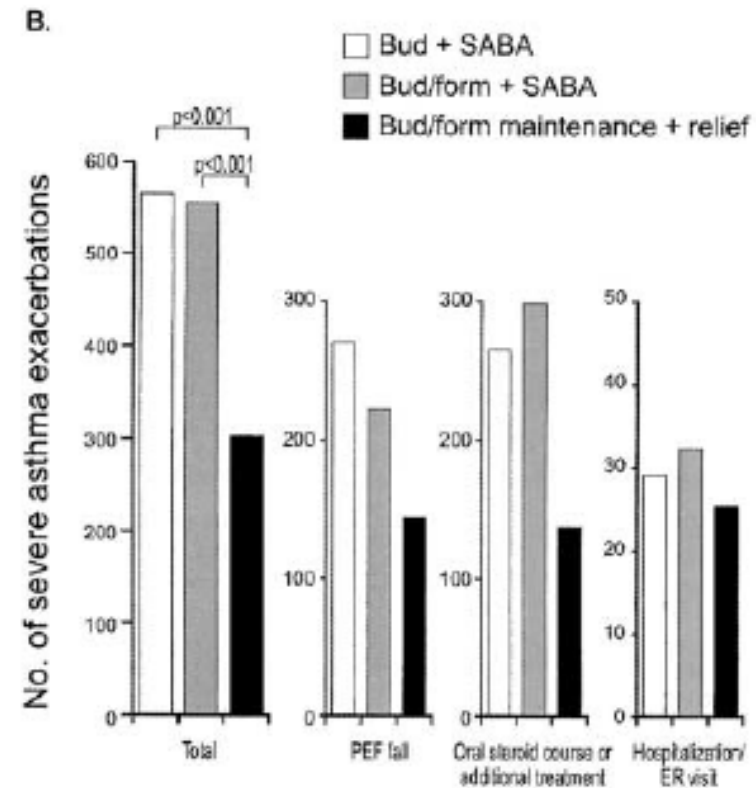
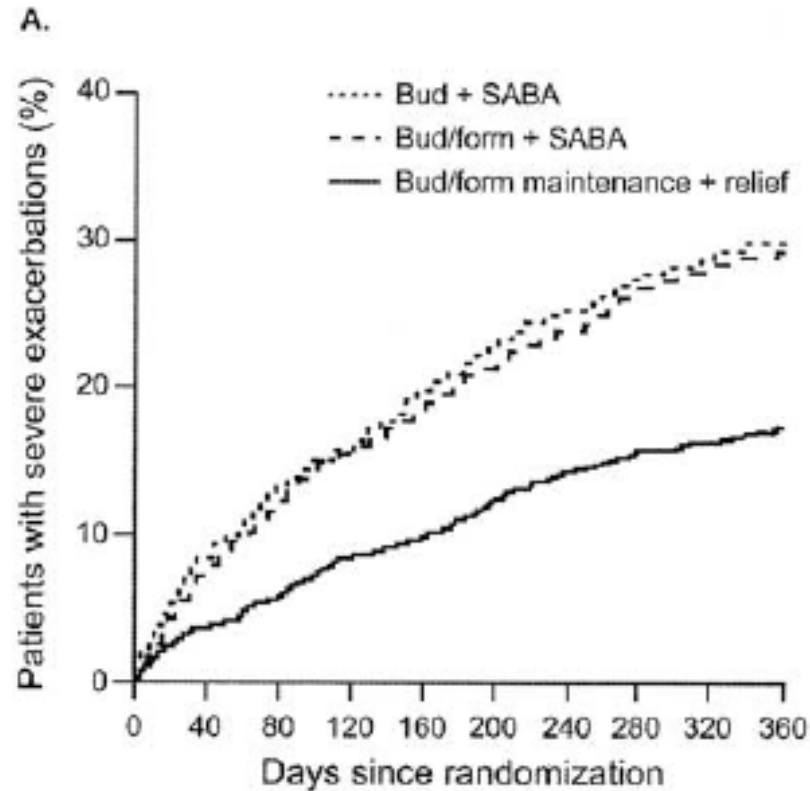
Solution: Give them at the same time!

SMART!

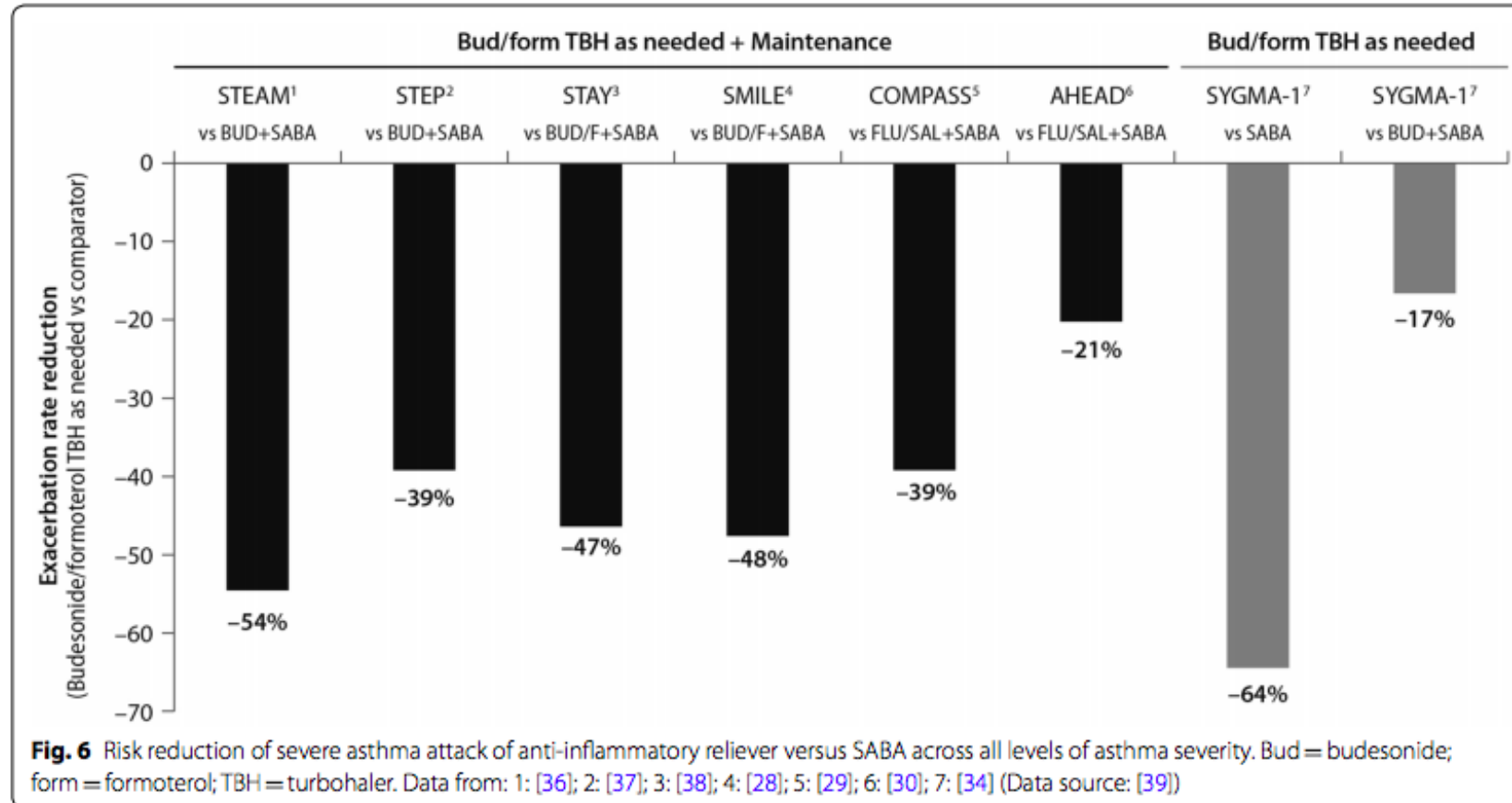


ICS/FABA
(ICS/SABA or ICS/LABA)

SMART approach: persistent asthma



Exacerbations: SMART vs various therapies, all SABA as reliever



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

- Meta-analysis 16 RCTs; Persistent asthma (mild, moderate, severe)
- 22,000 patients
- SMART vs.
 - ICS + SABA
 - ICS/LABA +SABA
- **Lower risk of exacerbations**
 - ED, hospitalizations, oral steroids \geq 3 days
- No significant associations:
 - ACQ-5, FEV1, mortality



MILD asthma: use ICS/LABA prn (**no maintenance**)

Compared to SABA prn alone:

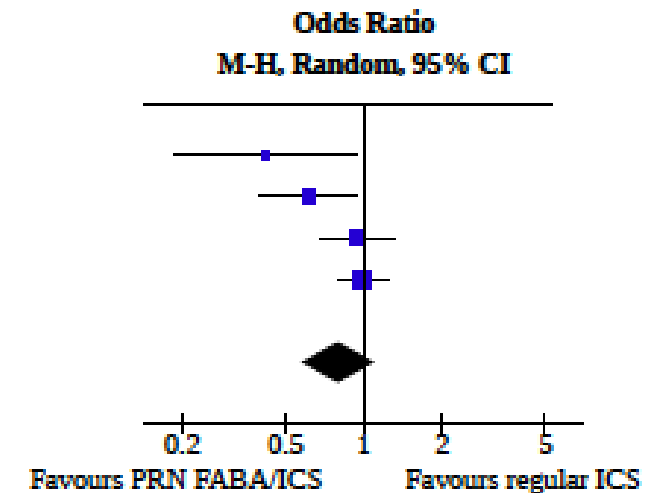
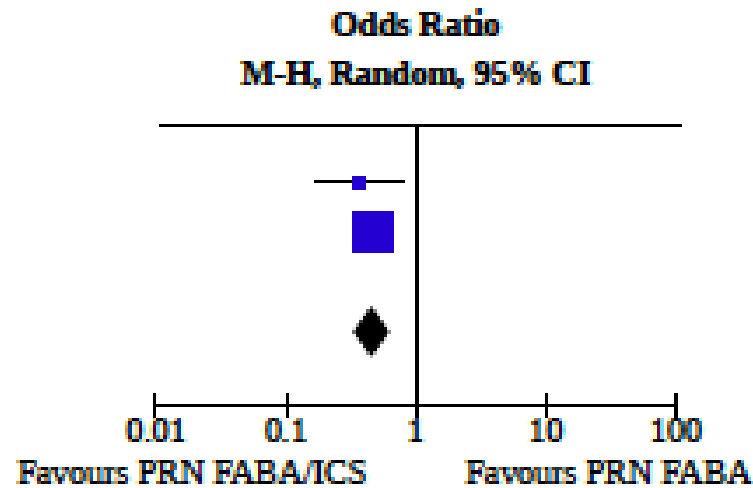
- LOWER exacerbation rates

Compared to ICS bid + SABA prn:

- No difference in exacerbations

AND

- **LOWER** overall steroid dose



Barriers to SMART or ICS/LABA prn approach

- Insurance
 - Must be ICS-formoterol
 - > 1 inhaler / month
- NOT FDA approved as reliever

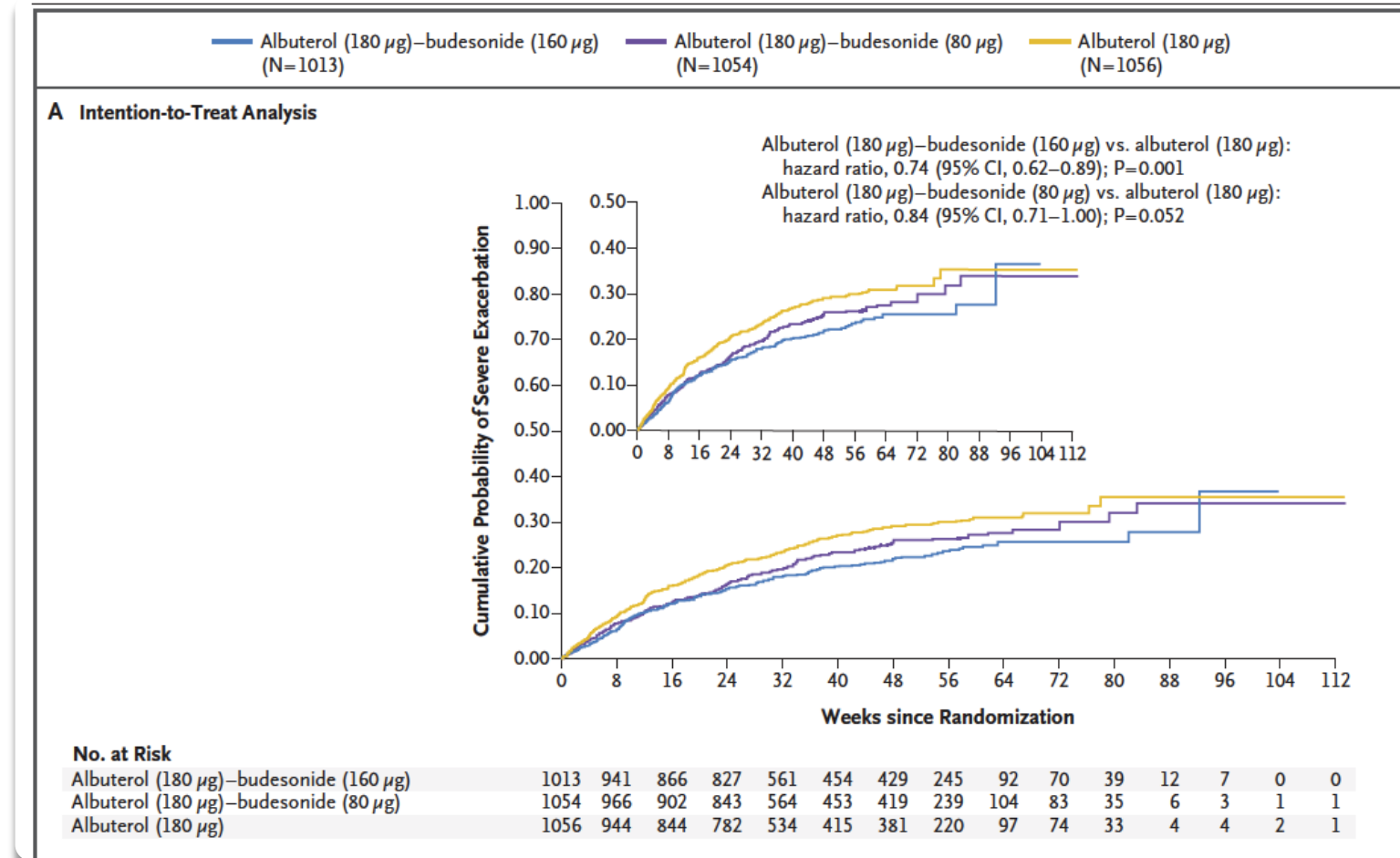


Other ways
to
implement
“AIR”



MANDALA trial

- Controller plus:
 - ICS/SABA
 - SABA as rescue
- Decreased exacerbations
- Annual dose of systemic steroids *50% lower* compared to SABA alone group



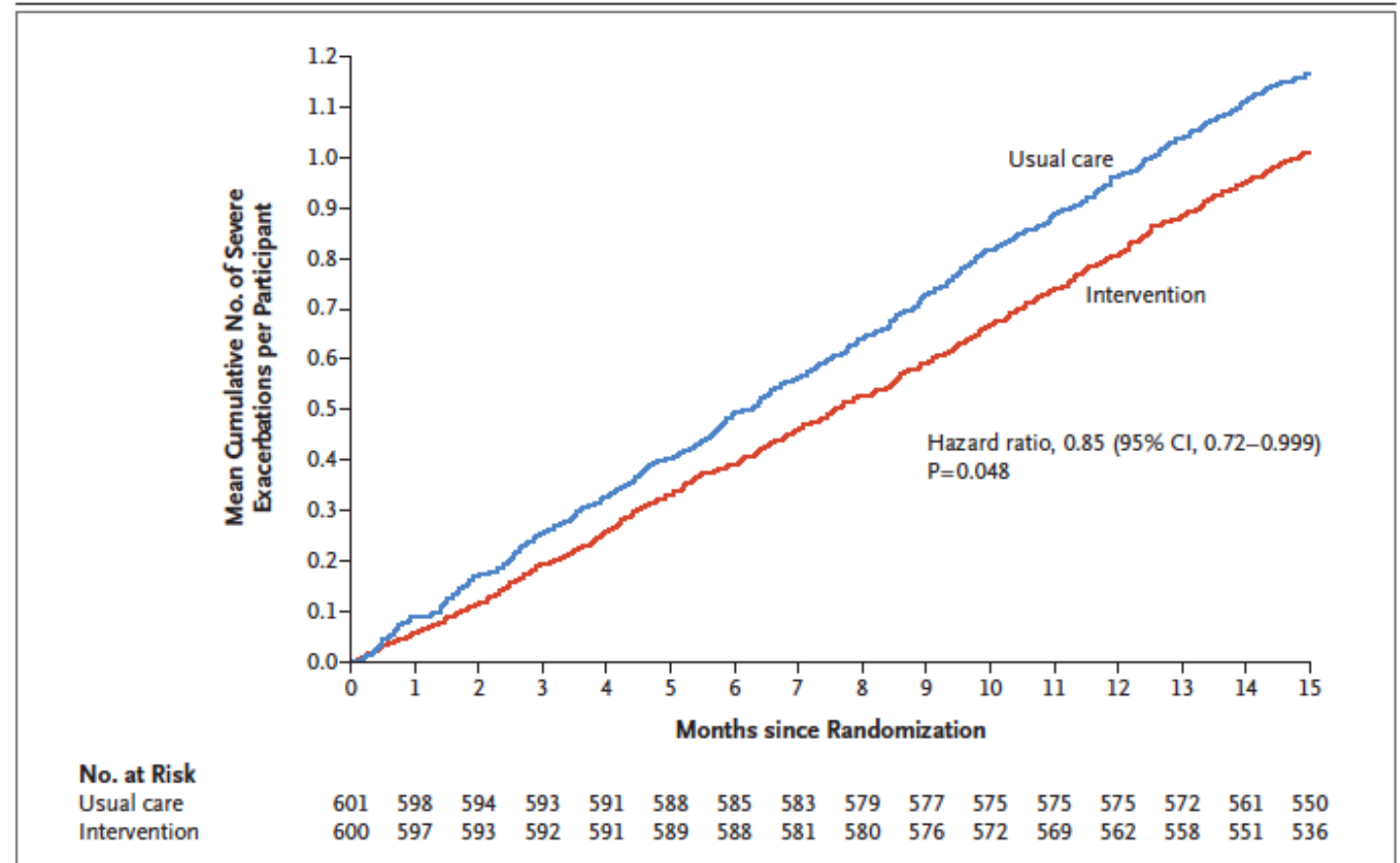


Albuterol/budesonide (80mcg) approved by FDA for use as rescue inhaler in people 18+ Jan 2023

- FDA – approved reliever inhaler (ICS/SABA)
- No need to change baseline controller medication
- Not required to have ICS-formoterol to implement “AIR”
- More like long-standing paradigm: controller + reliever
- BATURA trial 2025 – mild asthma

PREPARE: PeRson EmPowered Asthma RElief trial

- Controller plus:
 - SABA vs
 - ICS at time of SABA
- **↓ exacerbation rates**
- ↑ asthma control
- ↓ lost work / school days
- ↓ overall use of rescue medication



Principle is the same: VEGGIE BROWNIES!

AIR: Use ICS and FABA with any increase in symptoms

1. SMART: Single Maintenance And Reliever Therapy

- simpler since one overall inhaler
- BUT restricted to formoterol-containing ICS/LABA
 - financial, insurance coverage, change of controller regimen

2. MANDALA: ICS/SABA prn

- **Similar to current controller + rescue idea**
- No need to change maintenance therapy (if contains other LABA)
- BUT 2 different inhalers, approval for NEW inhaler

3. PREPARE: Add ICS when use prn SABA

- **improved flexibility**, use additional ICS when you need a nebulizer OR MDI for rescue
- BUT 2 different medications for rescue along with controller

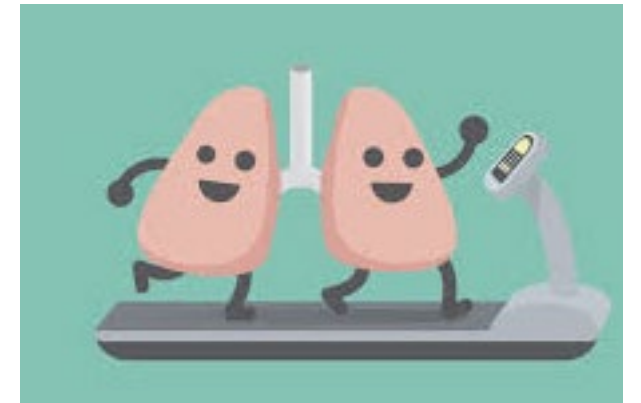
Goals of asthma treatment

- Reduce mortality
- Reduce exacerbations

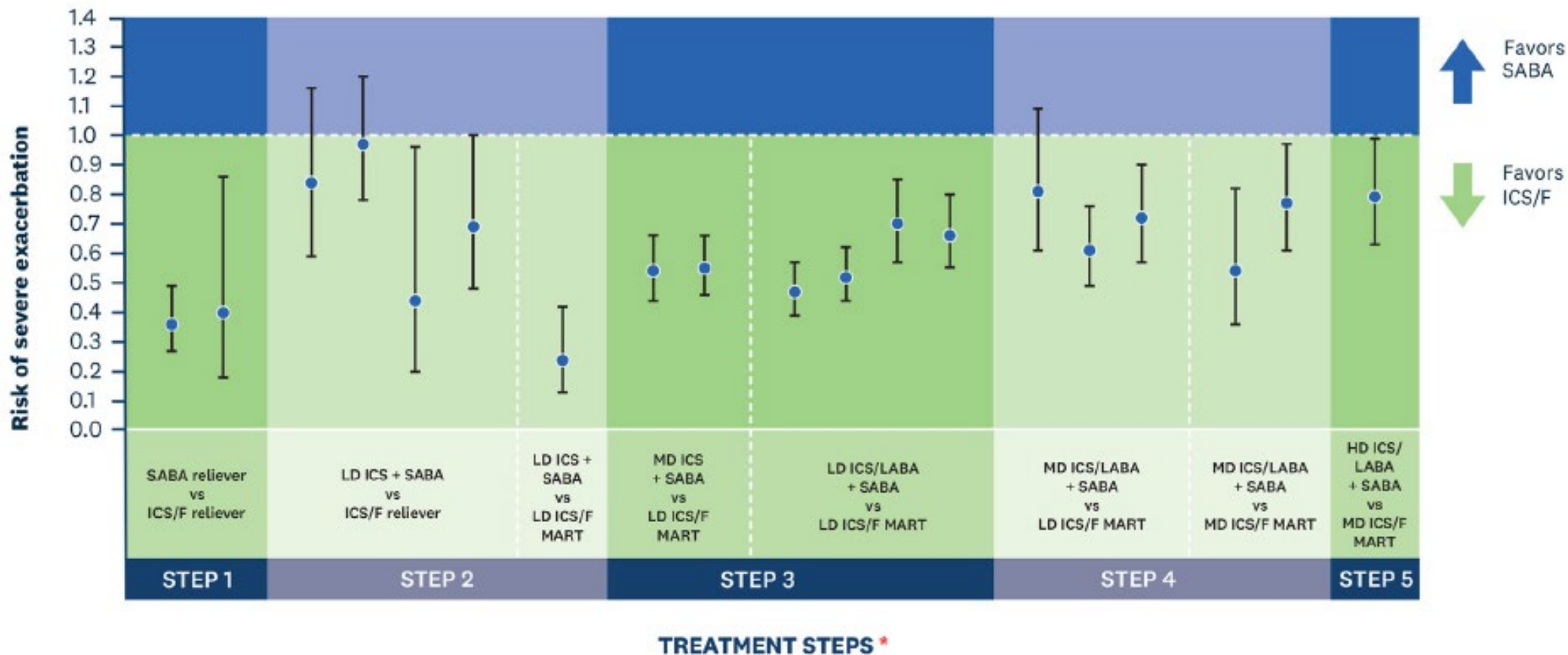


AND PEOPLE WILL USE IT!

- Minimize side effects of treatment (including cost)



AIR and ↓exacerbation risk



Additional benefits beyond exacerbations

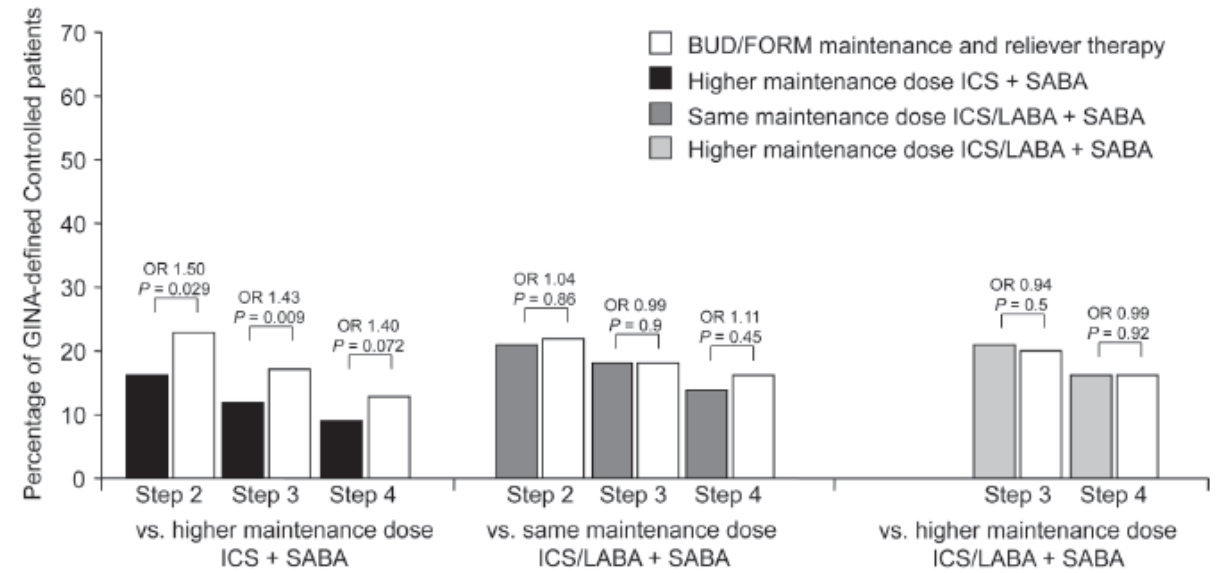
- Asthma control
- FEV₁
- Type 2 / non type 2
- High-use episodes
- Patient empowerment
- Safety
- Steroid dose



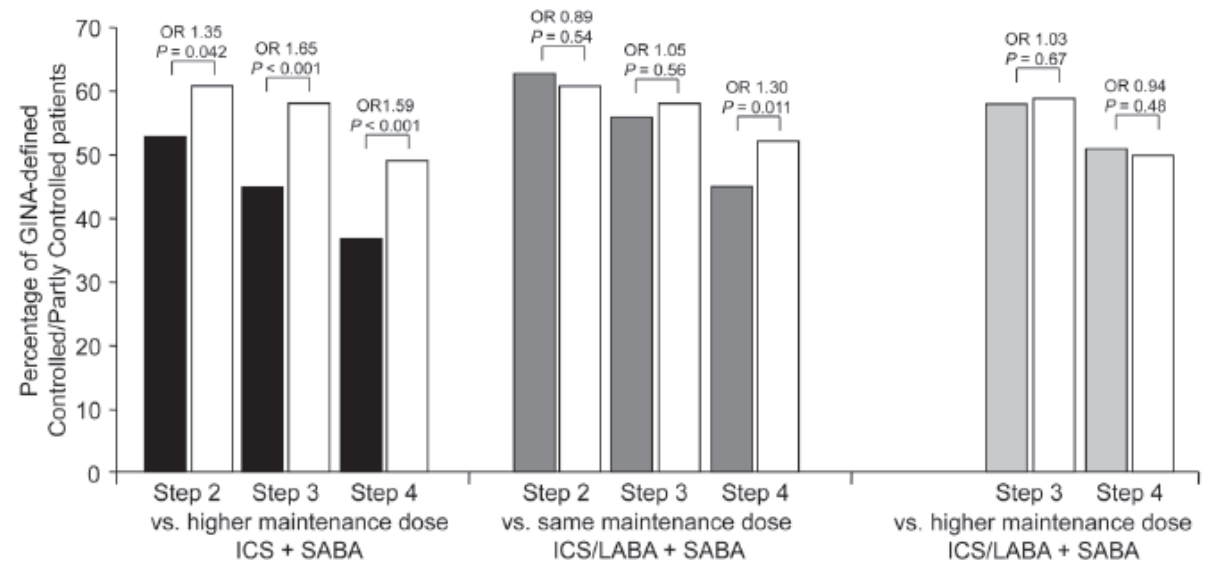
Asthma control

- BUD/FORM maintenance and reliever therapy
- Higher maintenance dose ICS + SABA
- Same maintenance dose ICS/LABA + SABA
- Higher maintenance dose ICS/LABA + SABA

A) Controlled asthma patients

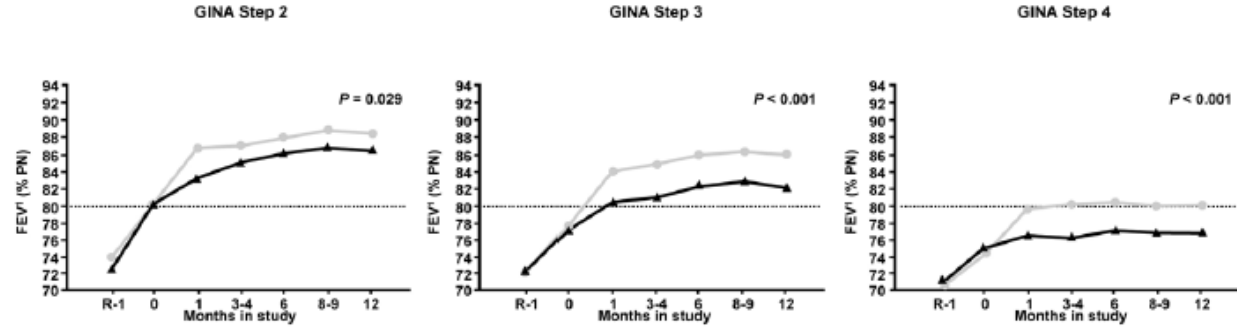


B) Controlled or Partly Controlled asthma patients



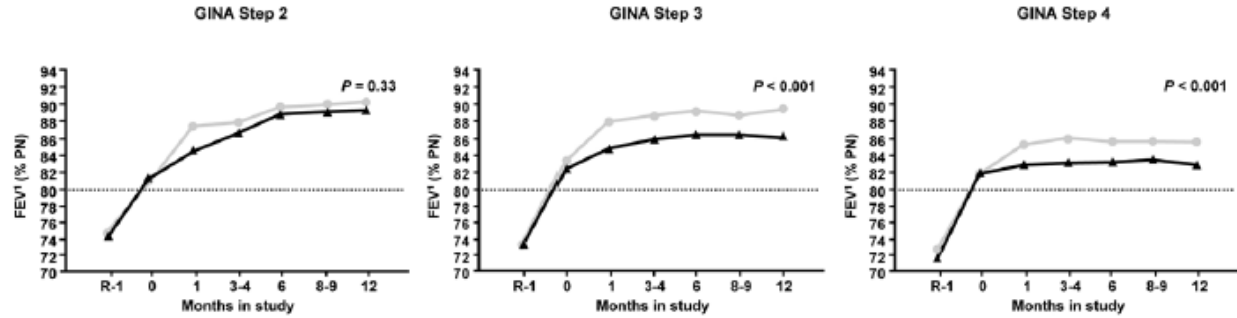
FEV₁

A) BUD/FORM maintenance and reliever therapy vs. higher maintenance dose ICS + SABA

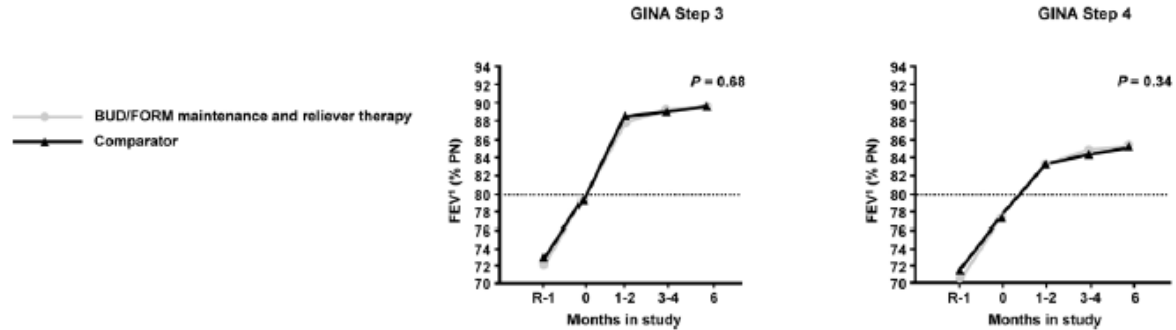


—●— BUD/FORM maintenance and reliever therapy
 —▲— Comparator

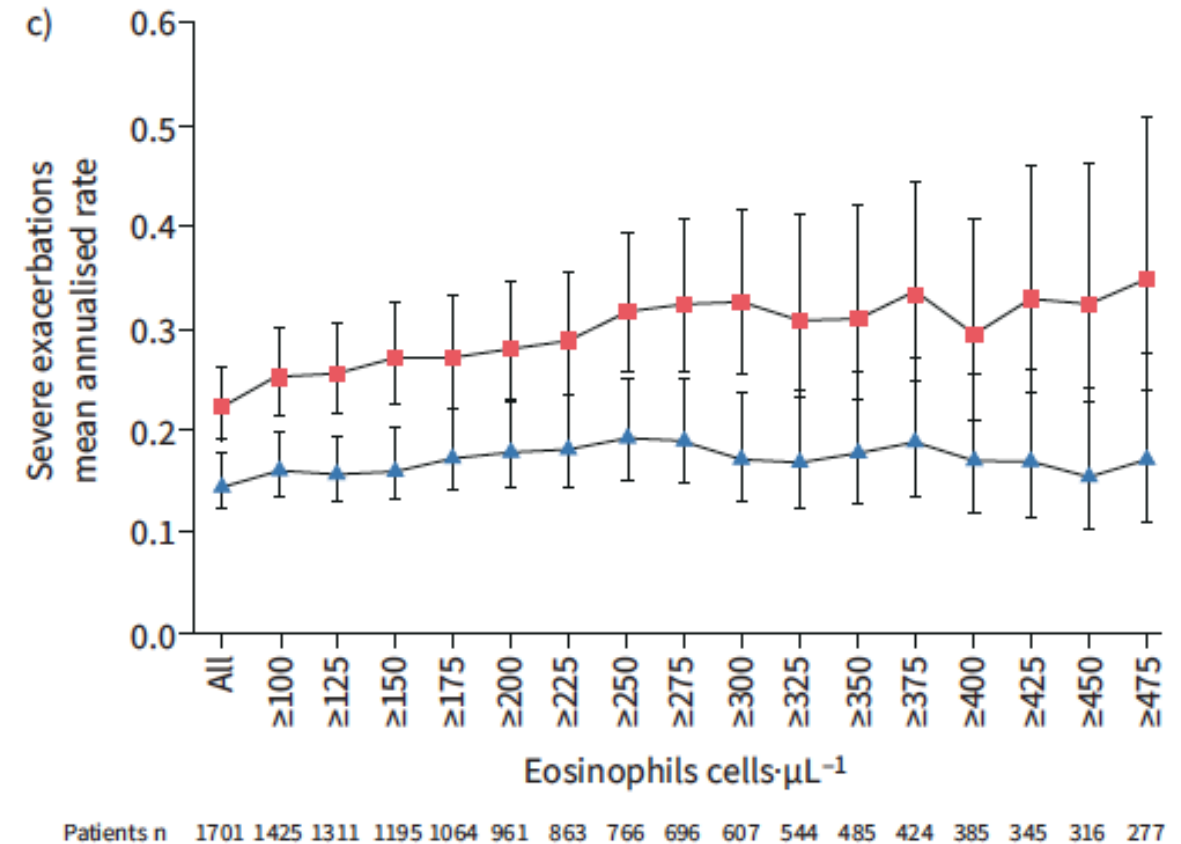
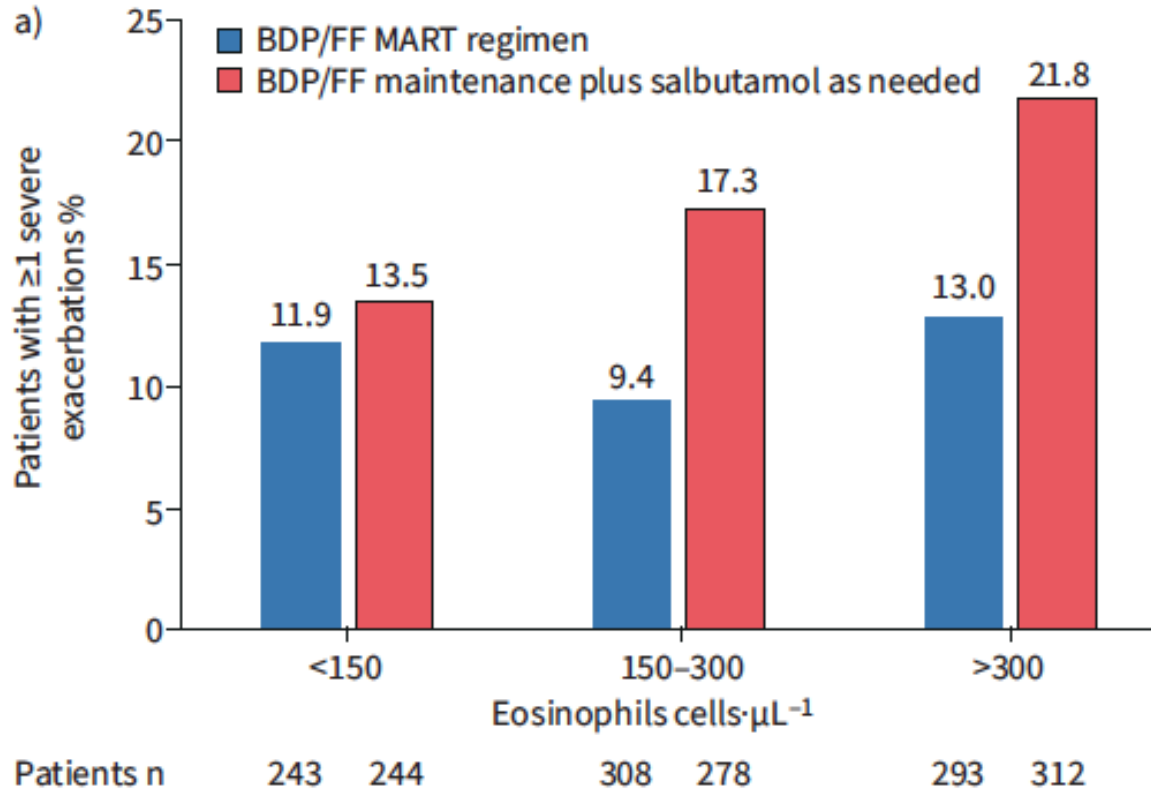
B) BUD/FORM maintenance and reliever therapy vs. same maintenance dose ICS/LABA + SABA



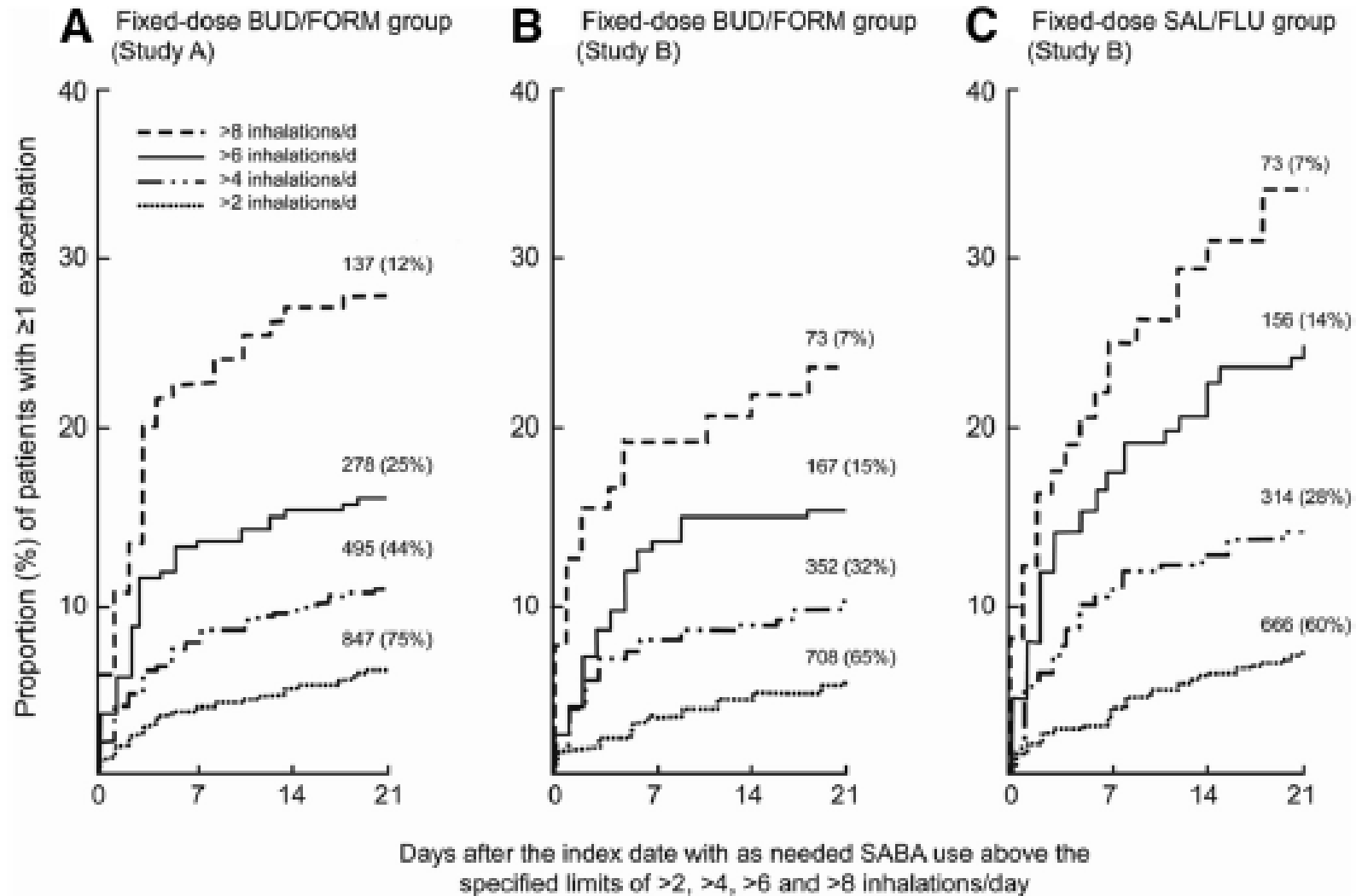
C) BUD/FORM maintenance and reliever therapy vs. higher maintenance dose ICS/LABA + SABA



SMART and absolute eosinophil count (AEC)

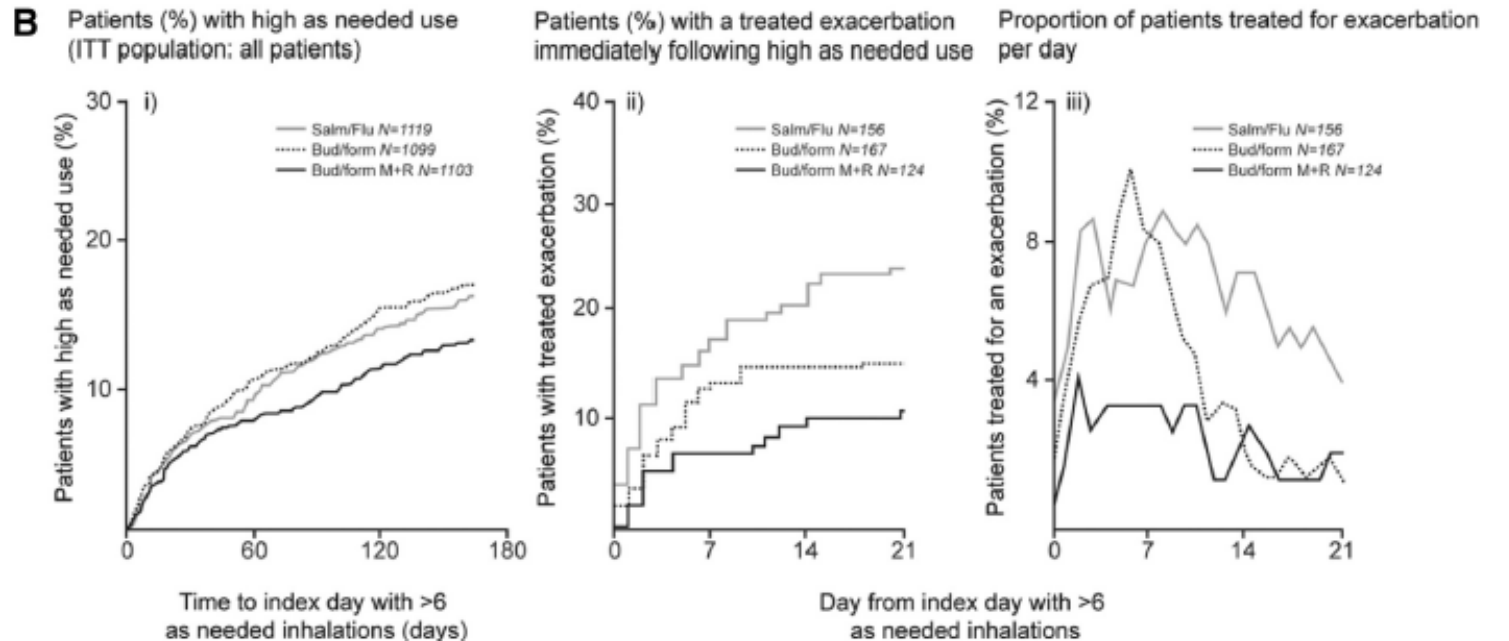
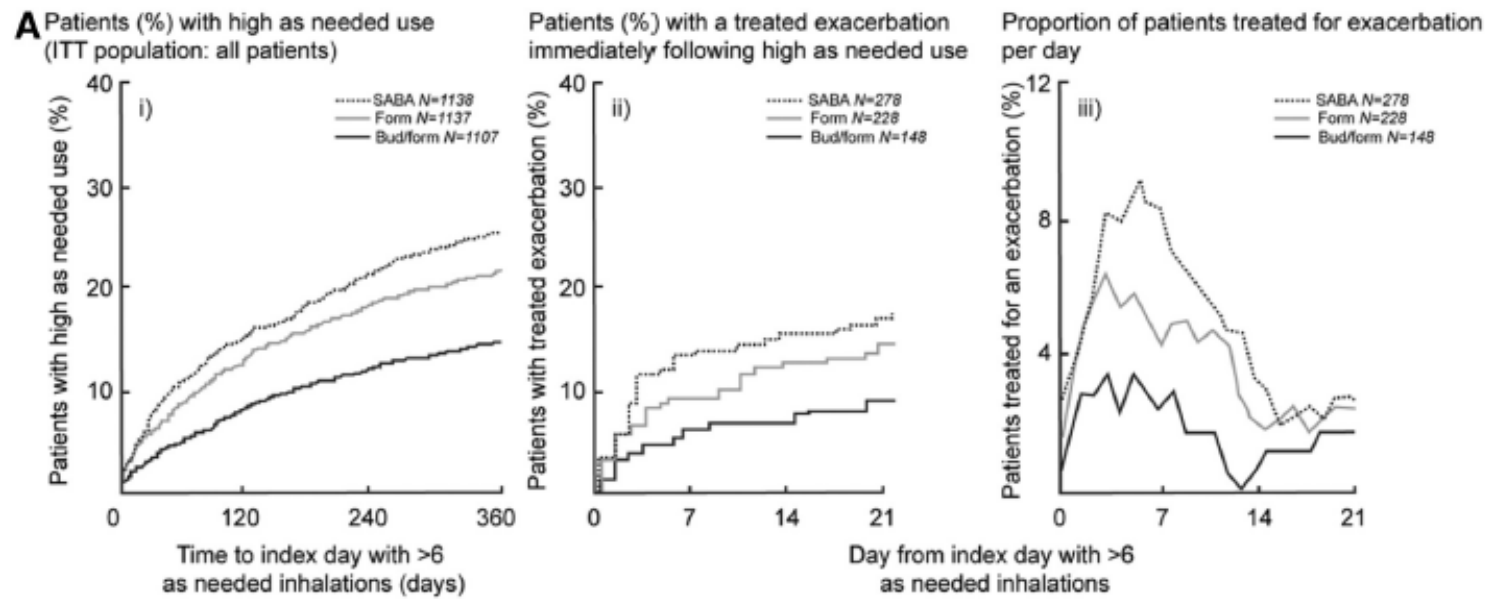


Reliever high-use episodes

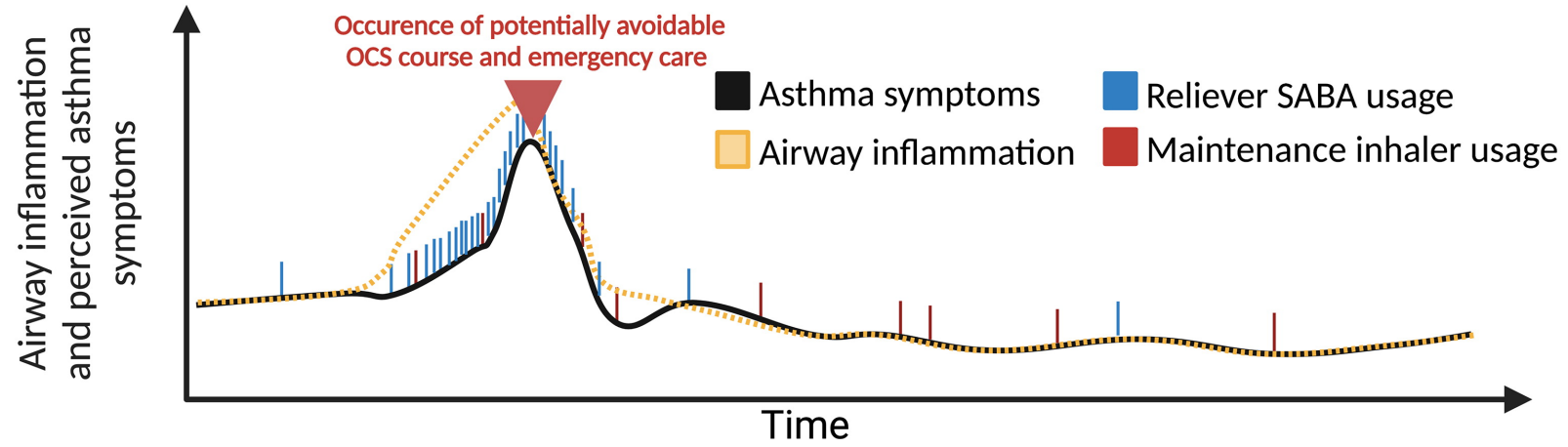


SMART group:

- ↓ high use episodes
- ↓ result in exacerbation

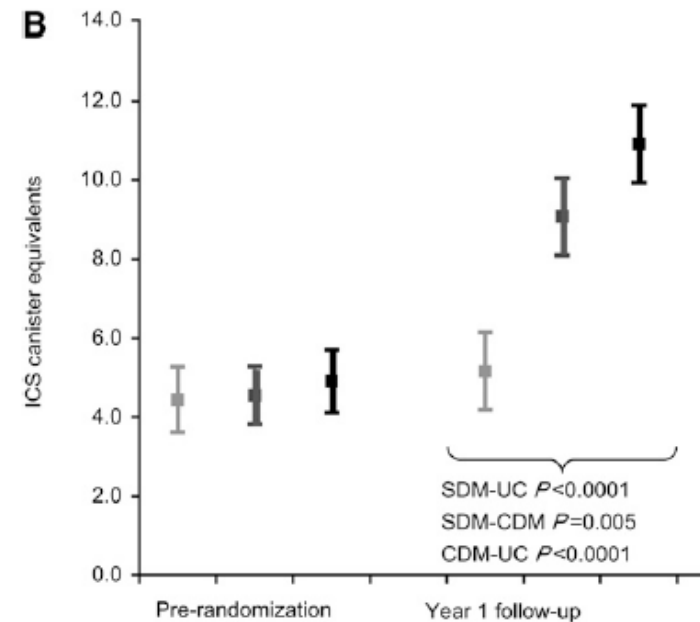
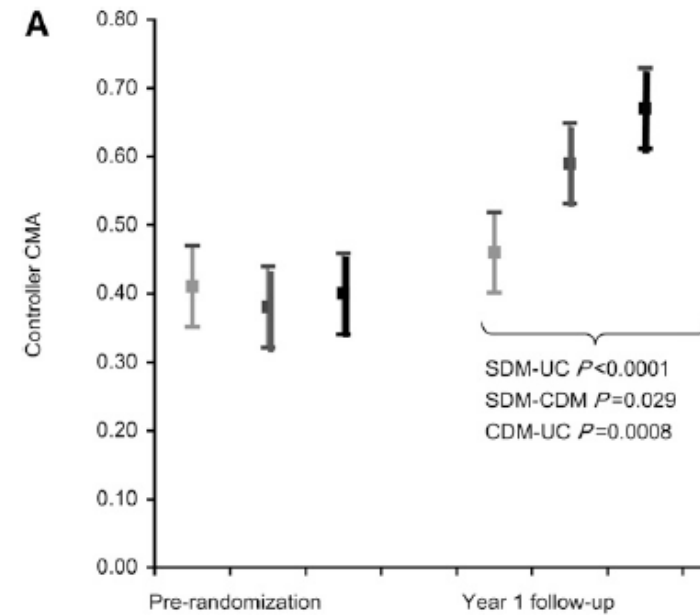


A Maintenance ICS and reliever SABA treatment paradigm in a patient with mild asthma and poor maintenance ICS adherence



Patient Empowerment and Adherence

- Shared decision making results in
 - Increased controller adherence
 - Better clinical outcomes
 - Asthma control
 - Lung function
 - Rescue use
 - Asthma-related QOL
 - Health care use



AIR and Patient Empowerment

- Patients are in control
- Targeting increased symptoms → increased therapy
- Adherence less of an issue
 - patients DO use the inhaler when symptomatic
- Gain in productivity
 - fewer school or work days missed



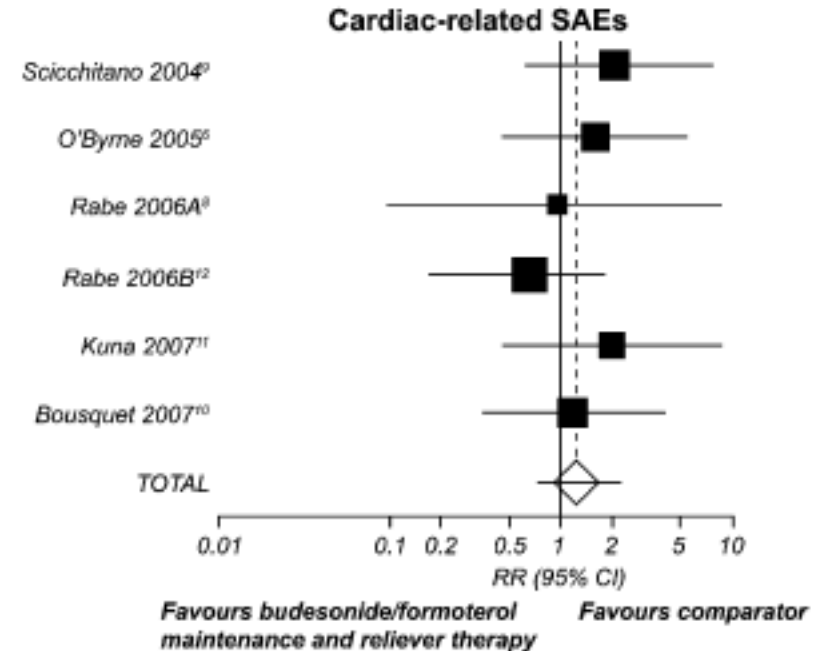
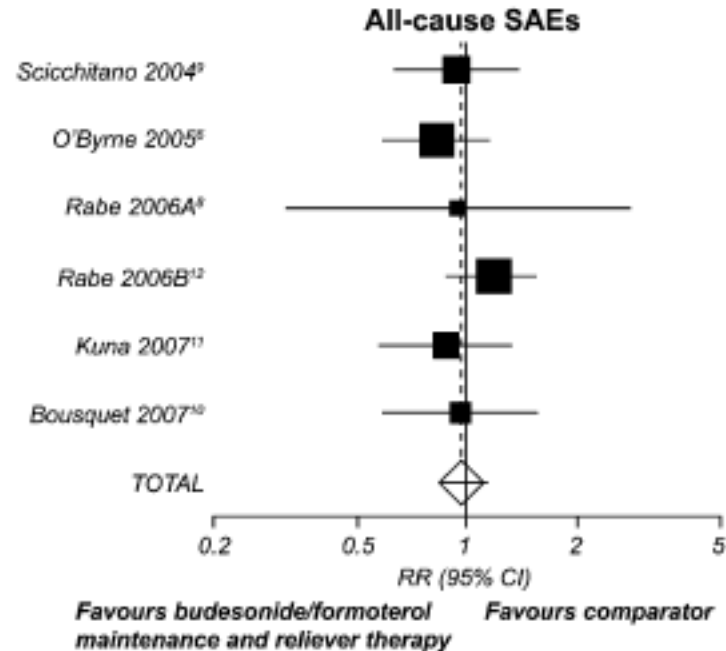
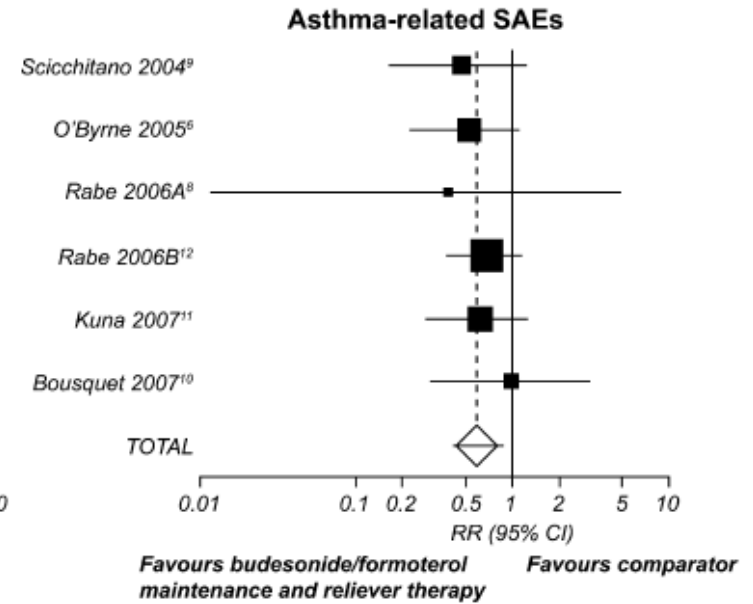
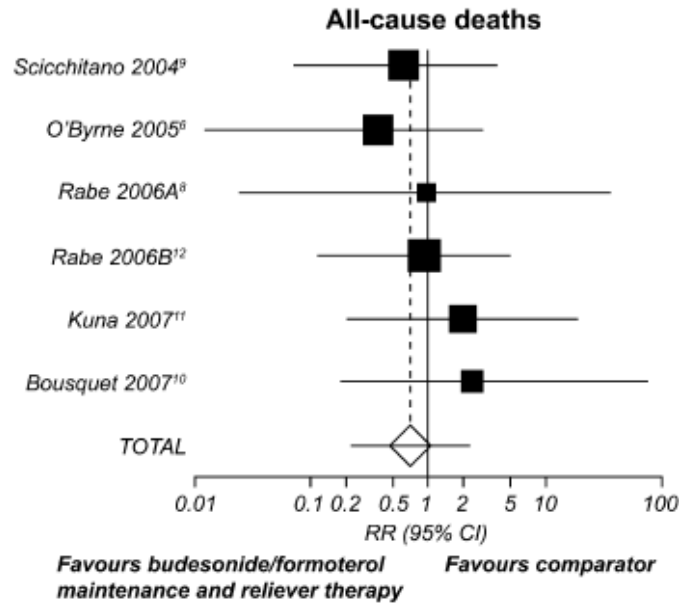
Safety

Lower

- Asthma SAEs

Similar

- All-cause
 - Deaths
 - SAEs
- Cardiac SAEs



Downsides of ICS

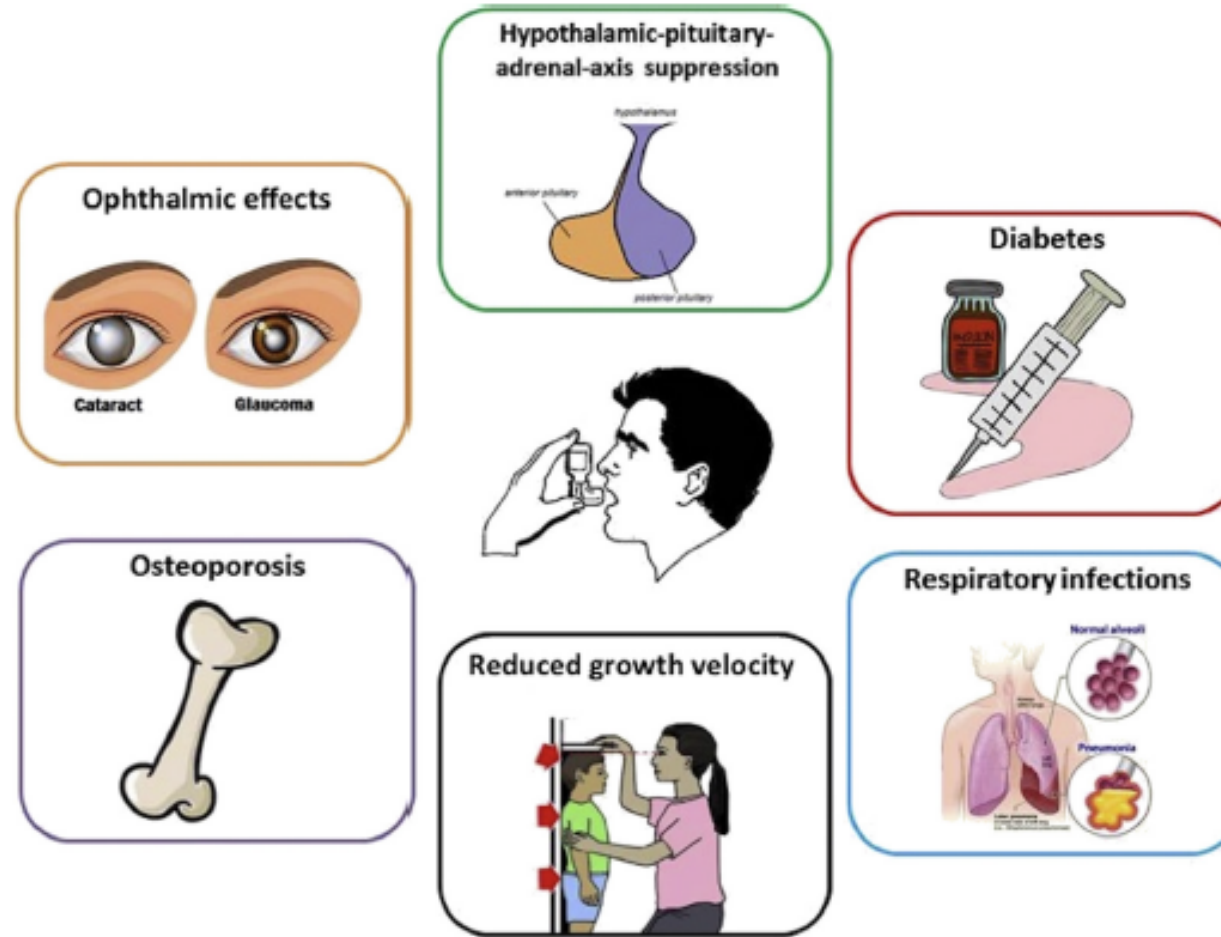
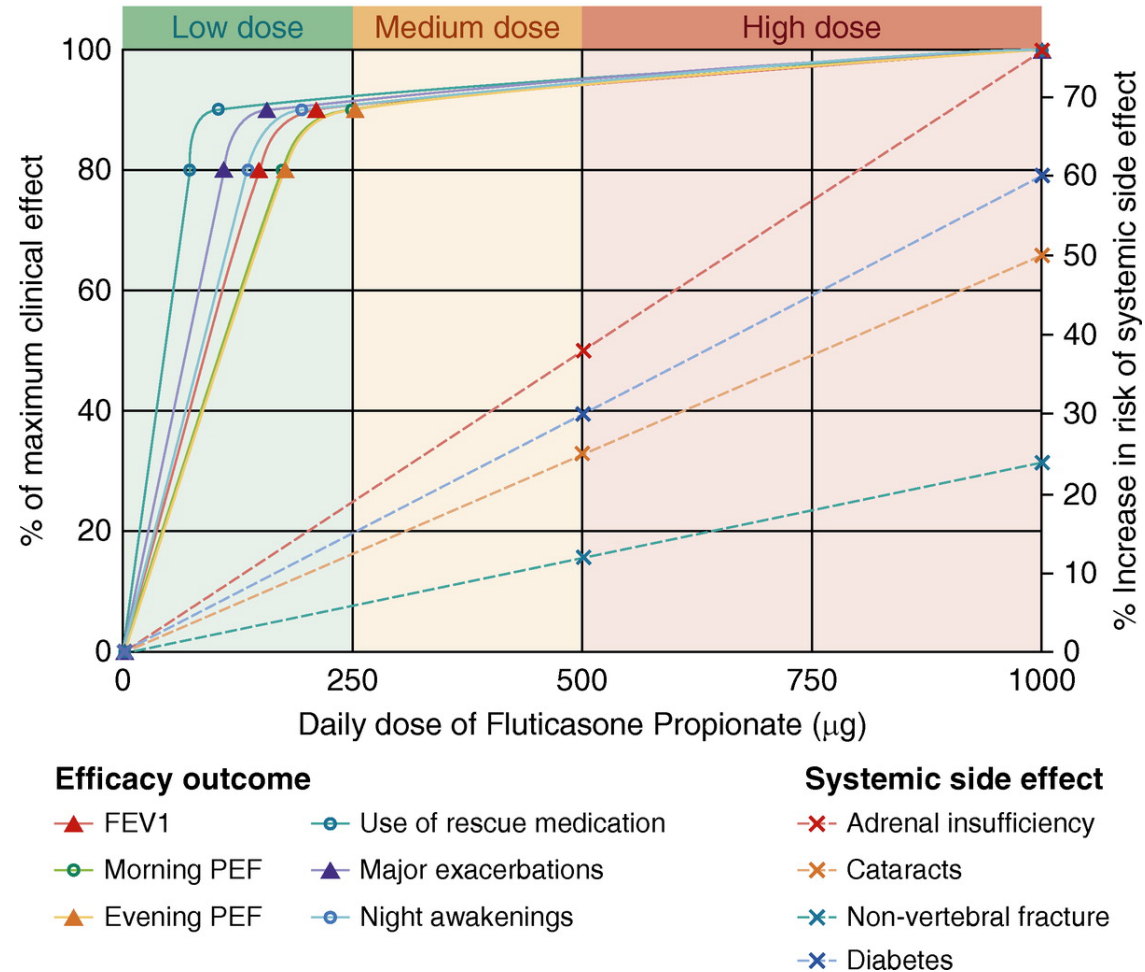


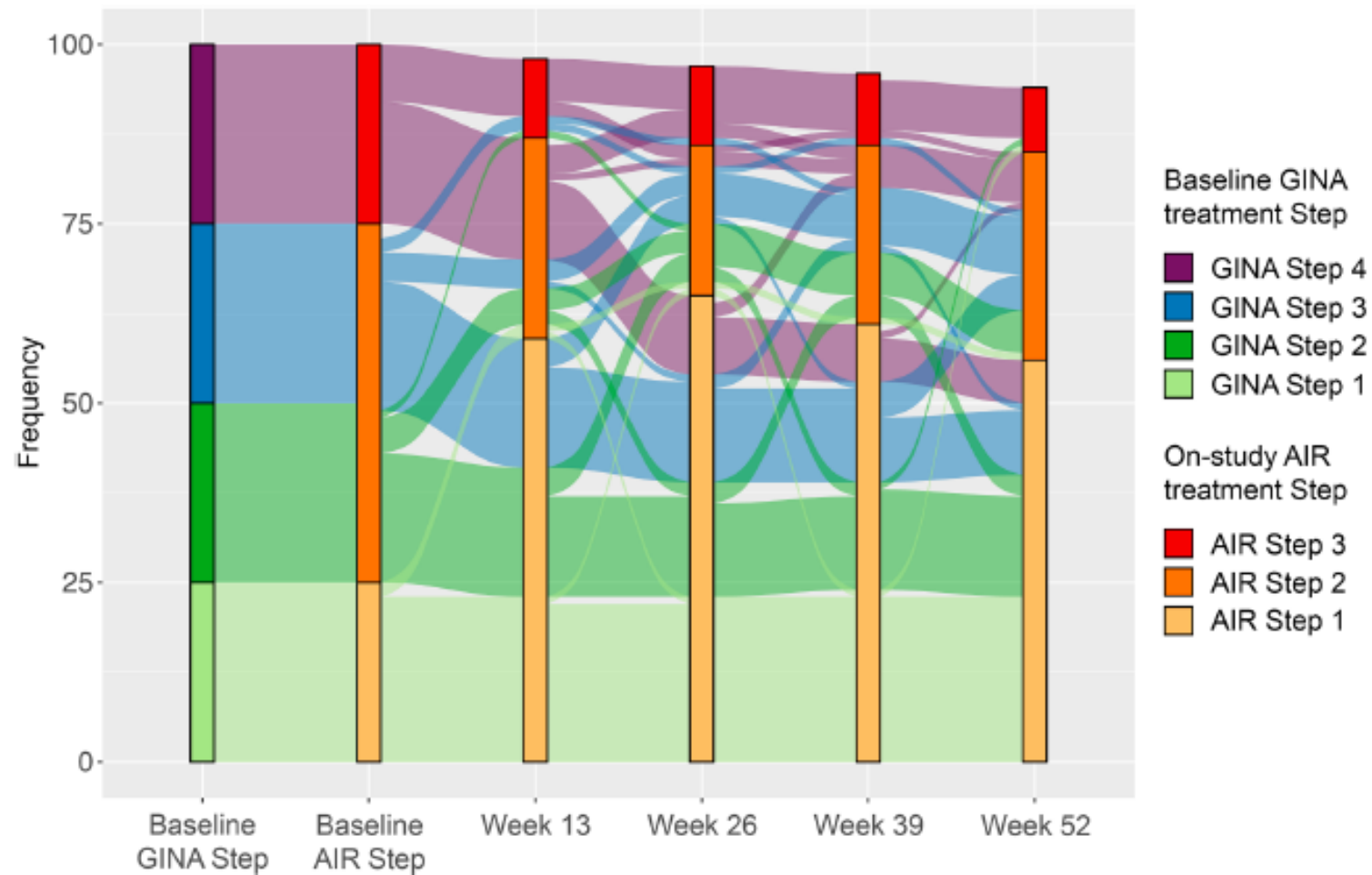
FIGURE 1. Common adverse effects related to the chronic use of inhaled corticosteroids.

Threshold effect with ICS

Relationship of Fluticasone Propionate dose, clinical effect, and risk of systemic side effects

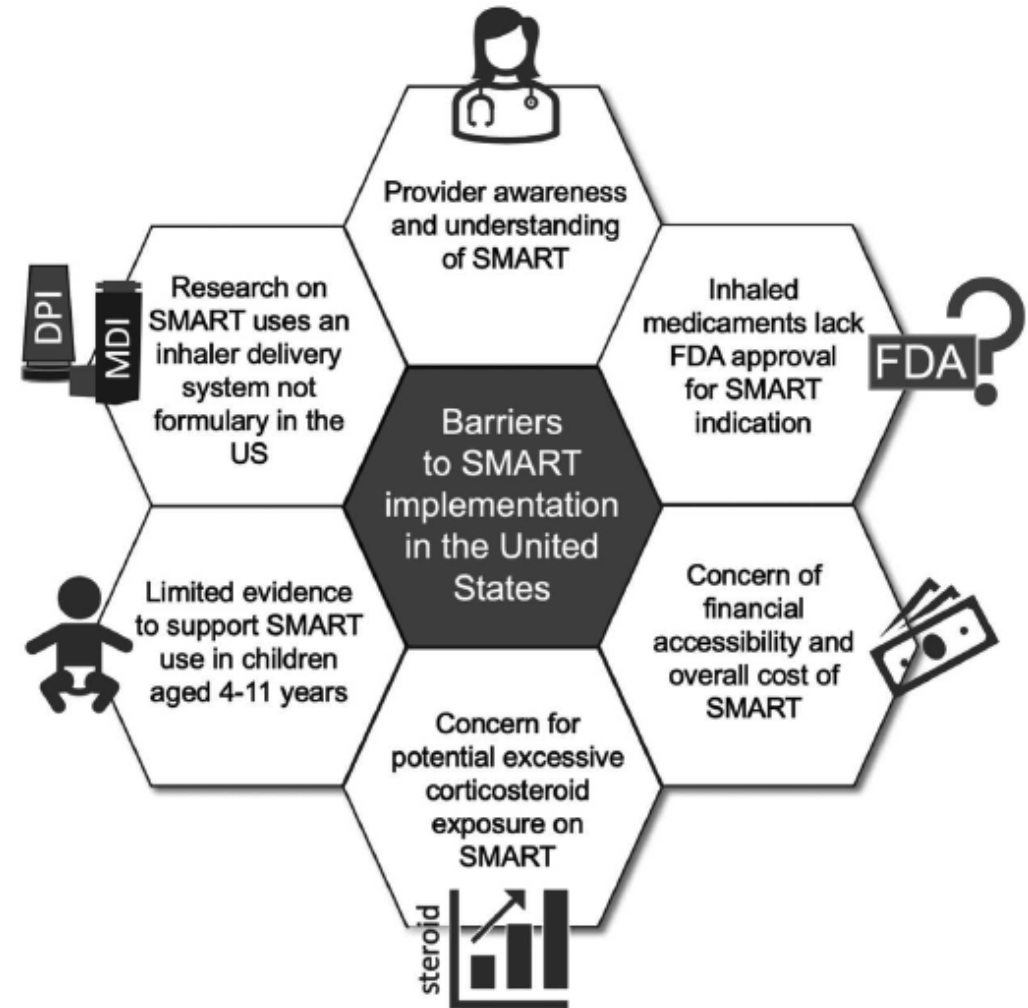


AIR may minimize / optimize ICS exposure



Barriers to AIR implementation

- Insurance
- Insurance
- Insurance
- Mindset / Education
 - Clinicians
 - Patients
- Cost



Barriers: Insurance

- Insurance
 - SMART:
 - ICS/formoterol only
 - Adequate number of inhalers per month
 - ICS/formoterol as reliever is off-label
 - Not FDA approved
 - ICS/albuterol: not always covered or \$\$\$
 - Adding ICS fewest insurance barriers



"I'm sorry, but stress caused by trying to figure out your health insurance is not covered by it."

Barriers: mindset and education

Clinicians

- Concerns about cost
- Insurance coverage
- Lack of FDA approval
- Time
- Confusion

Patients

- Confusion
- Underperceive symptoms
- Unaware of risks of SABA overuse



Barriers: Cost

- Albuterol \$55
- Budesonide/formoterol \$300
- Mometasone/formoterol \$400
- Budesonide/albuterol \$460-500

Varies based on insurance coverage

- Prednisone **\$20**

Need for prior authorization (time / personnel cost)

Cost savings of SMART/AIR: may not be experienced by the patient

- Health care utilization (UC/ED/hosp)
- Improved productivity
- Fewer missed school days



Summary

- Several options for AIR
 - SMART
 - ICS/SABA
 - Add ICS to SABA (inhaler or nebulizer)
- AIR > SABA for goals of asthma treatment
- Barriers to implementation persist



Thank
You!

