Anti-Inflammatory Rescue: Options and Challenges

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Disclosures

- Author, UpToDate

Outline

Why AIR is the greatest advance in asthma care in the last 2+ decades…but still very limited in implementation

- SABA as rescue
- SMART and other AIR options reduce exacerbations
- Additional advantages to AIR
- Barriers to implementation

Abbreviations

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

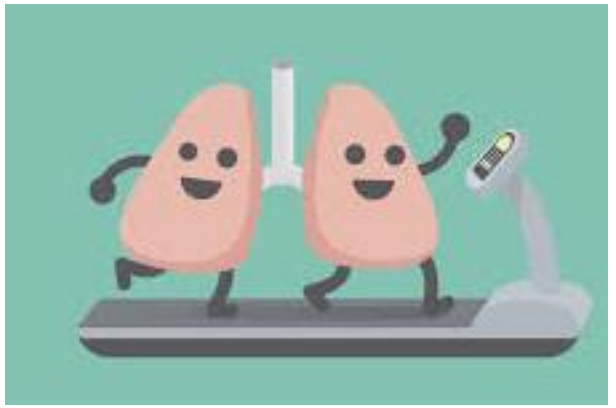
Asthma Burden

- 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

who.int
cdc.gov/nchs/fastats/asthma.htm
Aafa.org/asthma/asthma-facts

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*

- 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 ½ 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.

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

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

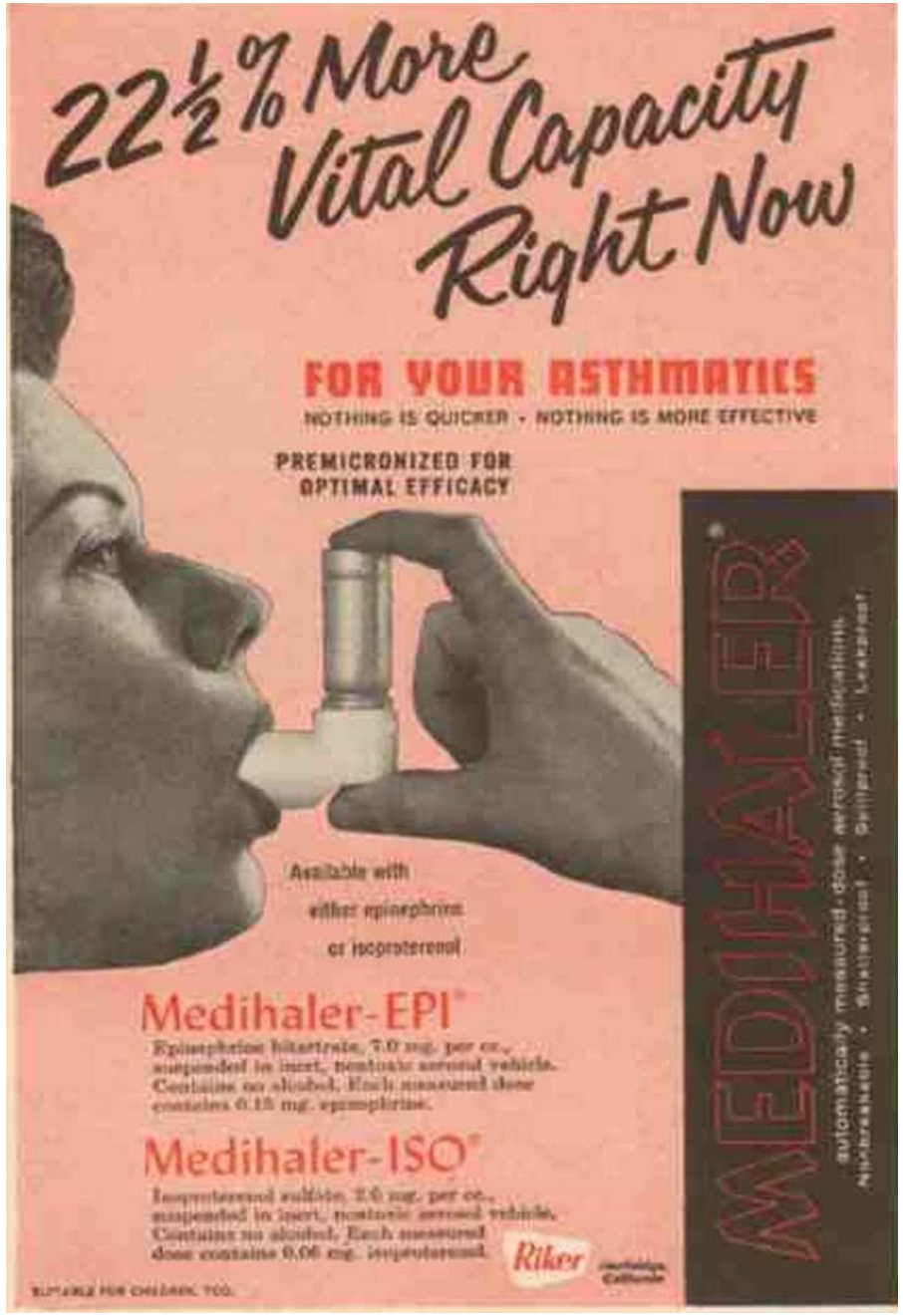
*MEDIHALER-EPI™
0.5% solution of epinephrine HCl U.S.P.

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

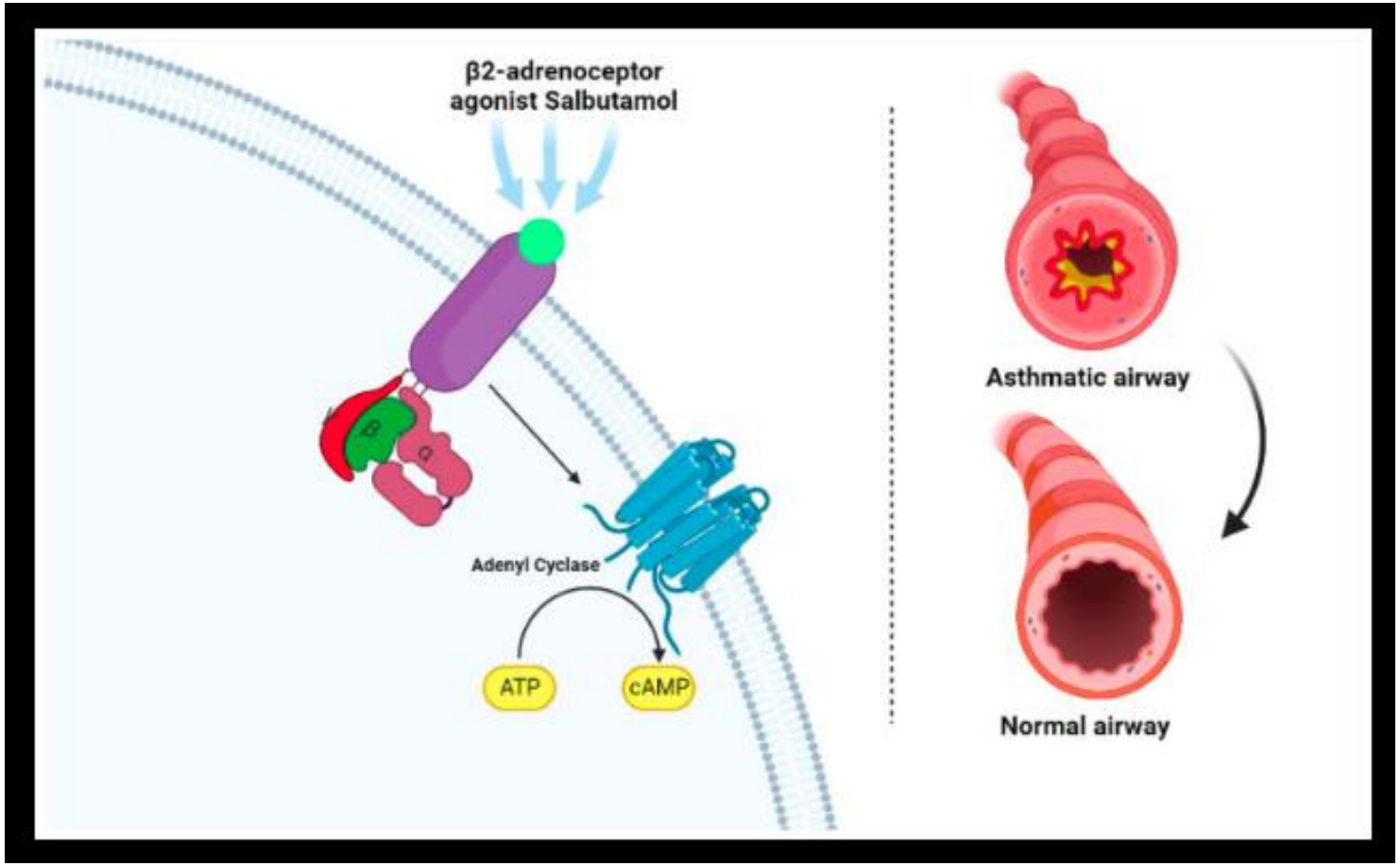
On your prescription be sure to write "Medihaler-Iso (or Medihaler-Epi) AND Medihaler Oral Adapter," since medication cannot be used without Adapter. For refills write for medication only.

℞ Medihaler-Iso and Medihaler Oral Adapter

Another First from Riker LOS ANGELES



Beta agonist: mechanism of action



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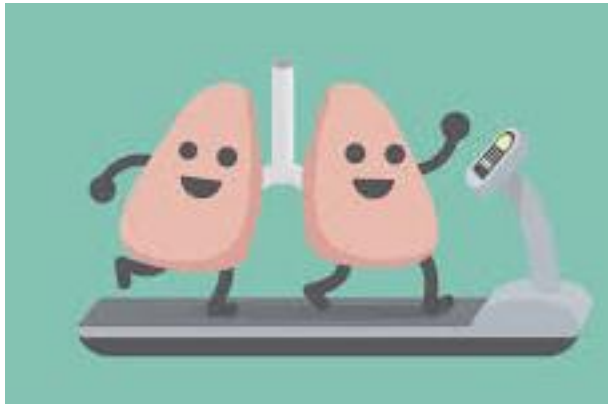
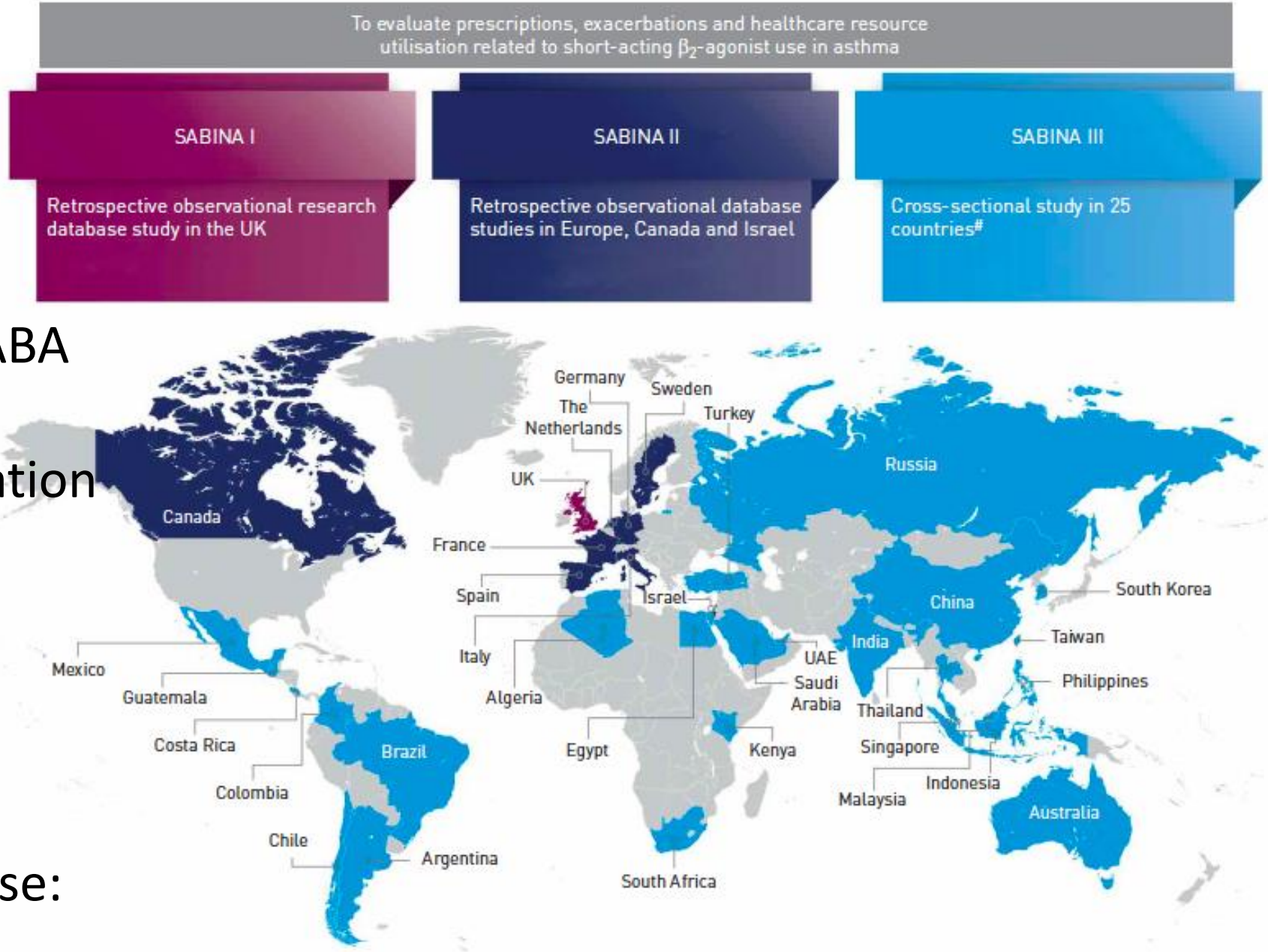


Disadvantages of SABA as rescue

- Physiology
  - Tolerance / tachyphylaxis
  - Rebound bronchoconstriction
  - Increased airway hyperresponsiveness
  - Increased eosinophilic inflammation
- Epidemiology
    - Exacerbations
    - Death

SABINA program

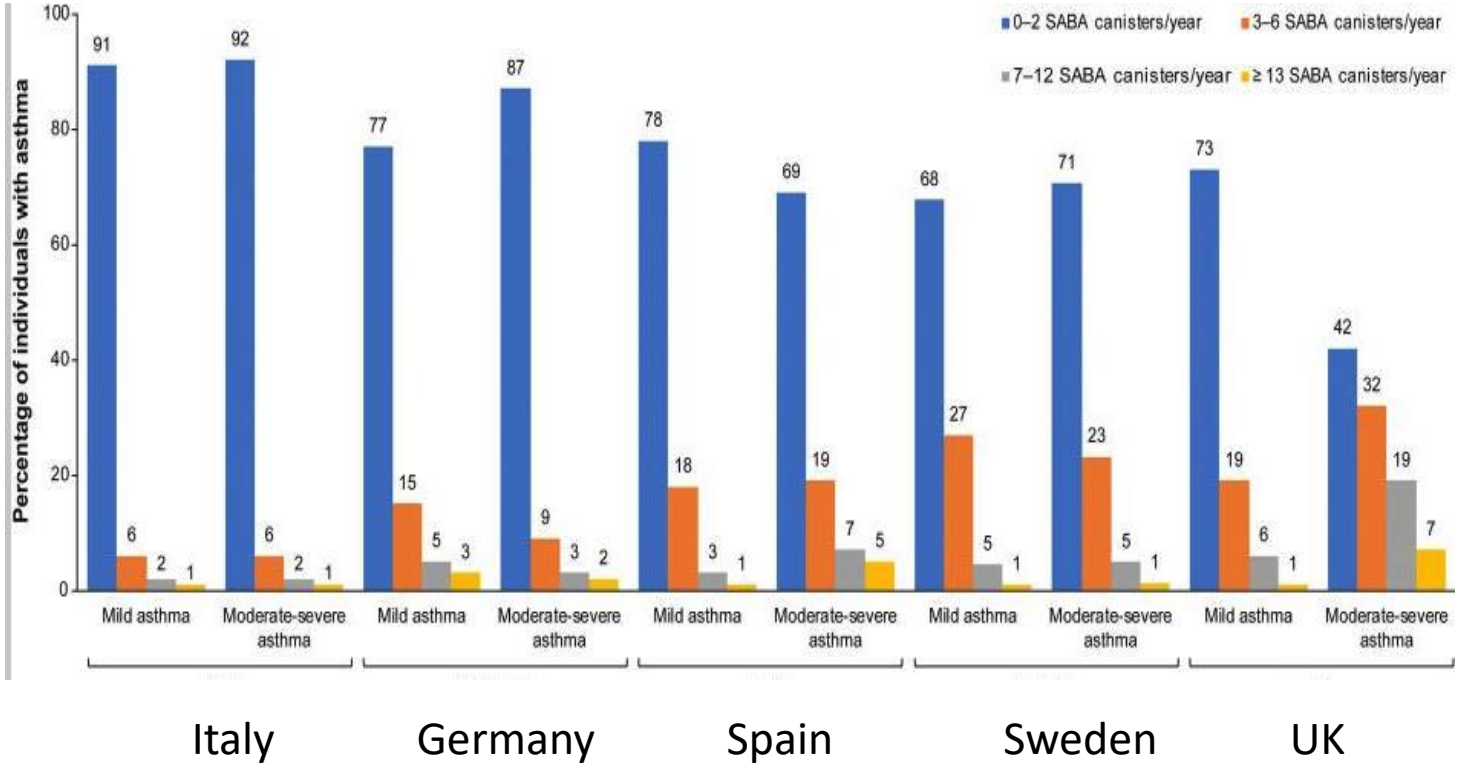


- How common is SABA overuse?
- What is the association with asthma outcomes?
  - Exacerbations
  - Death

- Definition of overuse: ≧ 3 canisters/year

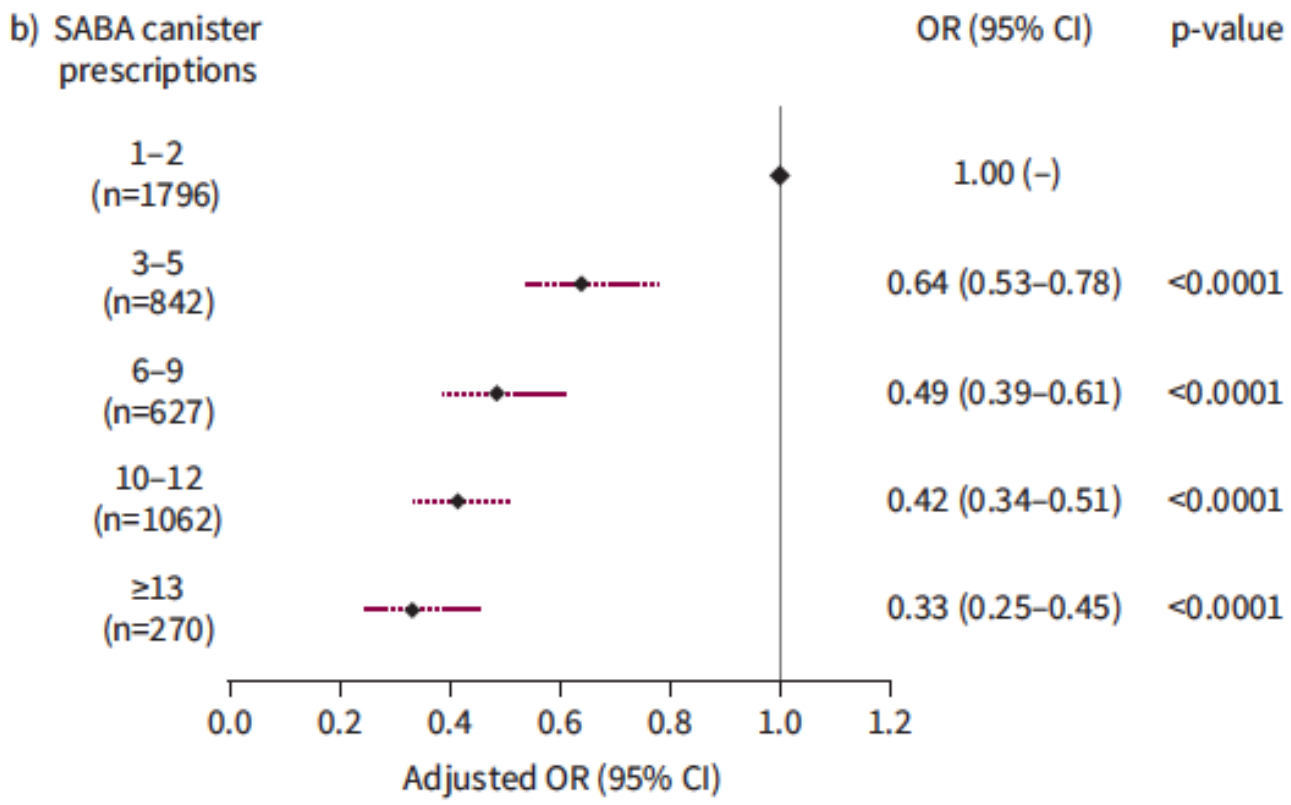
SABA overuse: prevalence

- >1,000,000 patients in 5 countries (UK, Germany, Italy, Spain, Sweden)
- Overuse (≧ 3canisters/year) prevalence
  - 9% to 38% depending on country



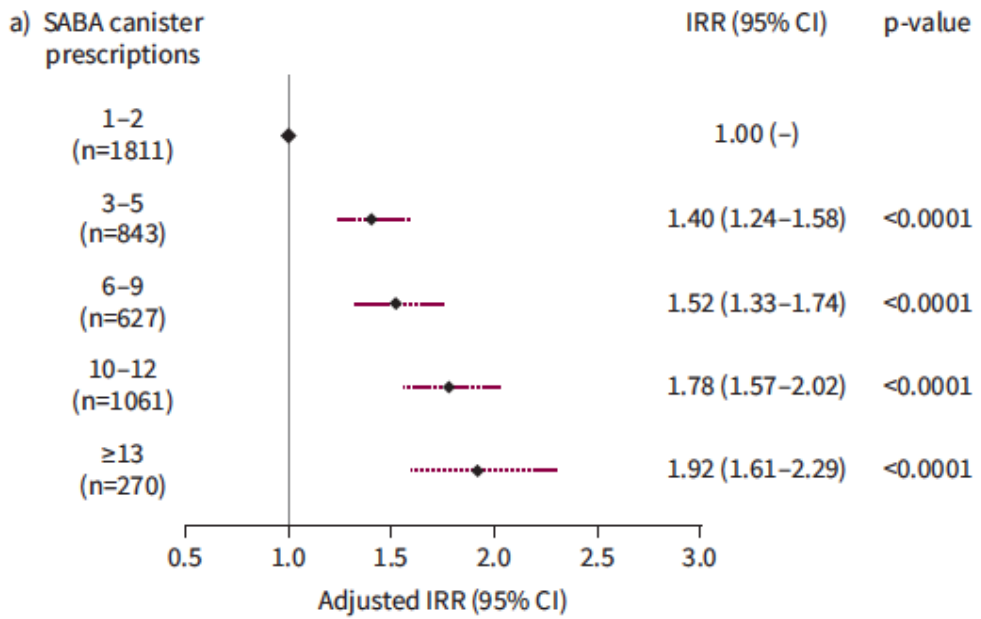
Janson Adv Ther 2020

SABA overuse and symptom control



Bateman ERJ 2022

SABA overuse and exacerbations



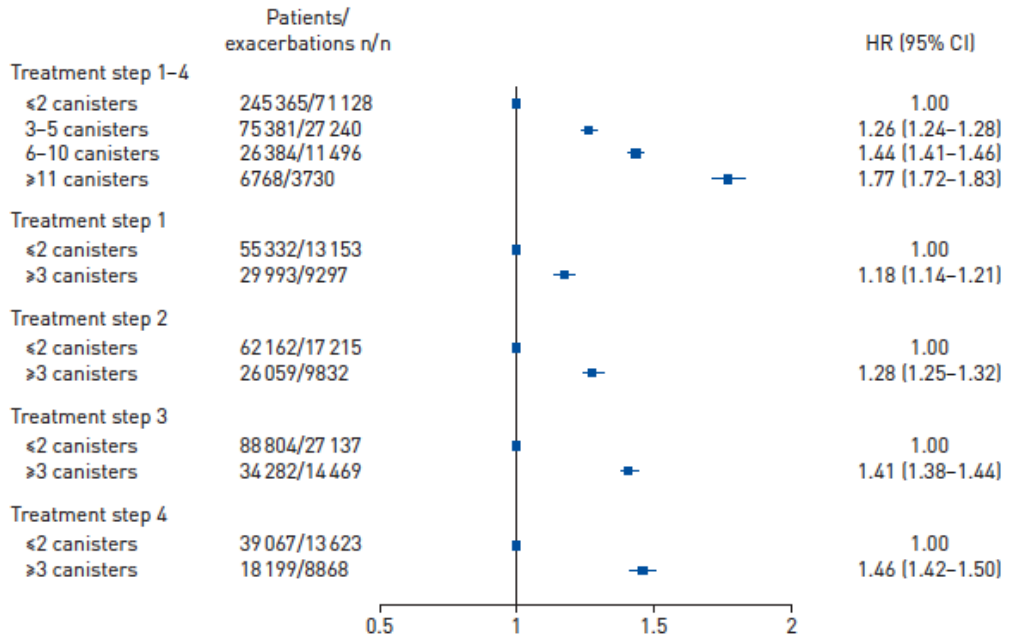
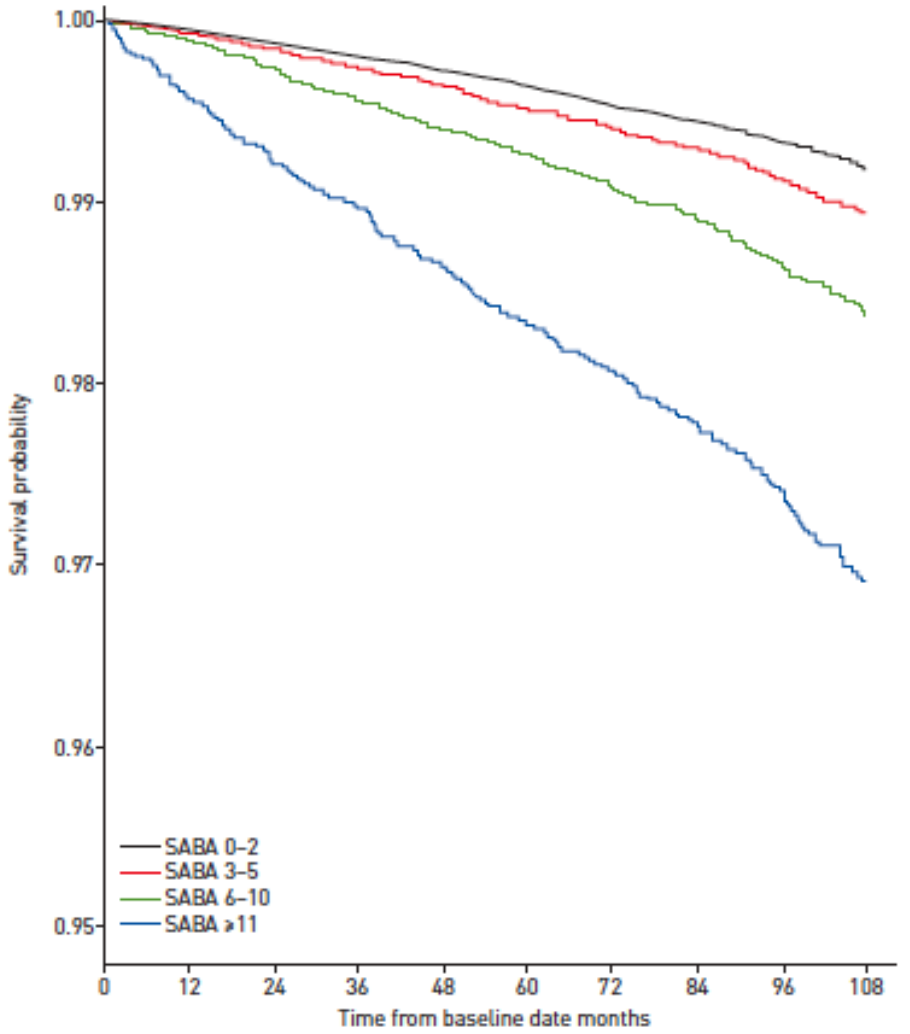


FIGURE 2 Associations between baseline short-acting β_2-agonist (SABA) use and treatment step and subsequent risk of asthma exacerbation. Adjusted for age at asthma diagnosis, sex, treatment step and comorbidity. ⩽2 canisters: patients collecting two or fewer SABA canisters during the baseline year; ⩾3 canisters: patients collecting three or more SABA canisters during the baseline year; HR: hazard ratio.

Nwaru ERJ 2019
Bateman ERJ 2022

SABA overuse and mortality

- ↑# of SABA canisters / year
  - ↑mortality (OVERALL and asthma-related)



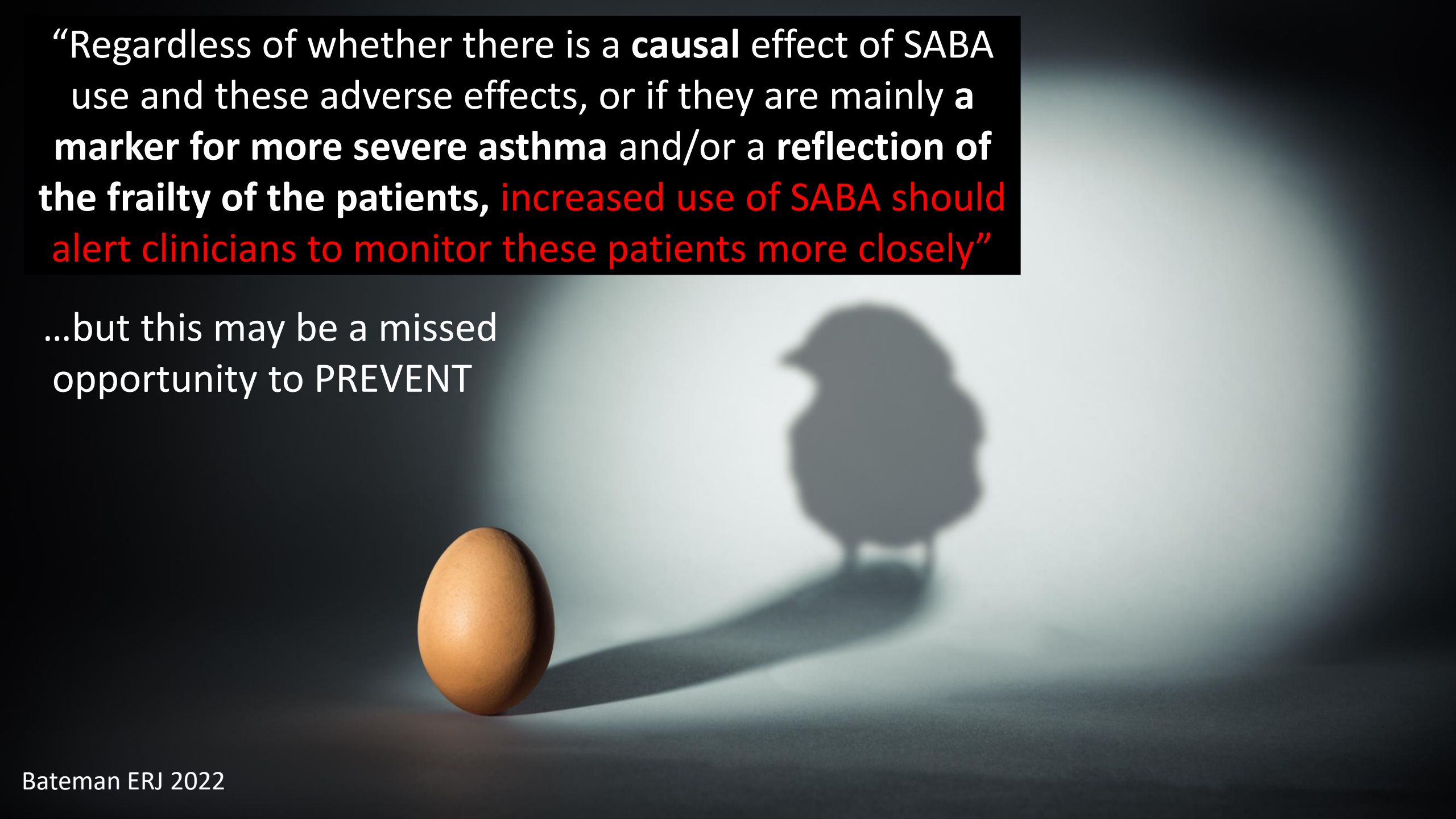
At risk n										
SABA 0–2	254 500	254 367	230 860	210 403	187 331	165 549	142 973	118 674	91 999	54 765
SABA 3–5	76 619	76 563	71 316	66 801	61 790	56 015	49 939	43 024	34 937	22 584
SABA 6–10	27 065	27 034	25 769	24 552	23 280	21 836	20 212	18 503	16 436	13 034
SABA ≥11	7140	7190	6912	6729	6539	6321	6078	5820	5500	4994

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

Nwaru ERJ 2019

"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"

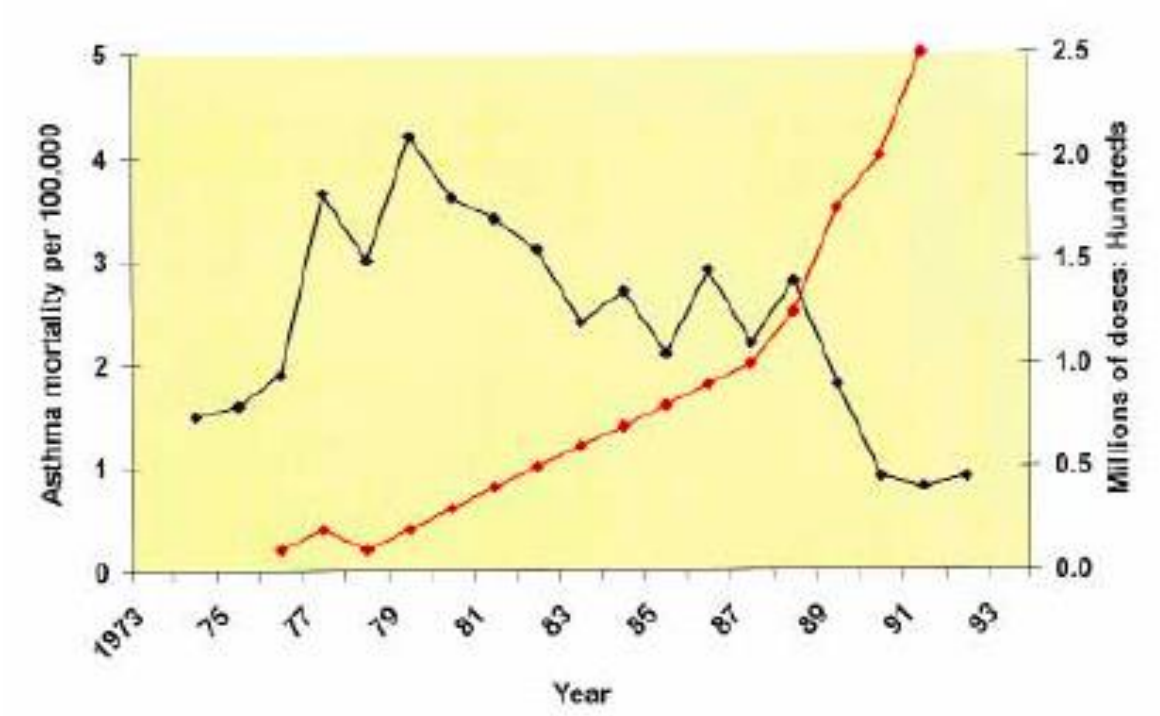
…but this may be a missed opportunity to PREVENT

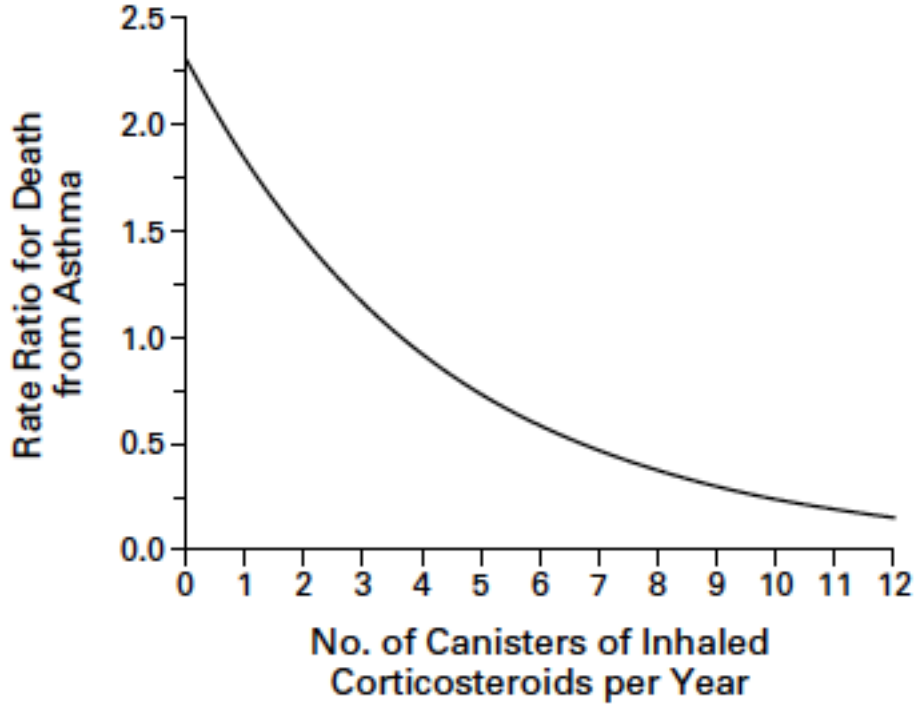


Bateman ERJ 2022


What about AIR

ICS and asthma mortality





Suissa NEJM 2000
Suissa JACI 2001

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- Reduce symptoms, interference with normal life / activity
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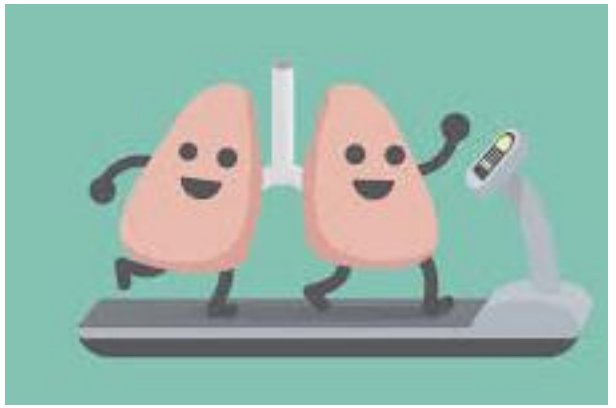


Adherence

40%

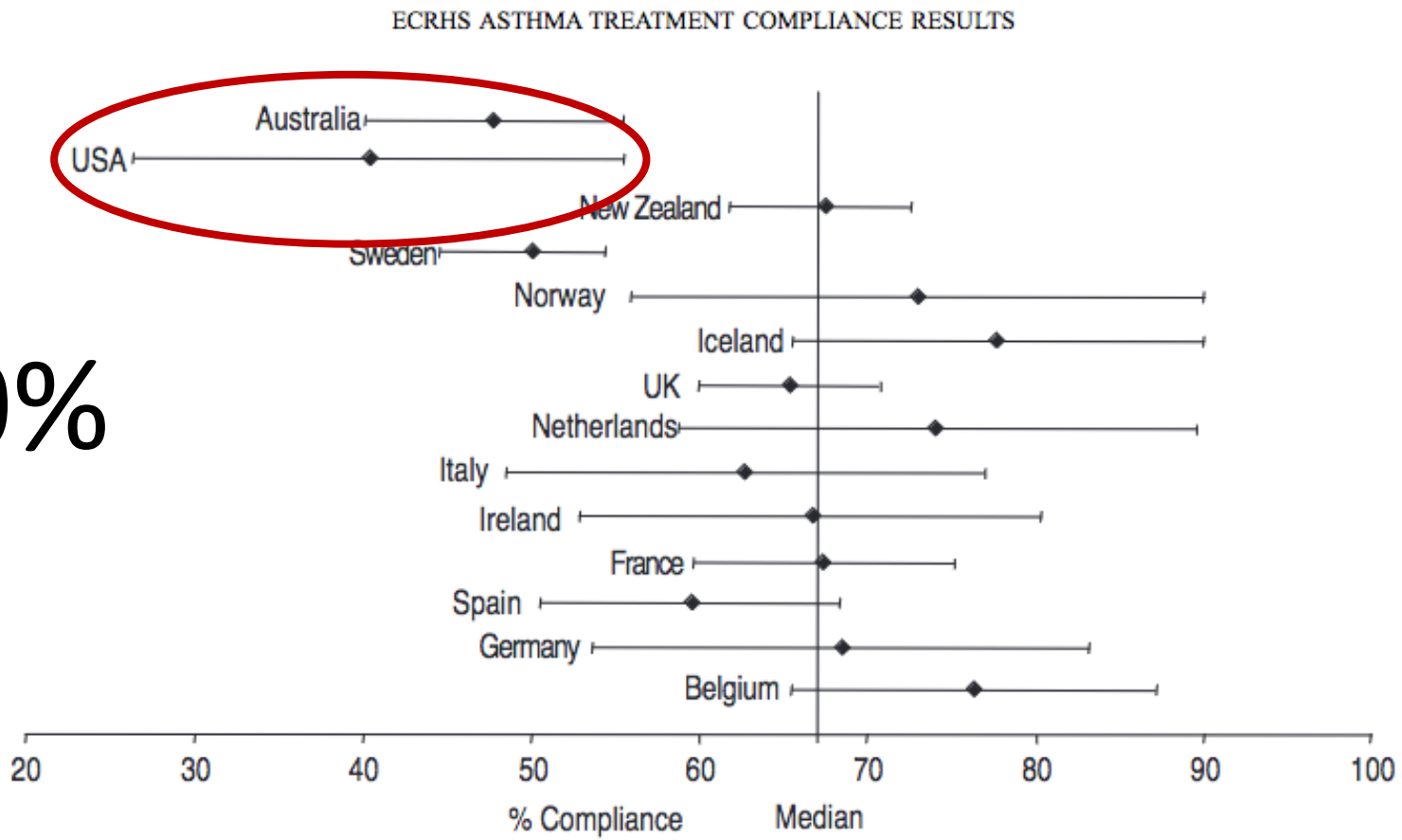
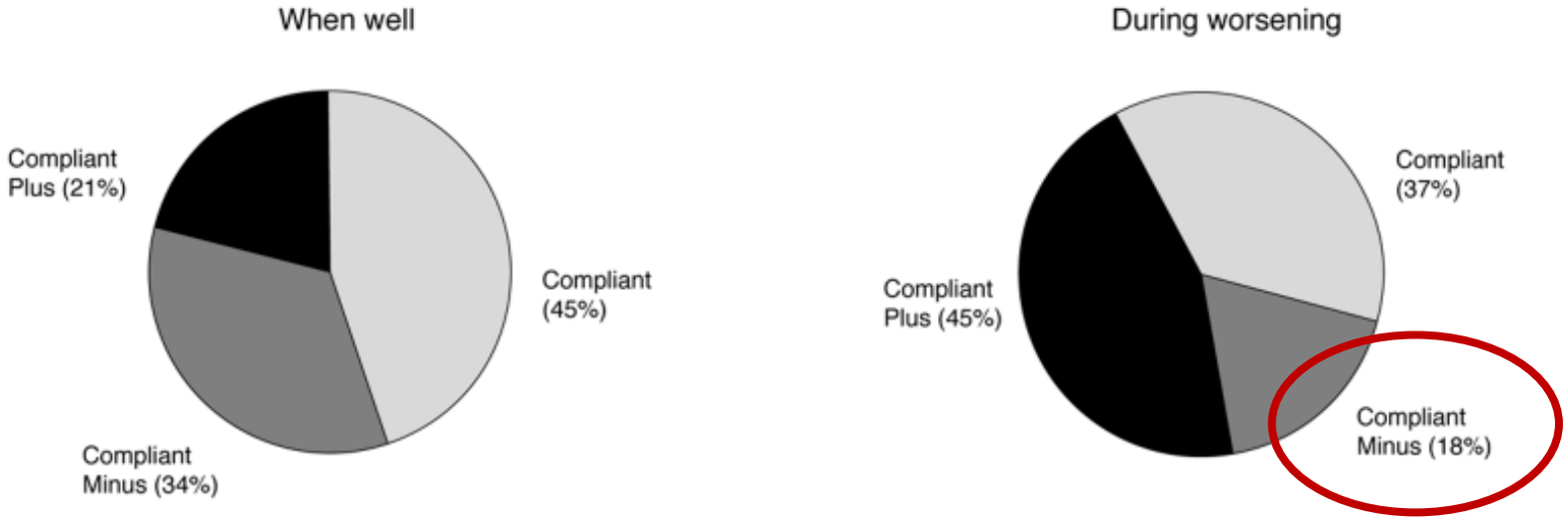


Fig. 2. – Prevalence (%) (♦) (95% confidence intervals (CI)) (——) of compliance between subjects with indications for treatment by country. A prevalence significantly different from the median is present when the 95% CI does not fit the vertical line of the median value.

Cerveri ERJ 1999

Patient behavior:
adherence to maintenance medication



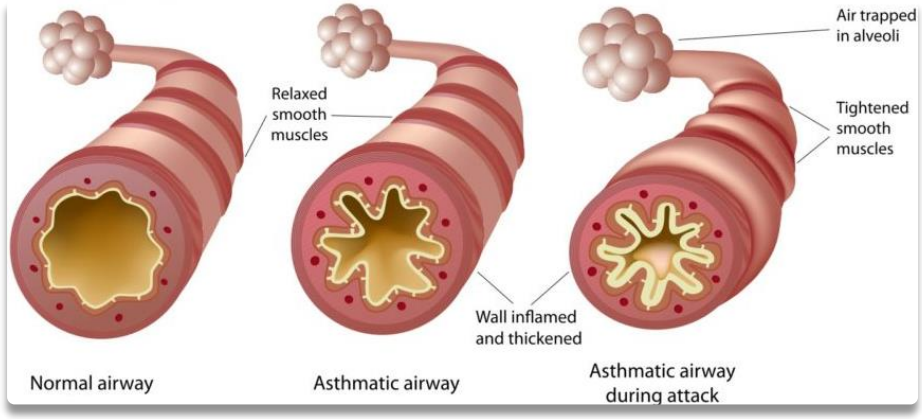
n=3415

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.

Partridge BMC Pulm Med 2006

Asthma: inflammatory, intermittent

- Triggers are unpredictable
  - Viruses
  - Pollens
  - Pollution



- Oral steroids: ~ 4–5 lifetime courses
  ↑ risk of:
  - Osteoporosis/fracture
  - Weight gain
  - Diabetes
  - Cataract

Price J Asthma All 2018

The story 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 death

  THUS….

- SMART approach

An analogy

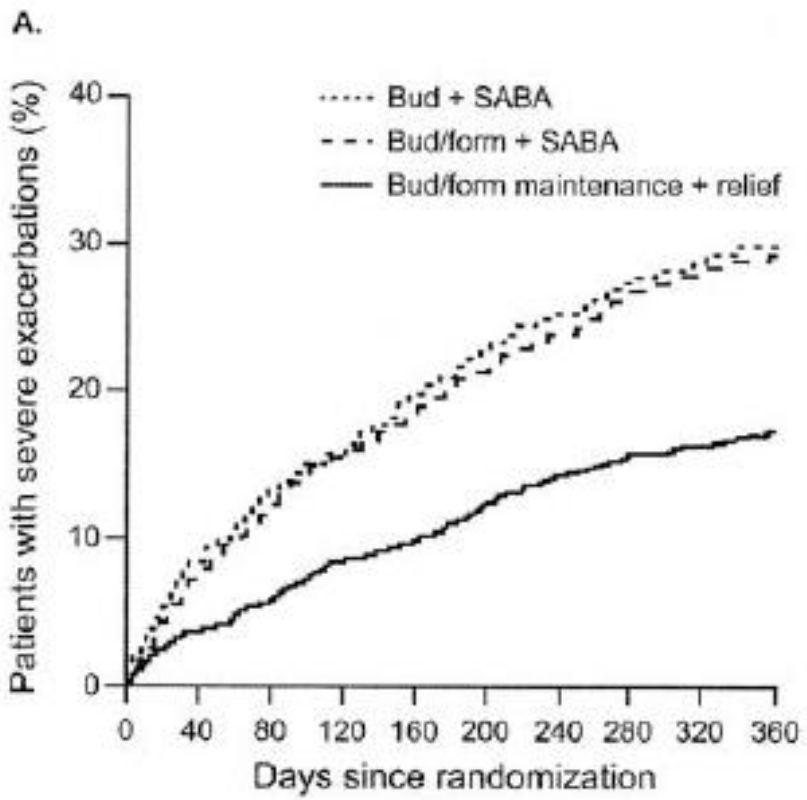
ICS

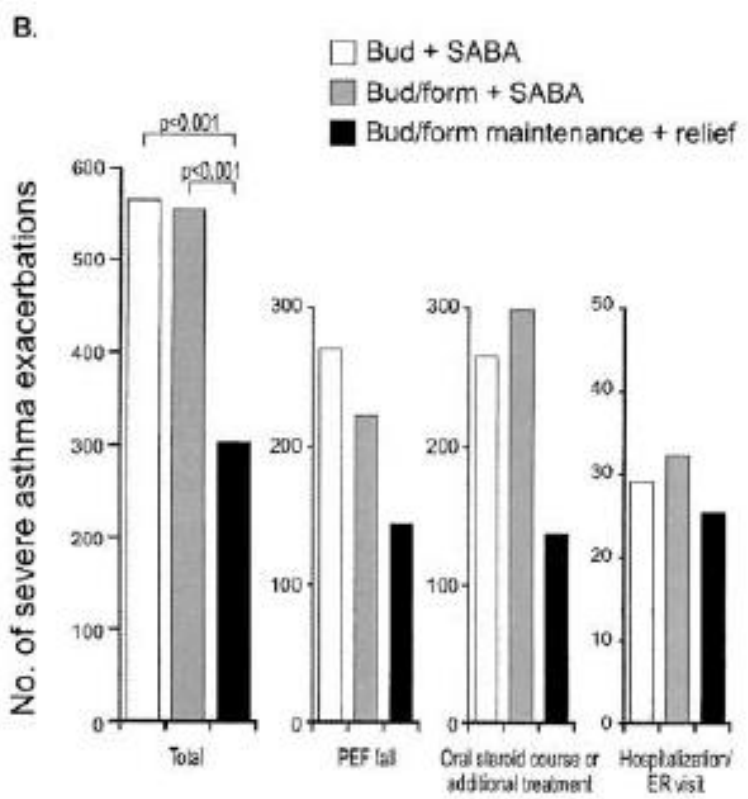
FABA

Solution: Give them at the same time!

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

SMART approach: persistent asthma





O'Byrne *AJRCCM* 2005

SMART vs various therapies, all SABA as reliever

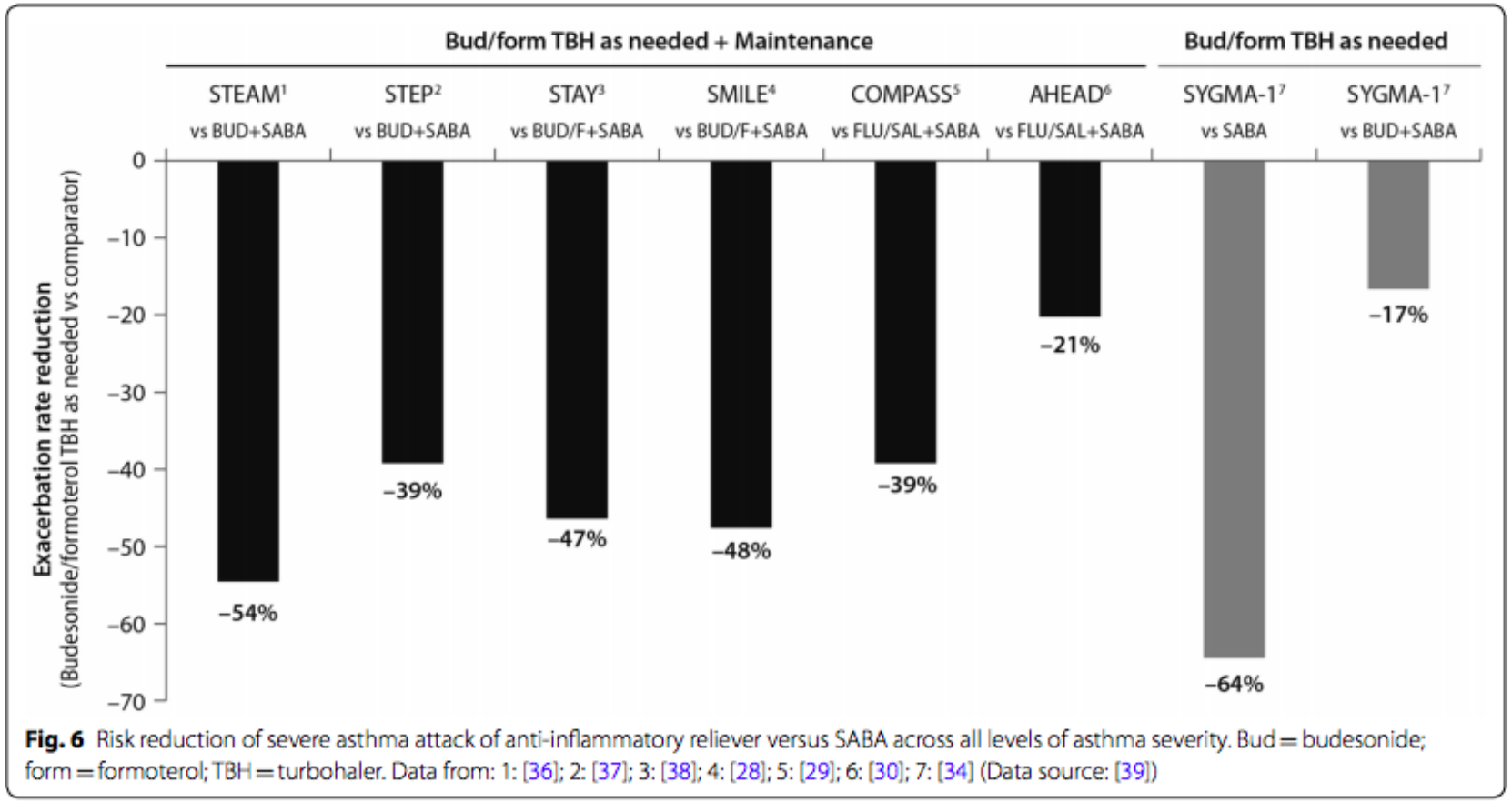


Fig. 6 Risk reduction of severe asthma attack of anti-inflammatory reliever versus SABA across all levels of asthma severity. Bud = budesonide; form = formoterol; TBH = turbohaler. Data from: 1: [36]; 2: [37]; 3: [38]; 4: [28]; 5: [29]; 6: [30]; 7: [34] (Data source: [39])

Papi *All Asthma Clin Imm* 2020

JAMA | Original Investigation

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 ≧ 3 days
- No significant associations:
  - ACQ-5, FEV1, mortality

Sobieraj *JAMA* 2018

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

Compared to SABA prn alone:

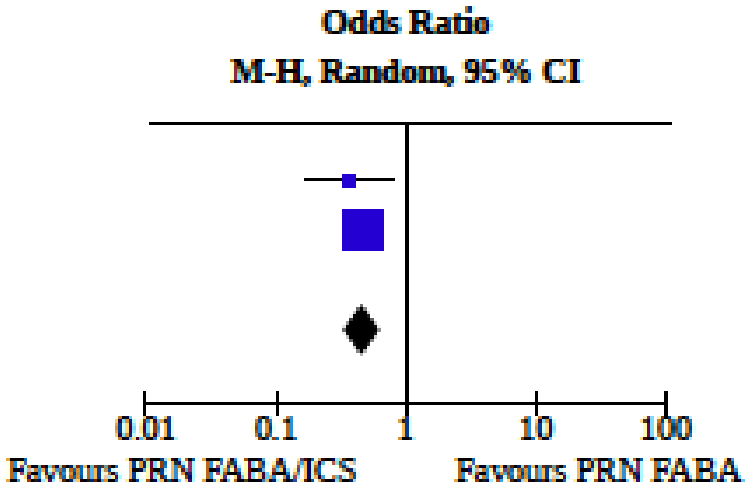
- LOWER exacerbation rates

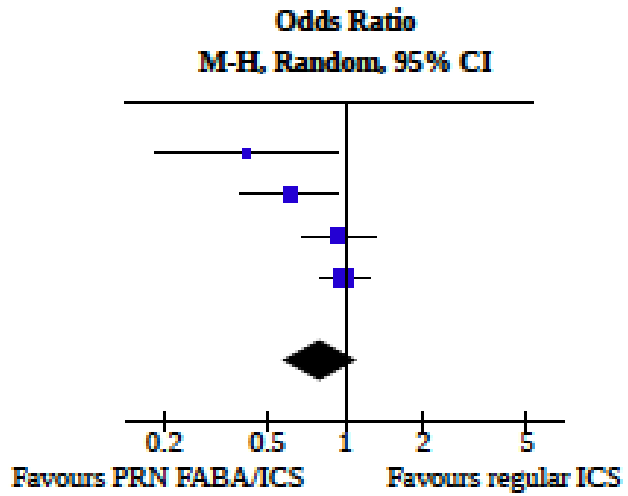
Compared to ICS bid + SABA prn:

- No difference in exacerbations

AND

- **LOWER** overall steroid dose





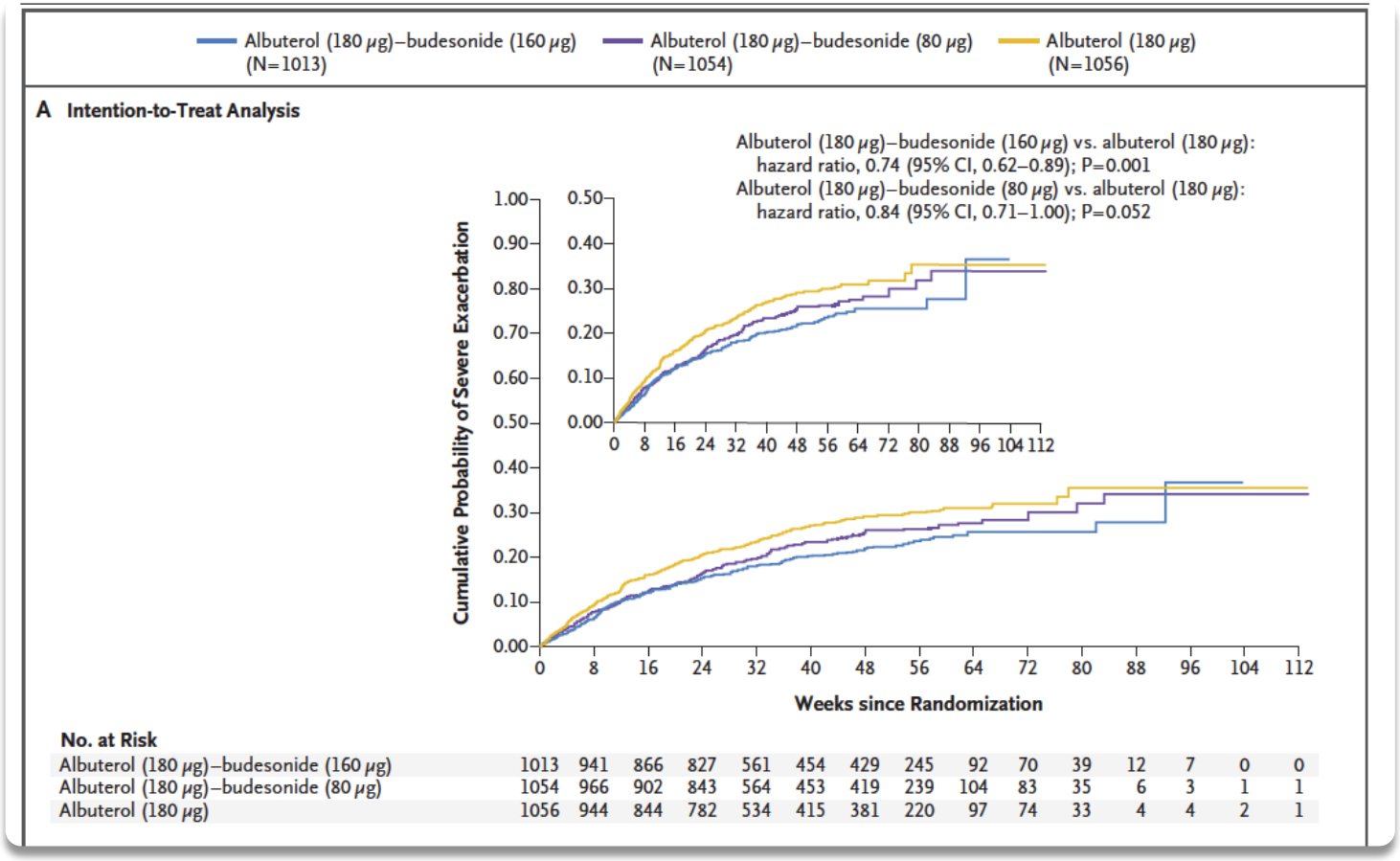
Crossingham Cochrane Data Sys Rev 2021

Barriers to SMART or ICS/LABA prn approach

- Insurance
  - Must be ICS-formoterol
  - > 1 inhaler / month

MANDALA trial

- Maintain controller
  - ICS/SABA vs SABA as rescue
- Decreased exacerbations
- Annual dose of systemic steroids 50% lower in ICS/SABA group



Papi NEJM 2022

Airsupra (PT027) approved in the US for asthma

albuterol/budesonide (160mcg)

PUBLISHED
11 January 2023

ICS/SABA approved by FDA for use as rescue inhaler in people 18+

PREPARE: PeRson EmPowered Asthma RElief trial

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

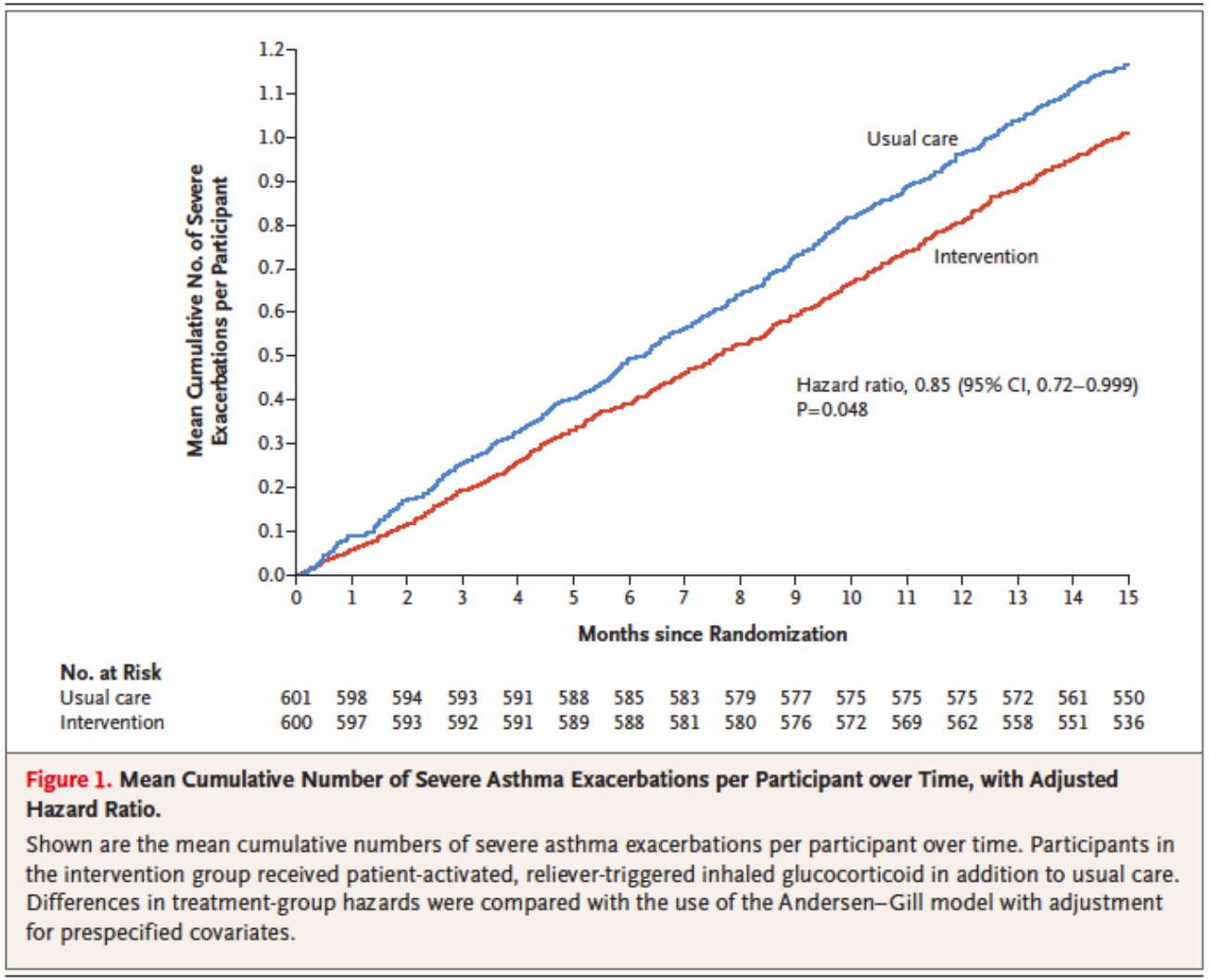


Figure 1. Mean Cumulative Number of Severe Asthma Exacerbations per Participant over Time, with Adjusted Hazard Ratio.

Shown are the mean cumulative numbers of severe asthma exacerbations per participant over time. Participants in the intervention group received patient-activated, reliever-triggered inhaled glucocorticoid in addition to usual care. Differences in treatment-group hazards were compared with the use of the Andersen–Gill model with adjustment for prespecified covariates.

Israel NEJM 2022

Principle is the same:VEGGIE BROWNIES!

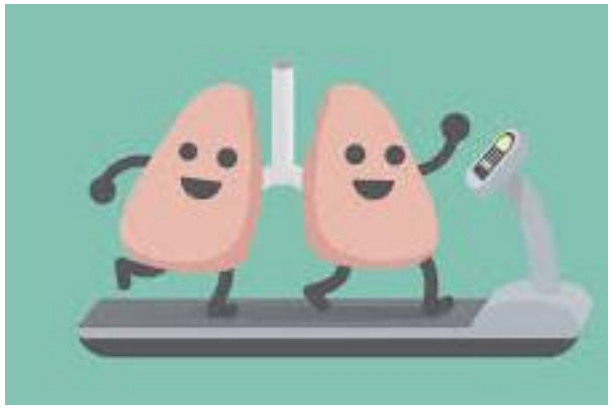
AIR: Use ICS at times of increased symptoms / need for rescue inhaler

1. SMART: Single Maintenance And Reliever Therapy
   - simpler since one overall inhaler
   - BUT restricted to formoterol-containing
     - 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
  - hospitalizations / ED / UC / systemic st
- ✓ Reduce symptoms, int f ctivity
  - Improve qu
- ✓ M ment

AND PEOPLE WILL USE IT!



But wait… there’s more

- Asthma control
- FEV_1
- 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

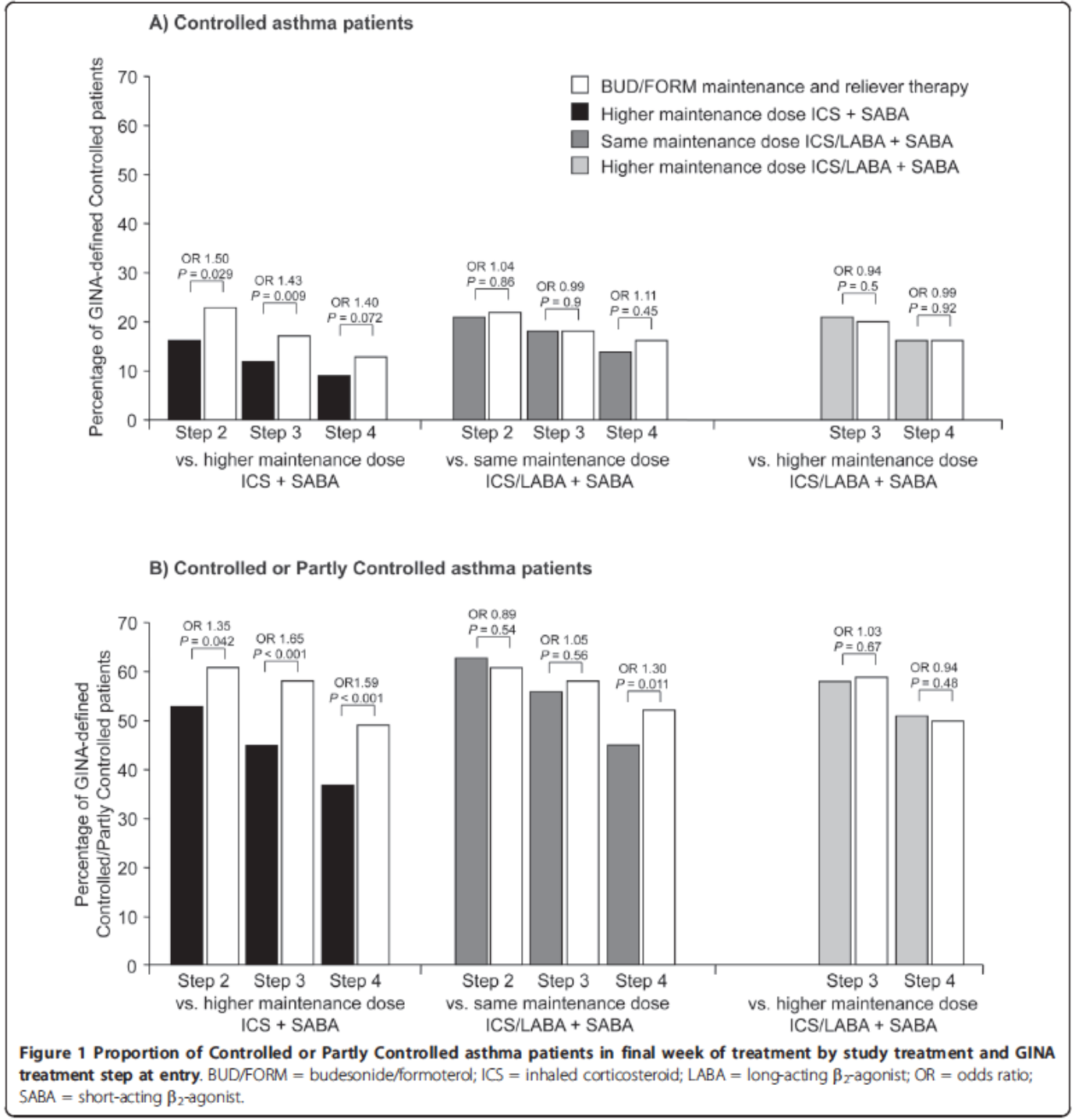
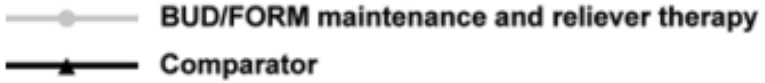
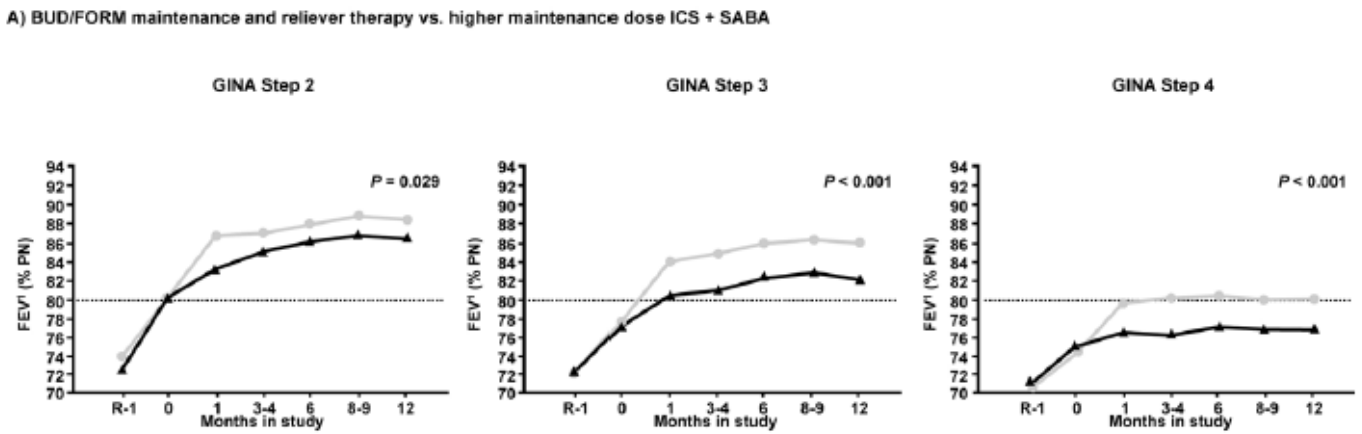


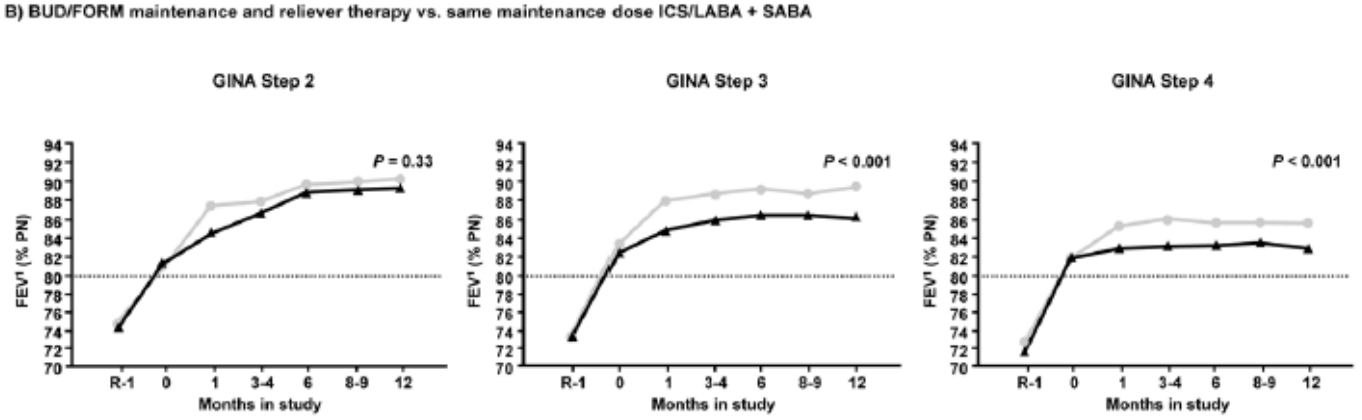
Figure 1 Proportion of Controlled or Partly Controlled asthma patients in final week of treatment by study treatment and GINA treatment step at entry. BUD/FORM = budesonide/formoterol; ICS = inhaled corticosteroid; LABA = long-acting β_2-agonist; OR = odds ratio; SABA = short-acting β_2-agonist.

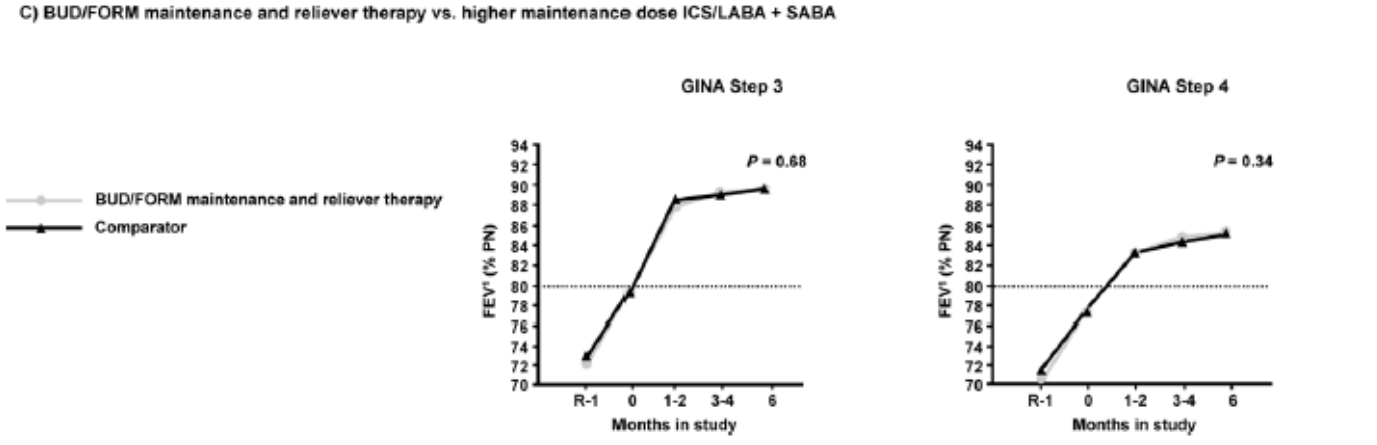
Bateman Resp Res 2011

FEV_1



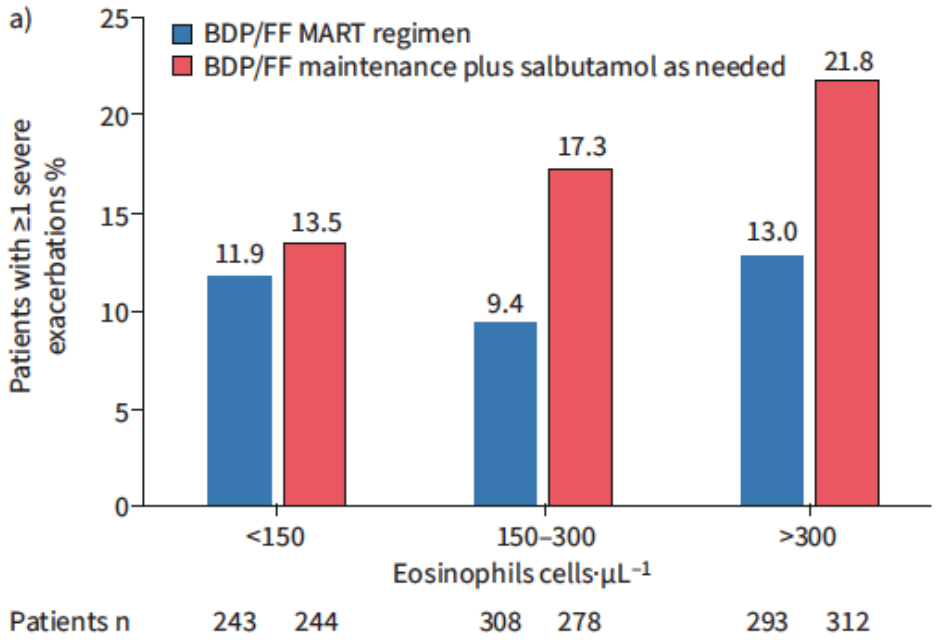


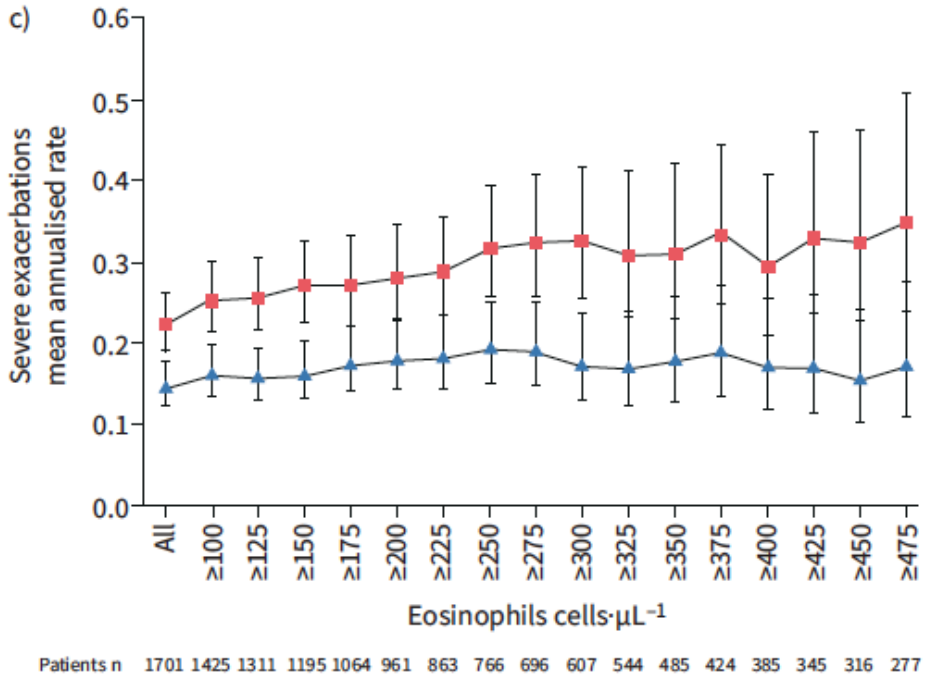




Bateman Resp Res 2011

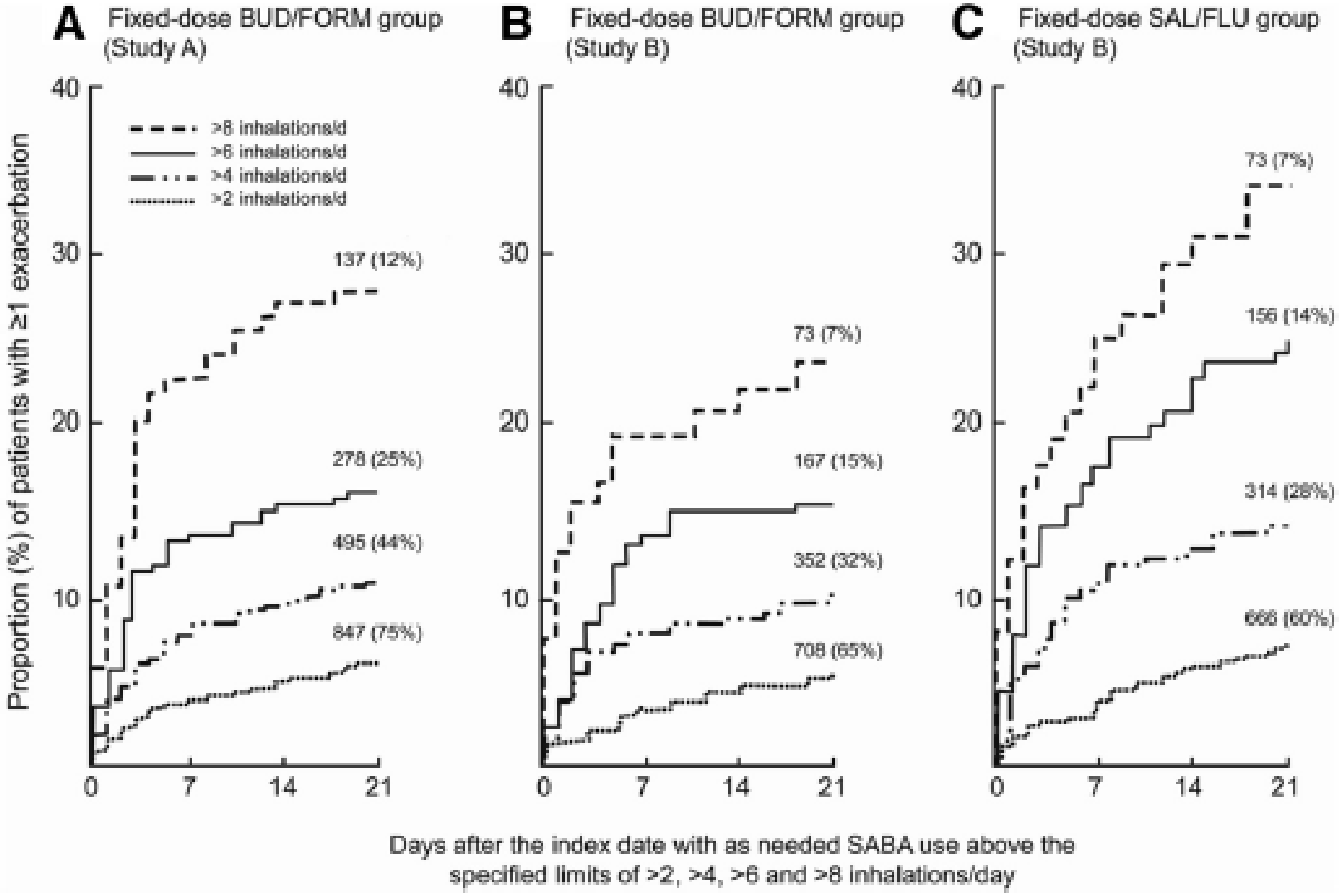
SMART and AEC





Brusselle ERJ 2021

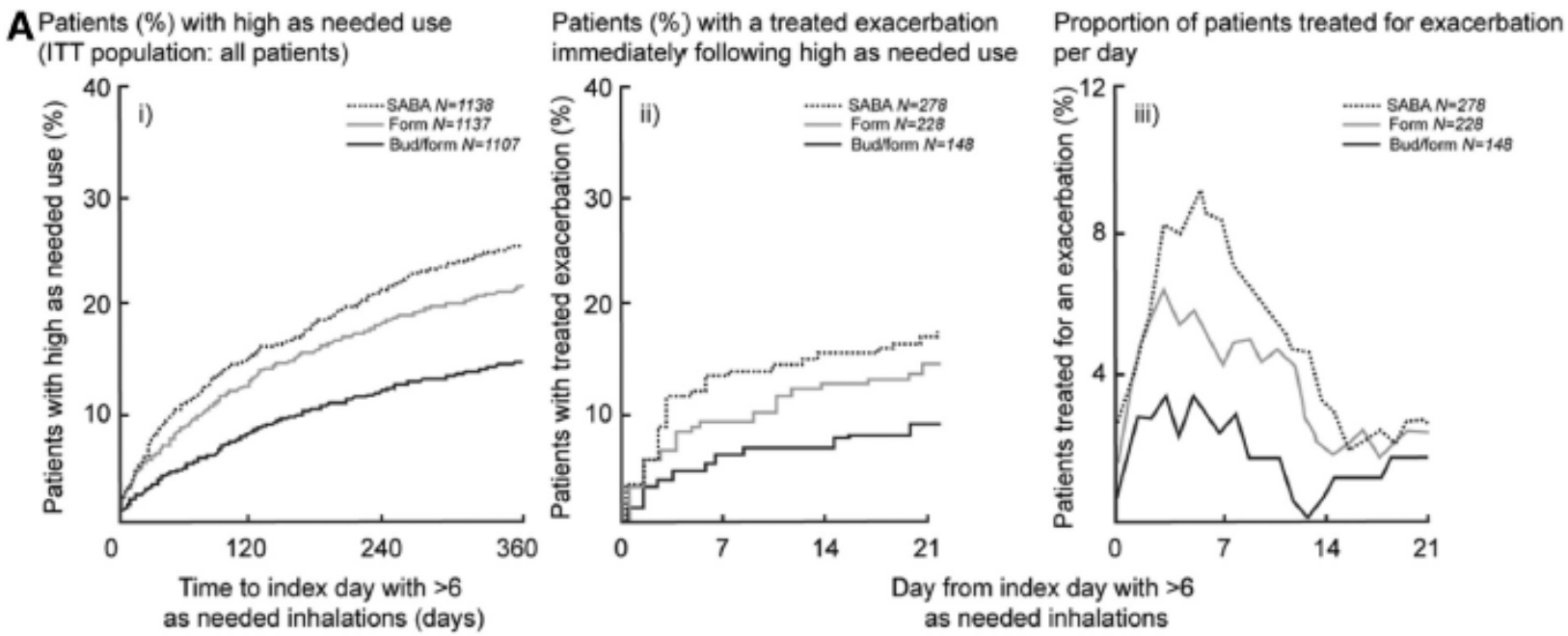
Reliever high-use episodes

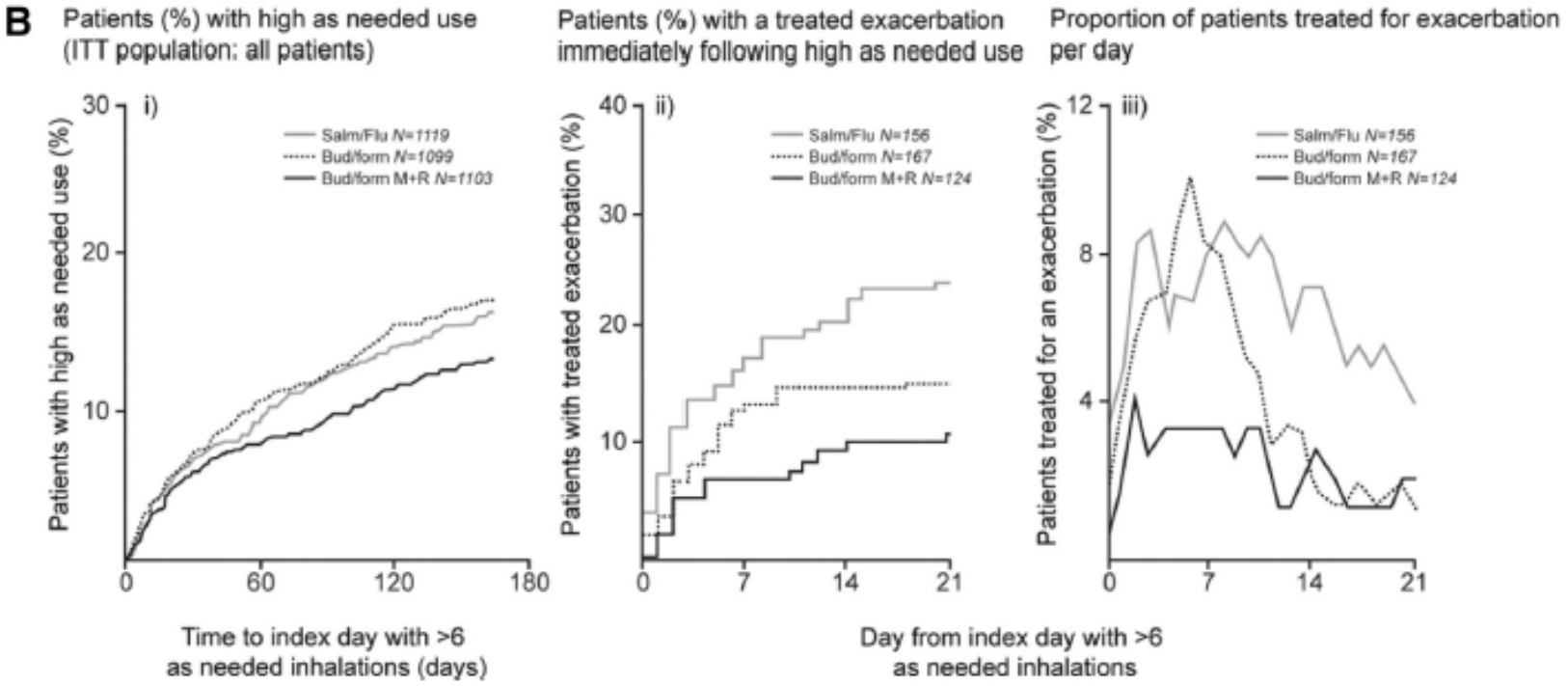


Buhl Resp Research 2012

SMART group:

- ↓high use episodes
- ↓ result in exacerbation

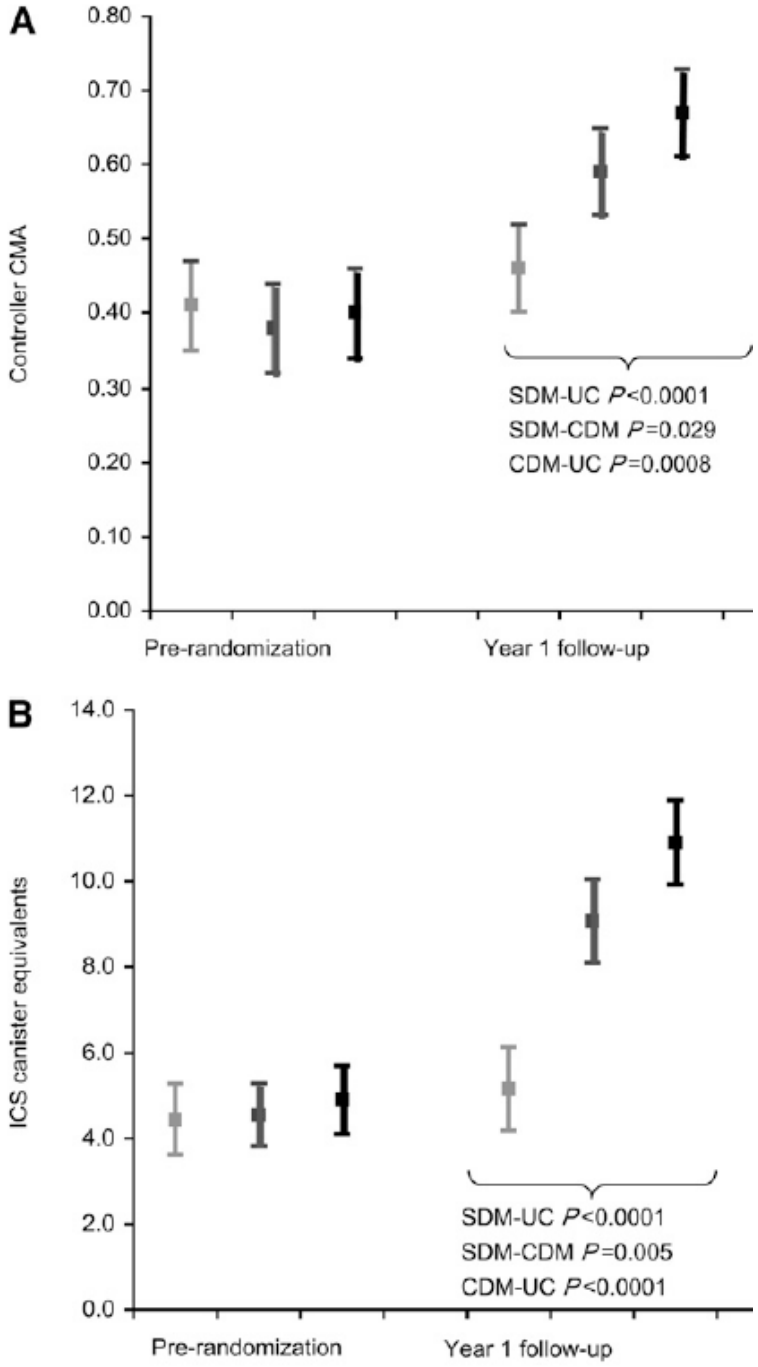




Buhl Resp Research 2012

Patient Empowerment and Adherence

- Shared decision making results in
  - Increased controller adherence
  - Better clinical outcomes



Wilson AJRCCM 2010

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

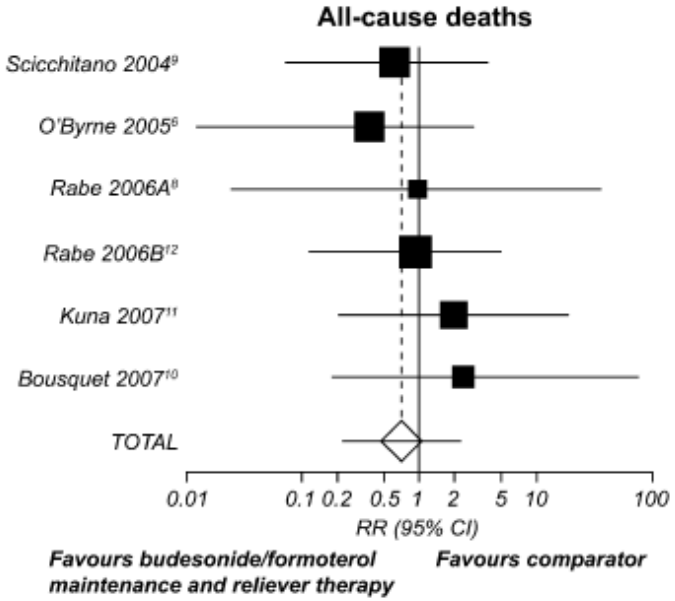
Safety

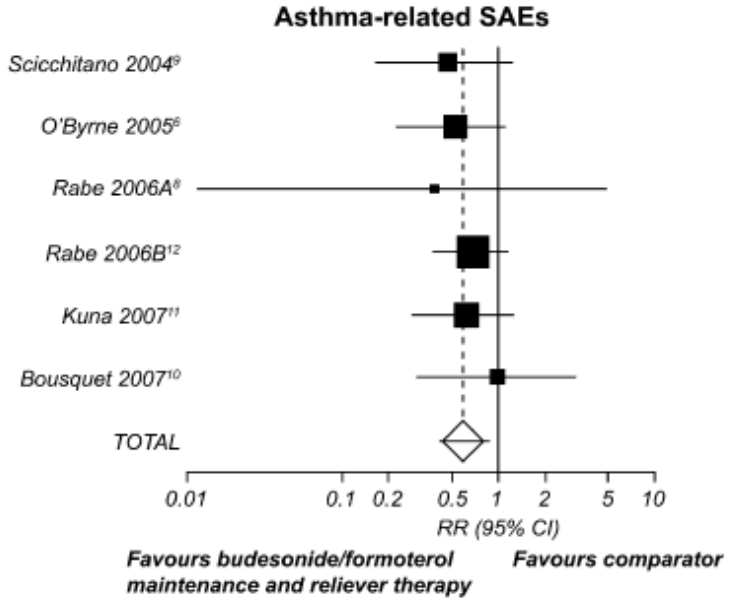
Lower

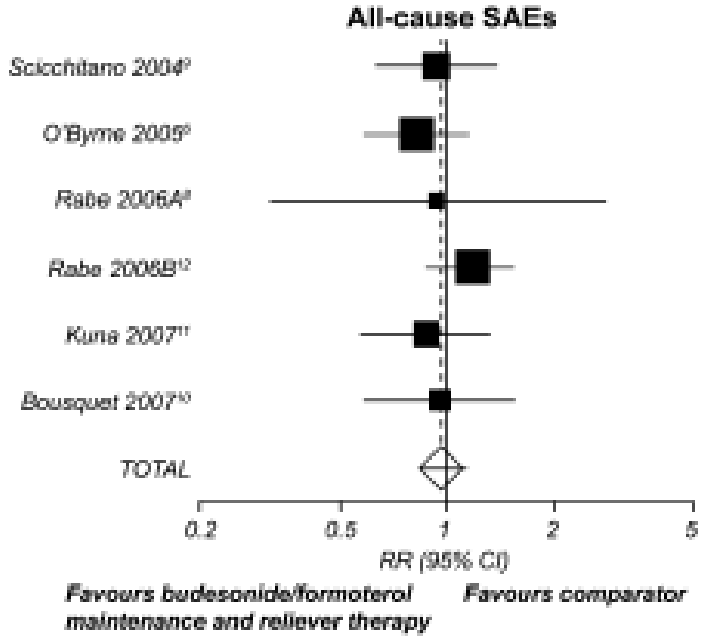
- Asthma SAEs

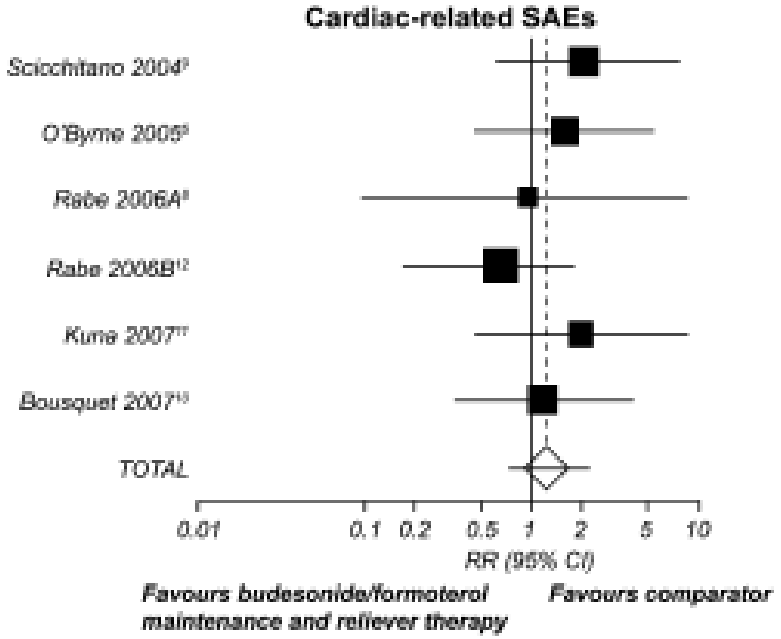
Similar

- All-cause
  - Deaths
  - SAEs
- Cardiac SAEs



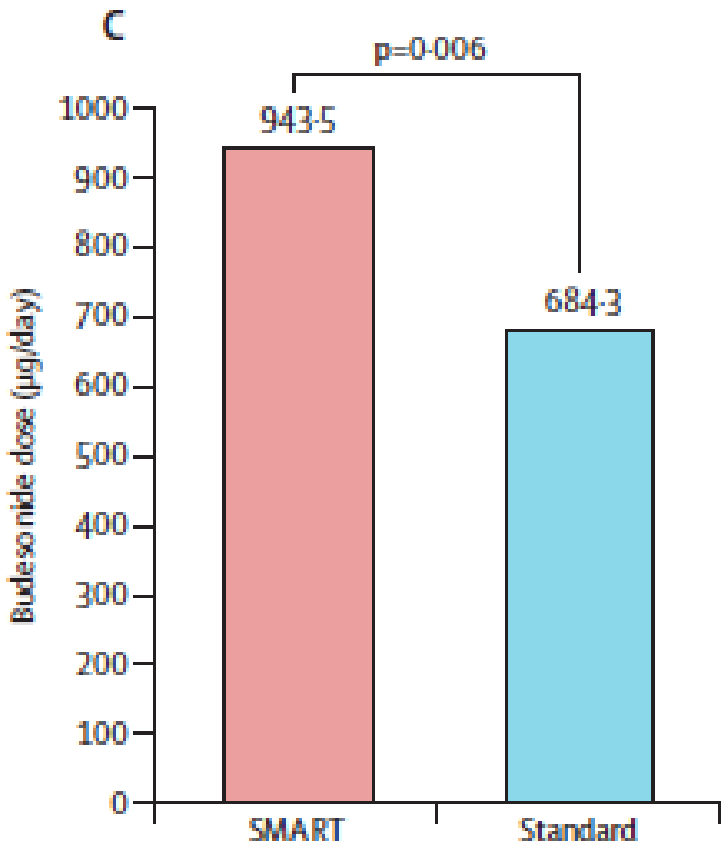


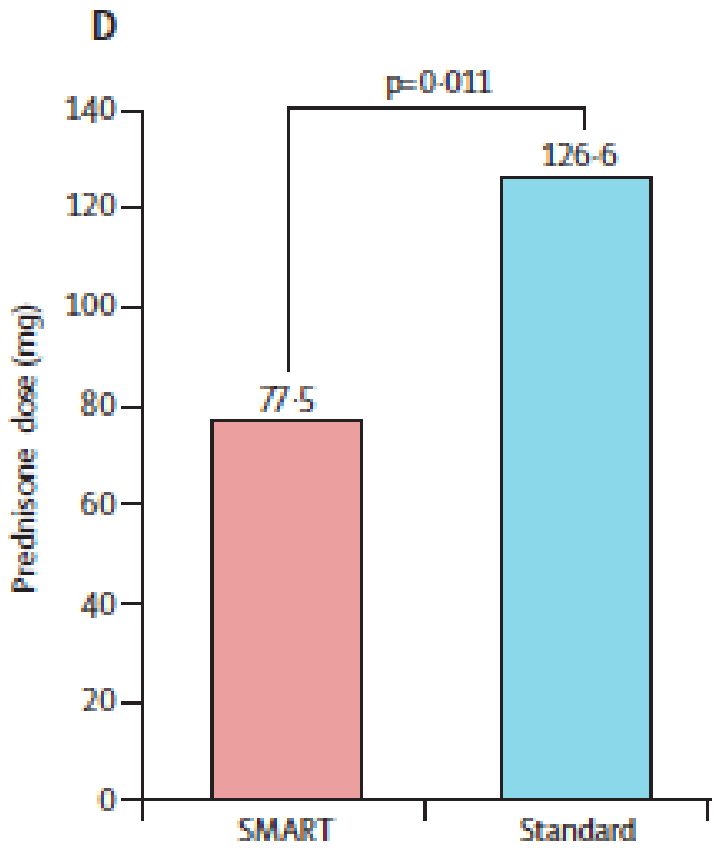


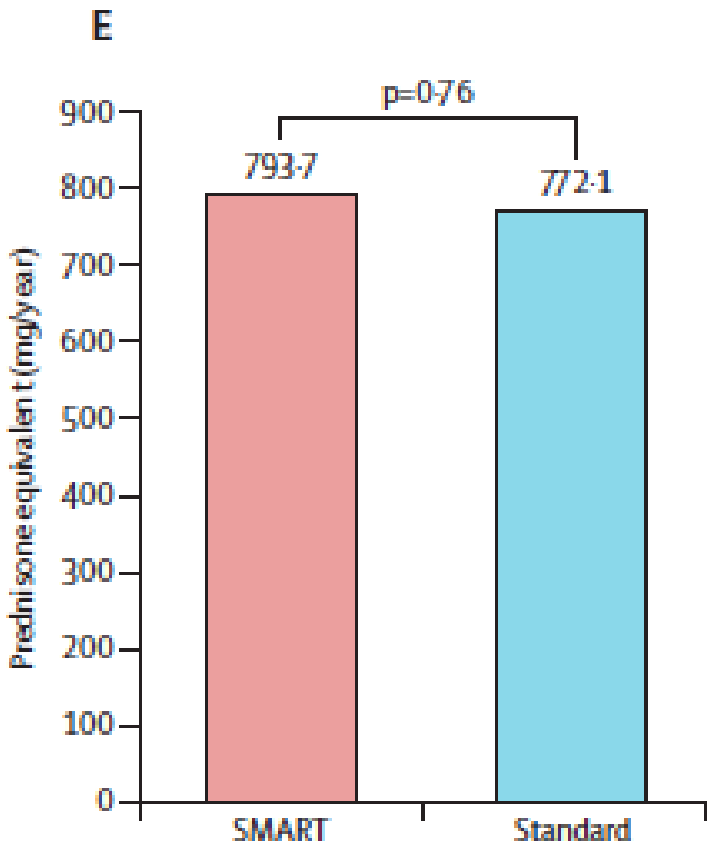


Sears Resp Res 2009

Steroid exposure: higher ICS, lower OCS





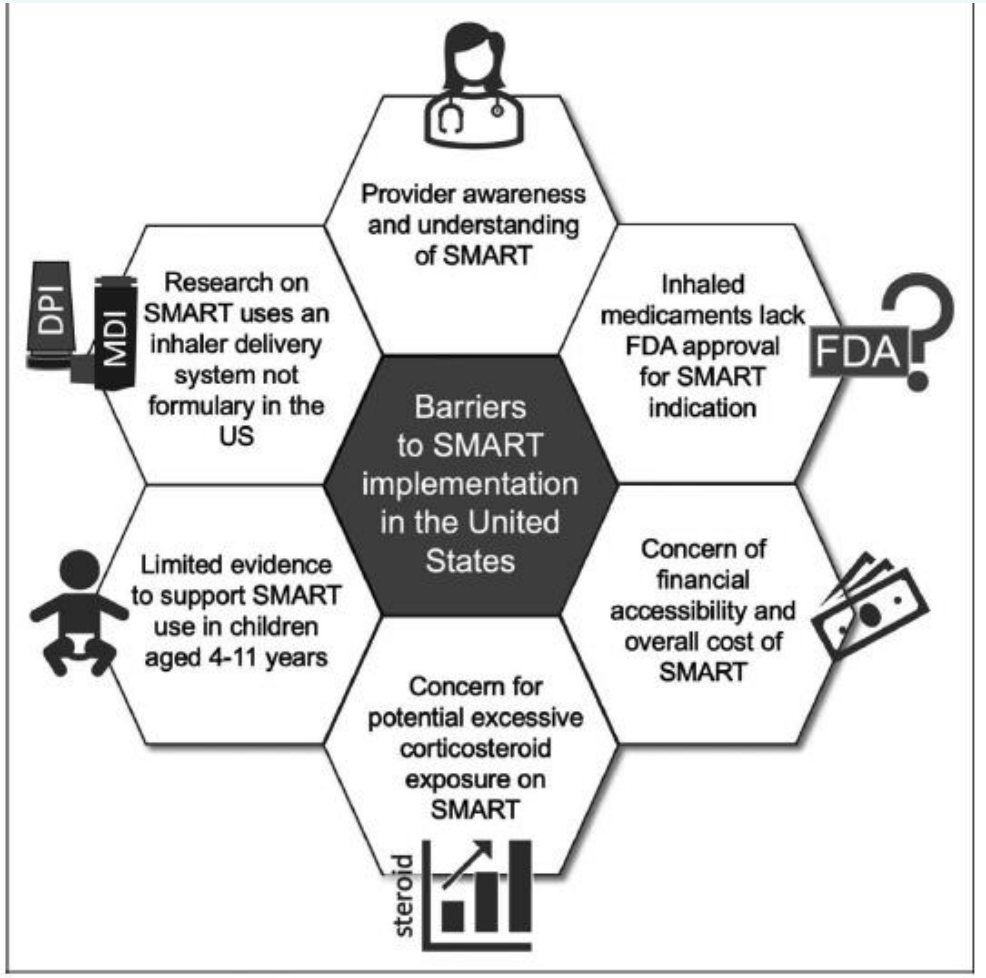


ICS **OCS** **Total systemic steroid dose**

Patel Lancet Resp Med 2013

Barriers to AIR implementation

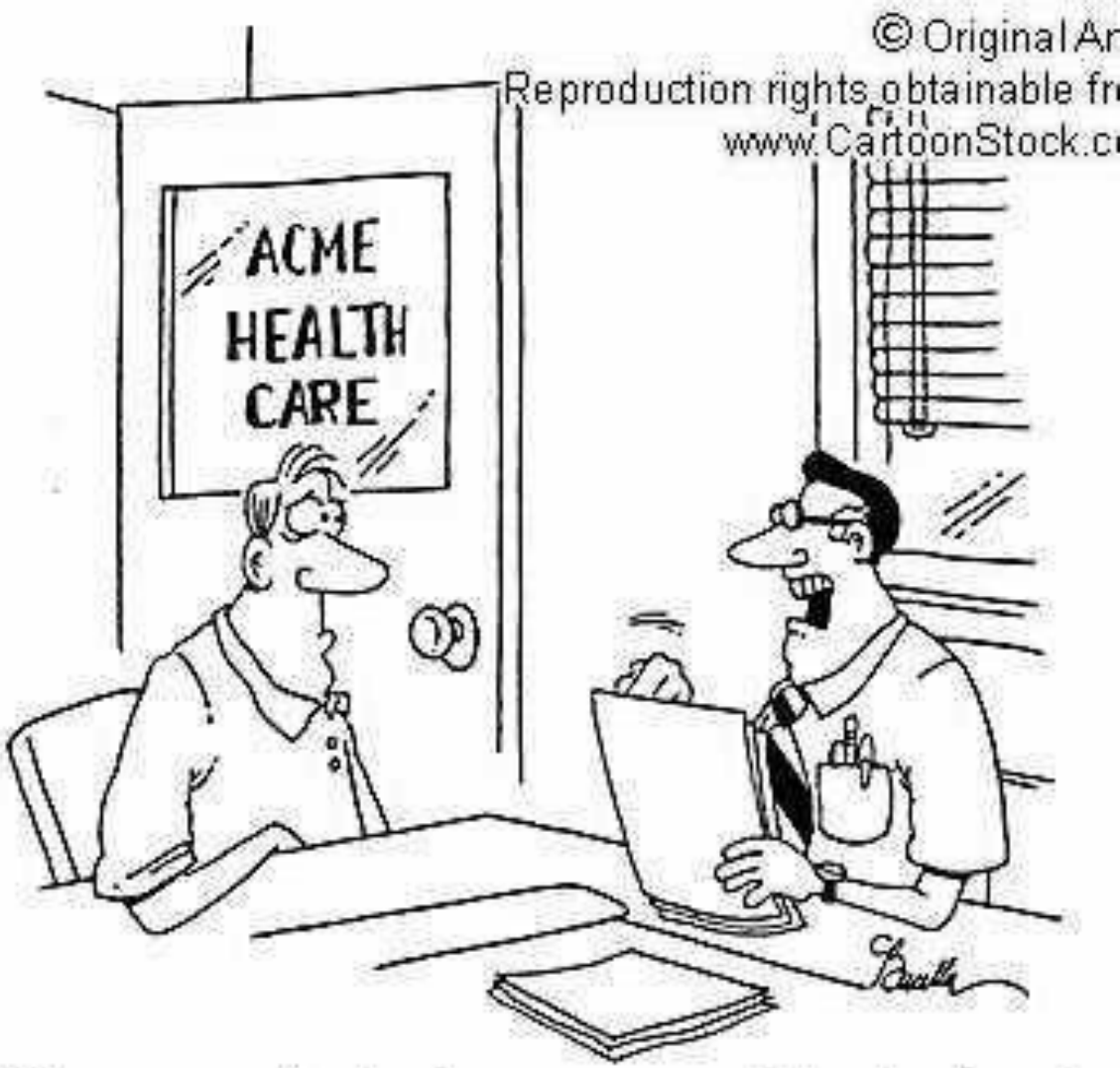
- Insurance
- Insurance
- Insurance
- Mindset / Education
  - Providers
  - Patients
- Cost



Norris Curr Opin Pulm 2022

Barriers: Insurance

- Insurance
  - Need ICS/formoterol for SMART
  - Adequate number of inhalers per month
  - ICS/form as reliever is off-label
    - Not FDA approved
  - ICS/albuterol (AirSupra): not covered by all insurance companies
  - Adding ICS fewest insurance barriers



Barriers: mindset and education

Providers

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

Patients

- Confusion
- Underperceive symptoms
- Risk of SABA overuse unknown

Krings JACI Practice 2023

Barriers: Cost

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

Varies based on insurance coverage

Need for prior authorization (time cost)

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

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

GoodRX
Norris 2022
Sadatsafavi Chest 2014

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!