

# “Anti-Inflammatory Rescue”: Is it Time to Abandon SABAs Alone?

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# Disclosures

- Author, UpToDate

# 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

# Outline

- Benefits of SABA as rescue
- Disadvantages of SABA as rescue
  
- Benefits of AIR “anti-inflammatory rescue”
- Disadvantages of AIR “anti-inflammatory rescue”



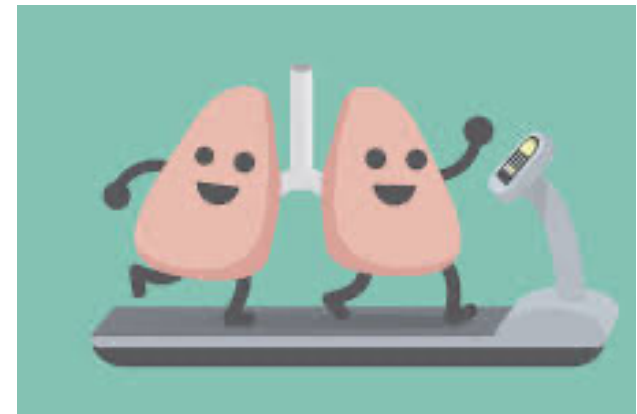
# Asthma Burden

- Over 260 million worldwide
  - In US Adults: 20 million; 8% (2021)
  - In US Children: 5.1 million; 6.5%
- 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



Part I:

Benefits of SABA rescue

At Last...  
UNIFORM DOSAGE NEBULIZATION  
in Asthma

**MEDIHALER**<sup>TM</sup>

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 1/4 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**<sup>TM</sup>

0.5% solution of epinephrine HCl U.S.P.

\* **MEDIHALER-ISO**<sup>TM</sup>

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.



Another First from



*22 1/2% 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**<sup>TM</sup>  
Epinephrine bitartrate, 7.0 mg. per cc., suspended in inert, nontoxic aerosol vehicle. Contains no alcohol. Each measured dose contains 0.15 mg. epinephrine.

**Medihaler-ISO**<sup>TM</sup>  
Isoproterenol sulfate, 2.0 mg. per cc., suspended in inert, nontoxic aerosol vehicle. Contains no alcohol. Each measured dose contains 0.05 mg. isoproterenol.

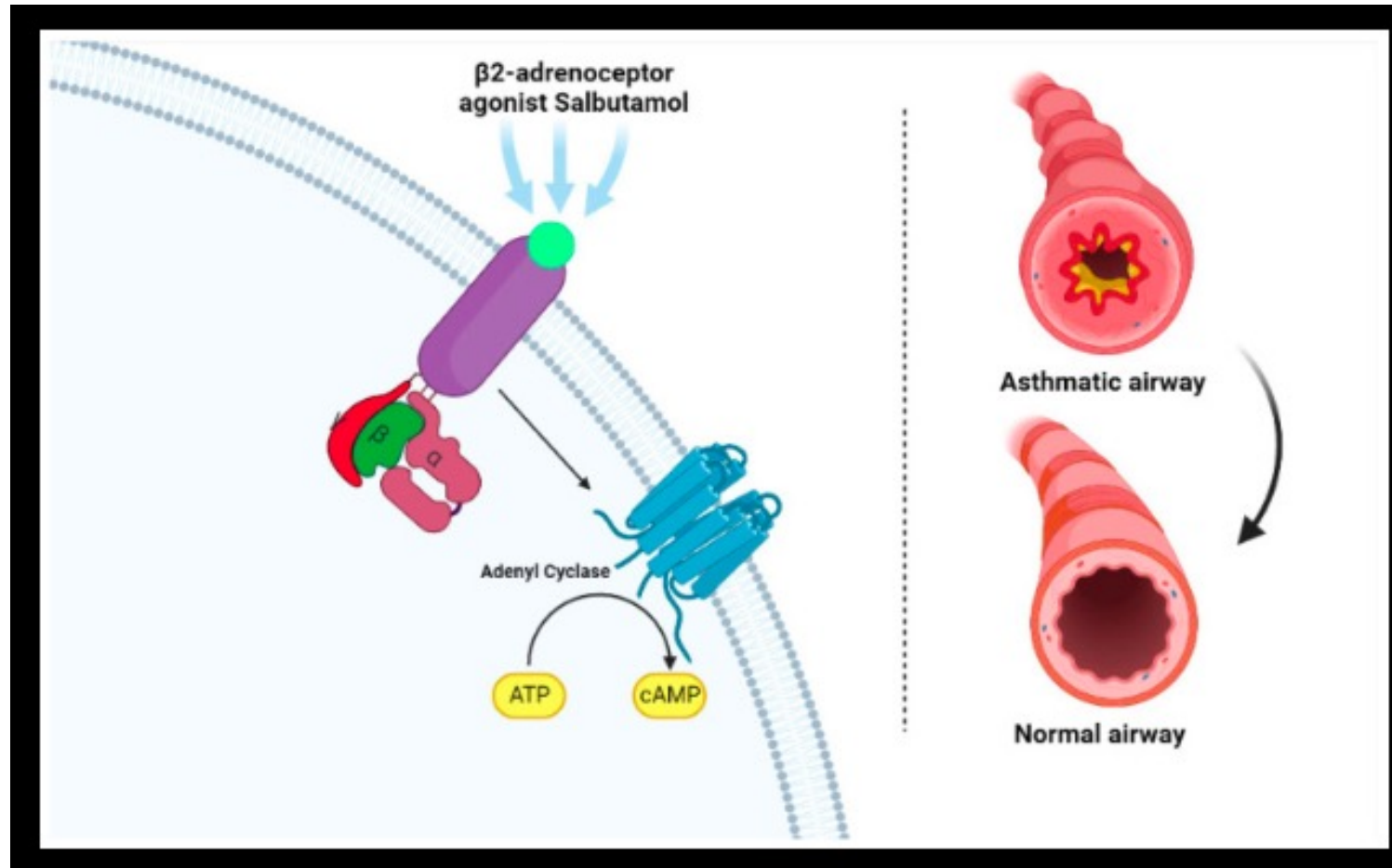
**MEDIHALER**<sup>TM</sup>  
automatically measured-dose aerosol medications.  
Nebulizer-free • Spill-proof • Leak-proof • Leak-proof

**Riker** Manufactured in California

AVAILABLE FOR CHILDREN, TOO.

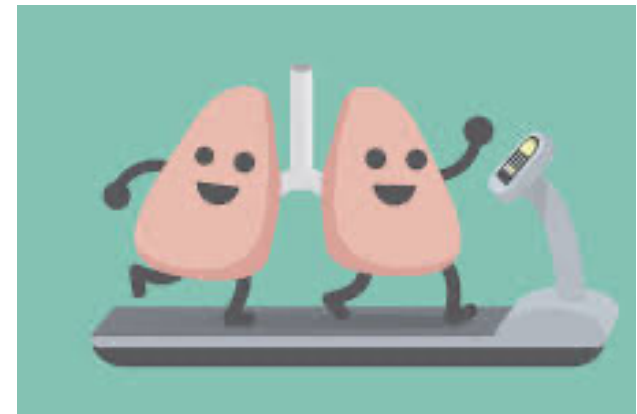


# Beta agonist: mechanism of action



# 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



Part II:  
Disadvantages  
of SABA as  
rescue



# Disadvantages of SABA as rescue

- **Physiology**

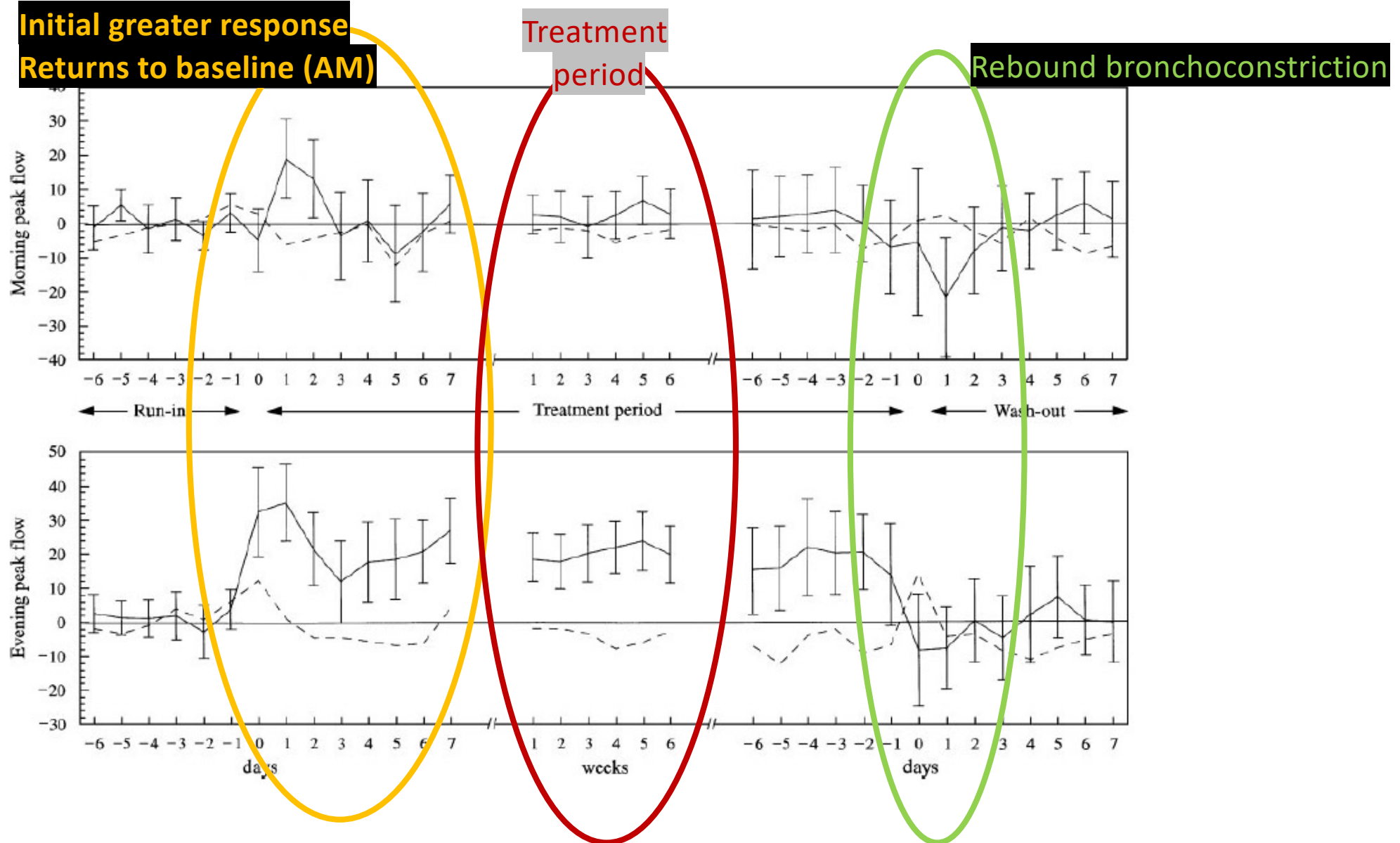
- Tolerance
- Reduced bronchodilator response
- Increased airway hyperresponsiveness
- Increased eosinophilic inflammation

- **Epidemiology**

- Exacerbations
- Death



# AM and PM Peak flow with SABA treatment

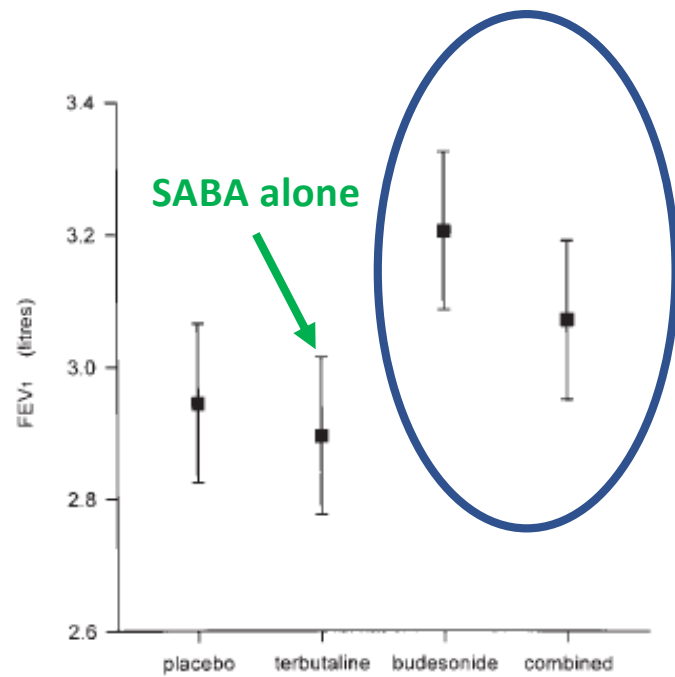


# Increased AHR and tolerance

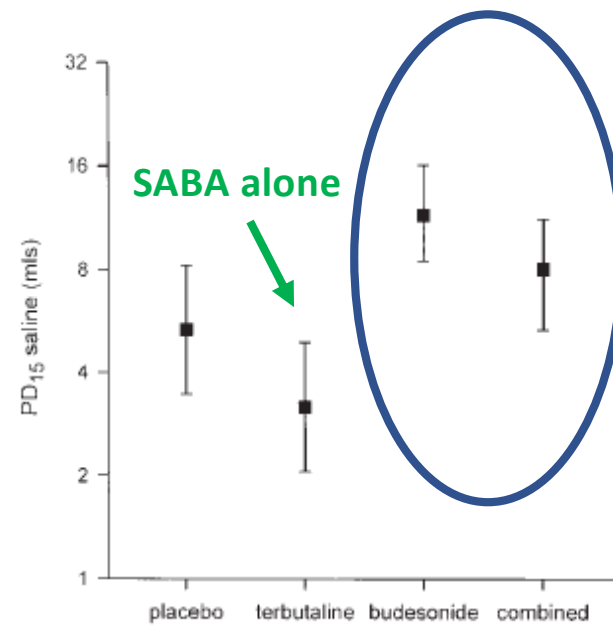
- **Increased sensitivity** to allergen provocation (PC20 reduced by 2 doubling doses)
  - Possibly due to enhanced mast cell mediator release due to beta2 receptor down-regulation
- **Reduced protective effect** after allergen / methacholine
- NO change in:
  - Baseline FEV<sub>1</sub>, BD response, methacholine responsiveness

# Effects of Terbutaline and Budesonide on Sputum Cells and Bronchial Hyperresponsiveness In Asthma

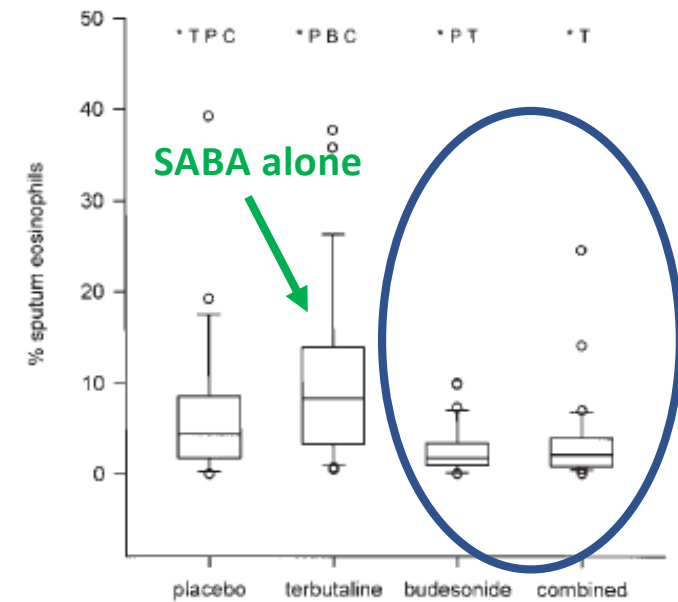
FEV<sub>1</sub> , PD<sub>15</sub> saline, sputum eosinophils



**Figure 2.** Treatment effects for FEV<sub>1</sub>. Data are displayed as mean (*square symbol*) with error bars representing the least significant difference at the 5% level.



**Figure 3.** Treatment effects for PD<sub>15</sub> saline. Data are displayed as geometric mean (*square symbol*) with error bars representing the least significant difference at the 5% level.



**Figure 5.** Treatment effect on % sputum eosinophils. Data are displayed as median with interquartile range, 10th and 90th percentiles, and outliers. \* P = significantly different from placebo, \* T = significantly different from terbutaline, \* B = significantly different from budesonide, \* C = significantly different from combined treatment, p < 0.05.

# Investigation into Use of Drugs Preceding Death from Asthma

F. E. SPEIZER,\* M.D. ; R. DOLL,† M.D., F.R.C.P., F.R.S. ; P. HEAF,‡ M.D., F.R.C.P. ; L. B. STRANG,§ M.D., F.R.C.P.

*Brit. med. J.*, 1968, 1, 339-343

*Thorax* 1991;46:105-111

## Prescribed fenoterol and death from asthma in New Zealand, 1981-7: a further case-control study

J Grainger, K Woodman, N Pearce, J Crane, C Burgess, A Keane, R Beasley

# The New England Journal of Medicine

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Number 8

### THE USE OF $\beta$ -AGONISTS AND THE RISK OF DEATH AND NEAR DEATH FROM ASTHMA

WALTER O. SPITZER, M.D., M.P.H., SAMY SUISSA, PH.D., PIERRE ERNST, M.D., M.Sc.,  
RALPH I. HORWITZ, M.D., BRIAN HABBICK, M.B., CH.B., DONALD COCKCROFT, M.D.,  
JEAN-FRANÇOIS BOIVIN, M.D., Sc.D., MARY McNUTT, M.Sc., A. SONIA BUIST, M.D.,  
AND ANTHONY S. REBUCK, M.D.

# Another “SMART”

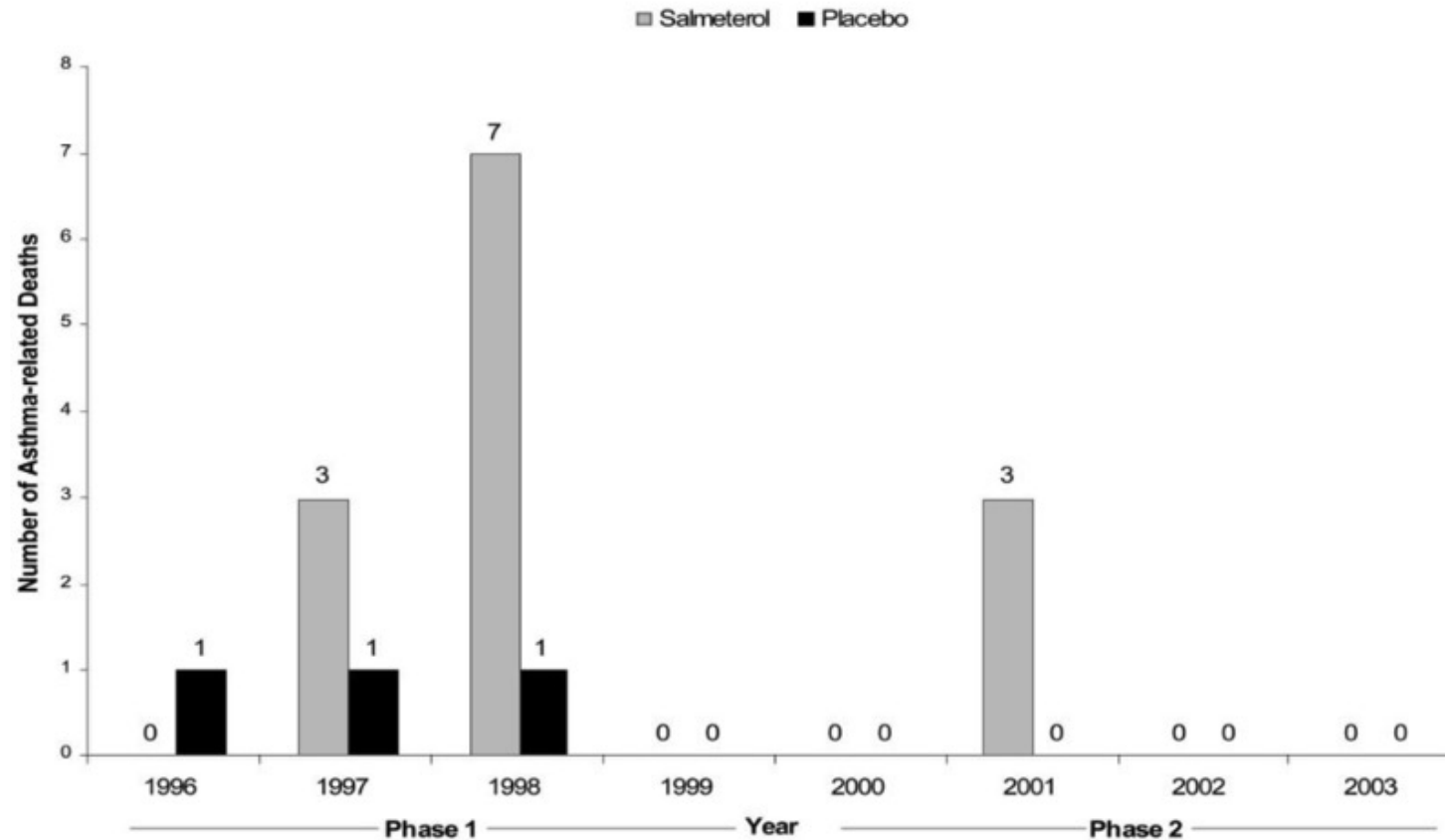


FIGURE 2. Occurrence of asthma-related deaths by phase and study year.

# Asthma mortality rates worldwide

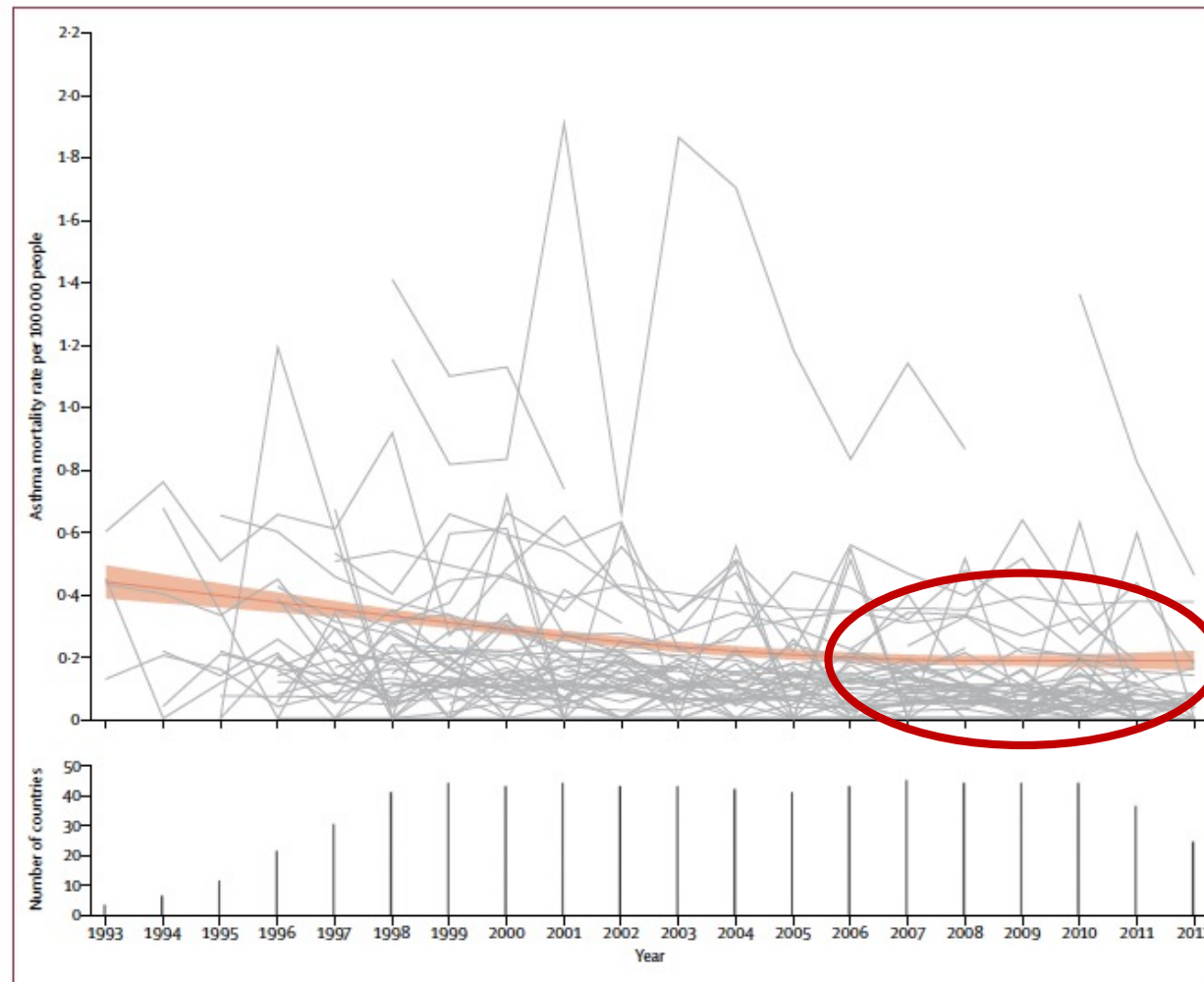


Figure 1: Age-standardised asthma mortality rates for the 5–34-year age group in 46 countries, for the years 1993–2012

The LOESS rates with 90% confidence limits, weighted by country population, are shown in red. The countries included are: Australia, Austria, Belgium, Bulgaria, Canada, Croatia, Czech Republic, Denmark, Egypt, Estonia, Finland, France, Georgia, Germany, Greece, Hong Kong, Hungary, Iceland, Israel, Italy, Japan, Kuwait, Kyrgyzstan, Latvia, Lithuania, Luxembourg, Macedonia, Malta, Mauritius, Moldova, Netherlands, New Zealand, Norway, Poland, Portugal, Romania, Serbia, Singapore, Slovakia, Slovenia, South Korea, Spain, Sweden, UK: England and Wales, UK: Scotland, USA. LOESS=locally weighted scatterplot smoother.

# SABINA program: SABA use IN Asthma

- Capture current burden of SABA use globally
- Describe SABA prescription patterns, extent of high SABA use
- Impact on asthma-related outcomes
- Examine in diverse asthma management practices and health care systems
- SABINA 1:
  - Retrospective observational study in 1 country (UK)
- SABINA 2:
  - Retrospective observational study in 8 countries (Eur, N Am)
- SABINA 3:
  - 25 countries

# SABINA program

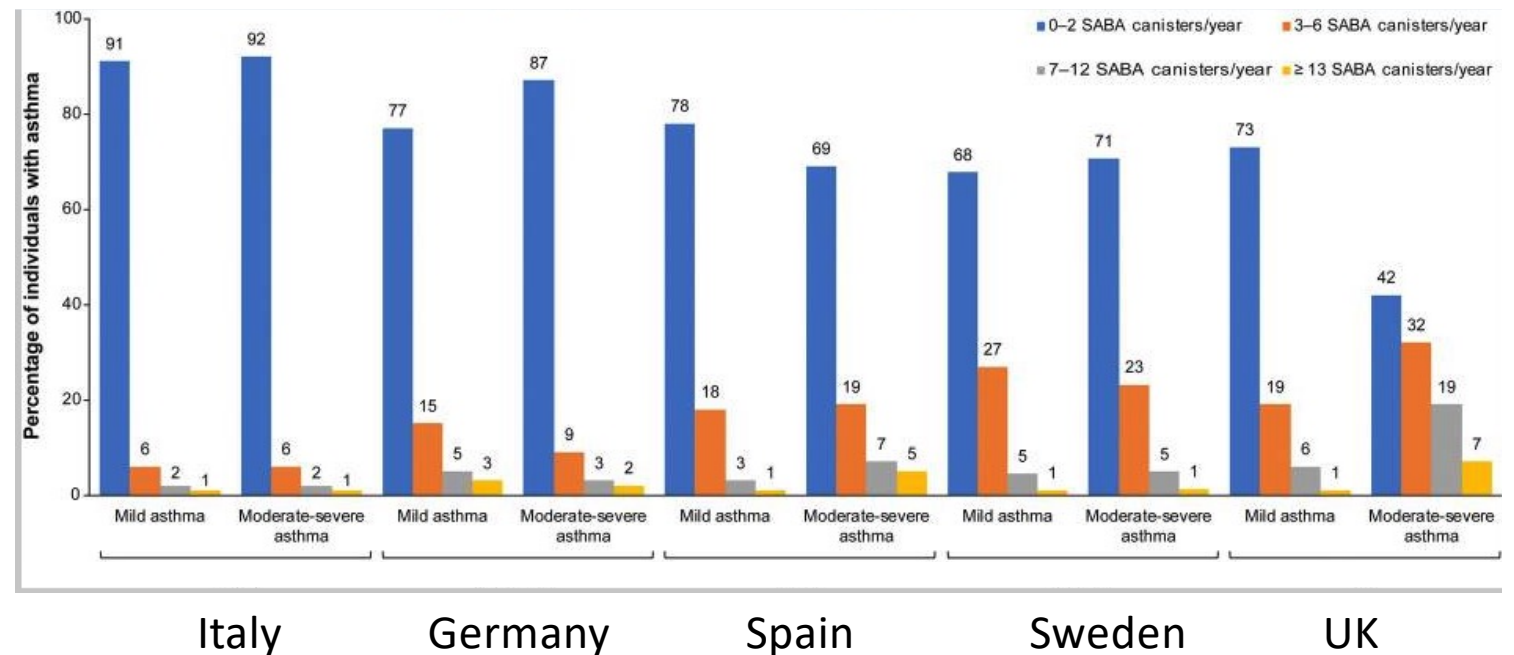
- $\geq 12$  years of age
- Current asthma diagnosis
- Severity characterized by step (GINA/BTS) based on treatment prescribed during baseline year
- SABA pattern during 12m before index date
- Categorized by SABA canisters/year in baseline year:
  - 0-2, 3-5, 6-10,  $\geq 11$  canisters/year
- High SABA use defined as  $\geq 3$  canisters per year
  - Based on GINA and BTS (British Thoracic Society) guidelines
  - 2 uses per week (2 puffs each=4 puffs total) over 1 year = 2 canisters / year
- Outcomes
  - Exacerbations: OCS, ED, hospitalization
  - Death

Notably: funded by AstraZeneca (budesonide/formoterol i.e. Symbicort)



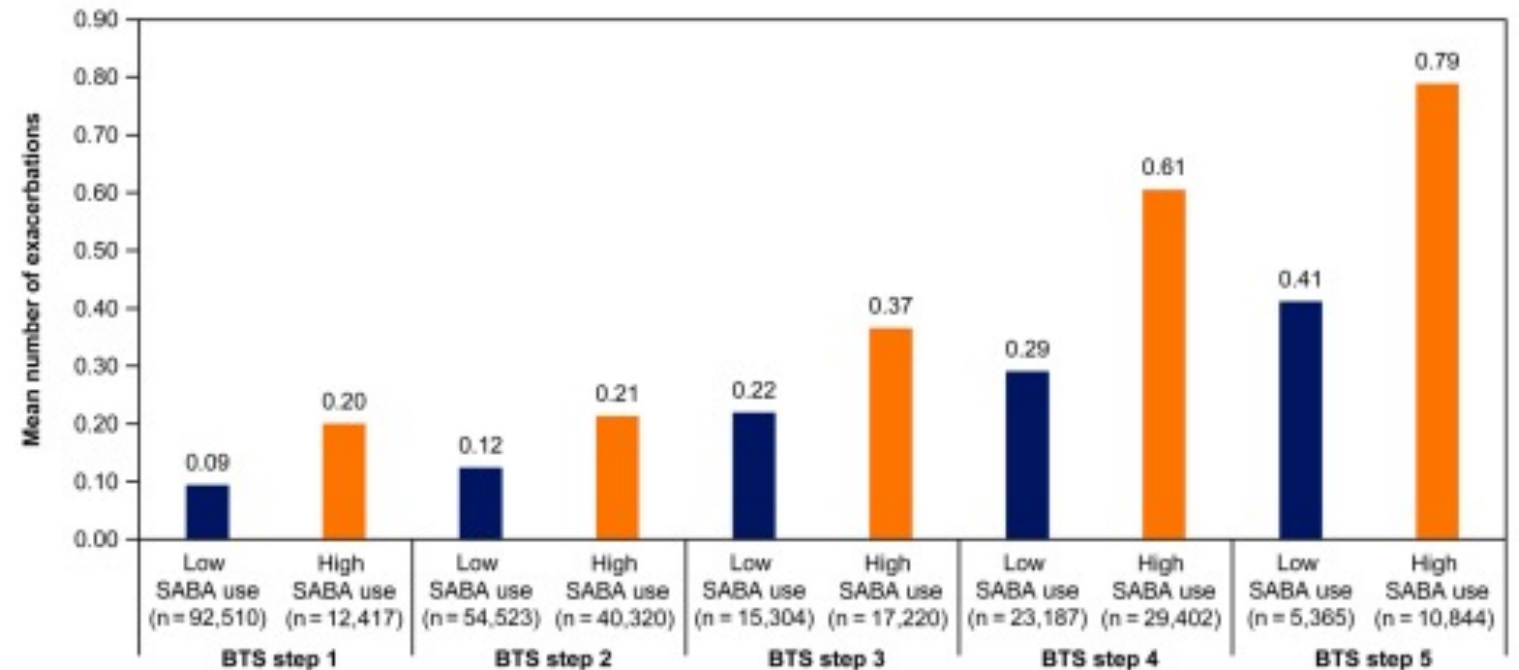
# SABINA: description of SABA use

- >1,000,000 patients in 5 countries (UK, Germany, Italy, Spain, Sweden)
- Overuse ( $\geq 3$  canisters/year) prevalence
  - 9% to 38% depending on country
  - In UK: more common in moderate-severe asthma than mild (58% vs 27%)
  - Other countries, similar among severity groups



# SABINA 1: UK

- 575,000 patients
- 38% high SABA use
  - $\geq 3$  canisters/year
- High use associated with
  - $\uparrow$  exacerbations
  - $\uparrow$  health care utilization



After multivariable adjustment and at all levels of severity

# SABINA (Sweden): exacerbations

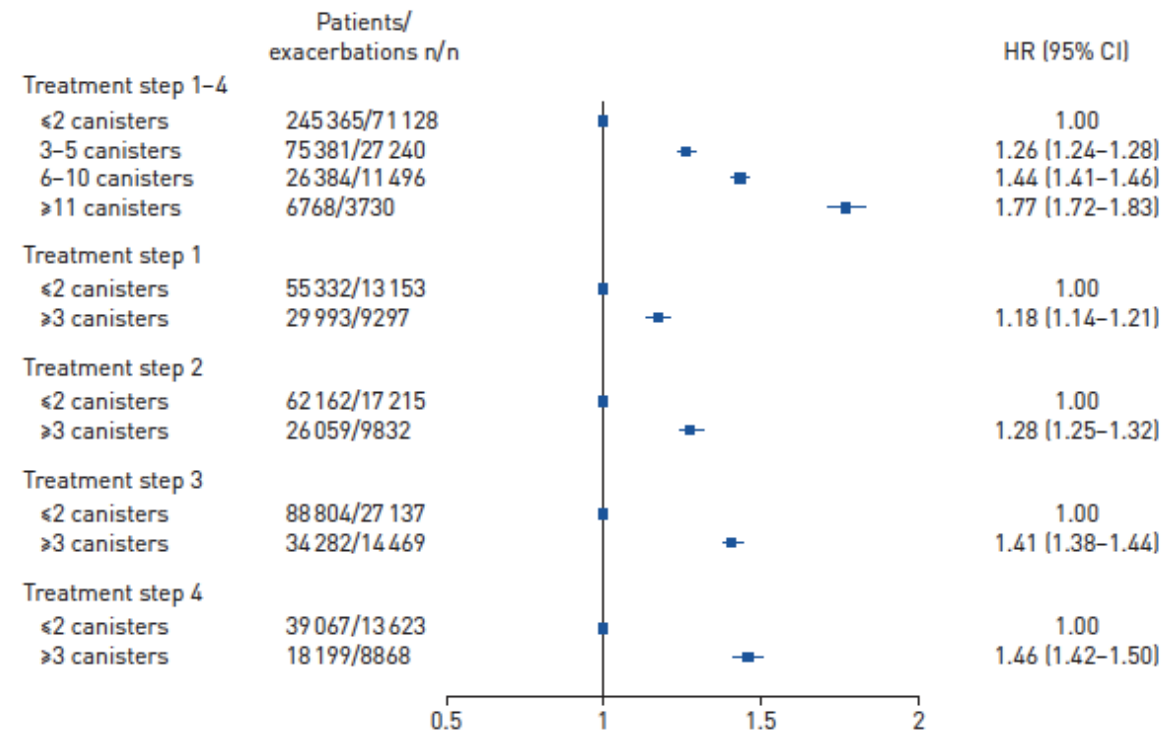
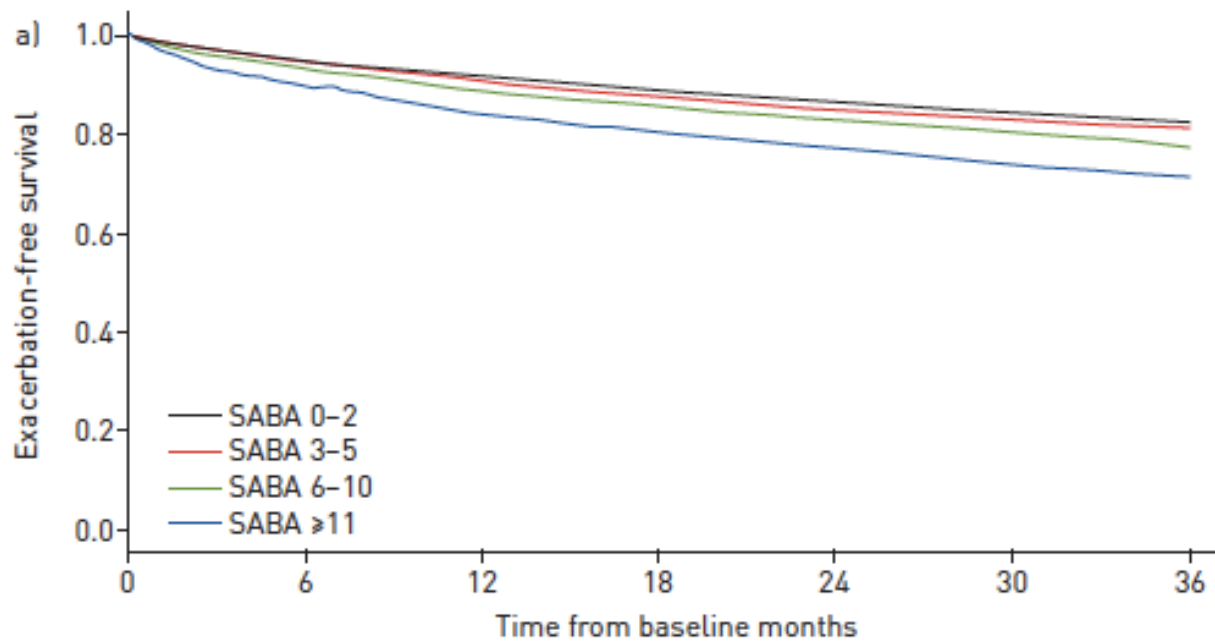
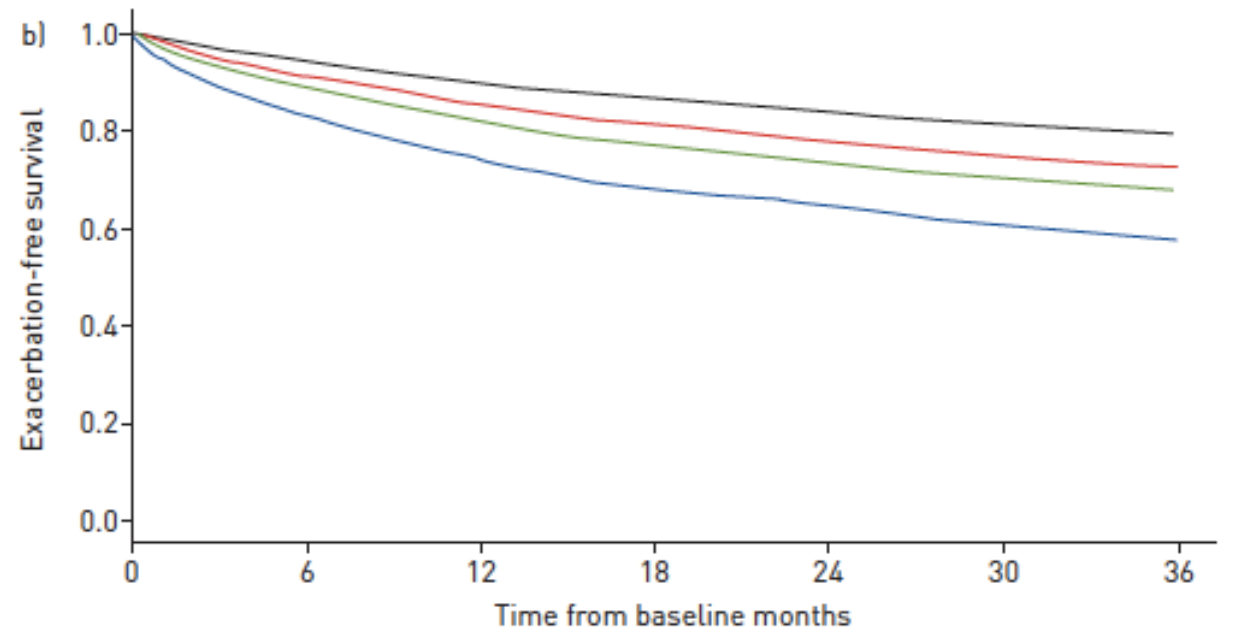


FIGURE 2 Associations between baseline short-acting  $\beta_2$ -agonist (SABA) use and treatment step and subsequent risk of asthma exacerbation. Adjusted for age at asthma diagnosis, sex, treatment step and comorbidity. ≤2 canisters: patients collecting two or fewer SABA canisters during the baseline year; ≥3 canisters: patients collecting three or more SABA canisters during the baseline year; HR: hazard ratio.

# SABINA (Sweden): Exacerbation rates: with or without ICS



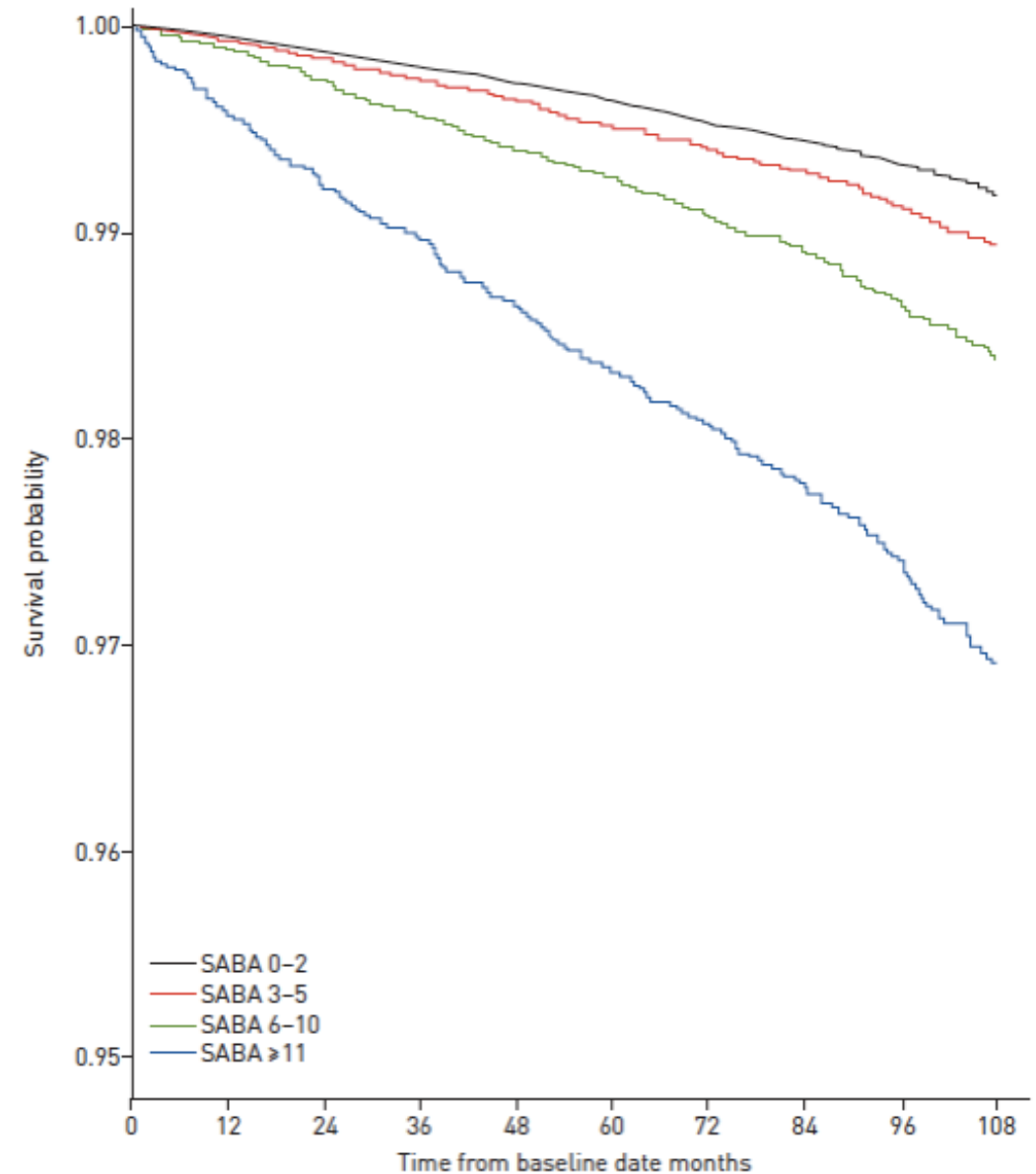
No ICS



ICS

# SABINA (Sweden): mortality

- Overall mortality ~2500 or 0.9%
  - 0.54% (1365) 0-2 canisters vs 1.07% (1199) in overusers
- Increased all-cause (figure) and asthma-specific mortality



At risk n	0	12	24	36	48	60	72	84	96	108
SABA 0-2	254500	254367	230860	210403	187331	165549	142973	118674	91999	54765
SABA 3-5	76619	76563	71316	66801	61790	56015	49939	43024	34937	22584
SABA 6-10	27065	27034	25769	24552	23280	21836	20212	18503	16436	13034
SABA ≥11	7140	7190	6912	6729	6539	6321	6078	5820	5500	4994

URE 4 Kaplan-Meier plot of overall survival by baseline short-acting  $\beta_2$ -agonist (SABA) use.

# SABINA (Sweden): mortality

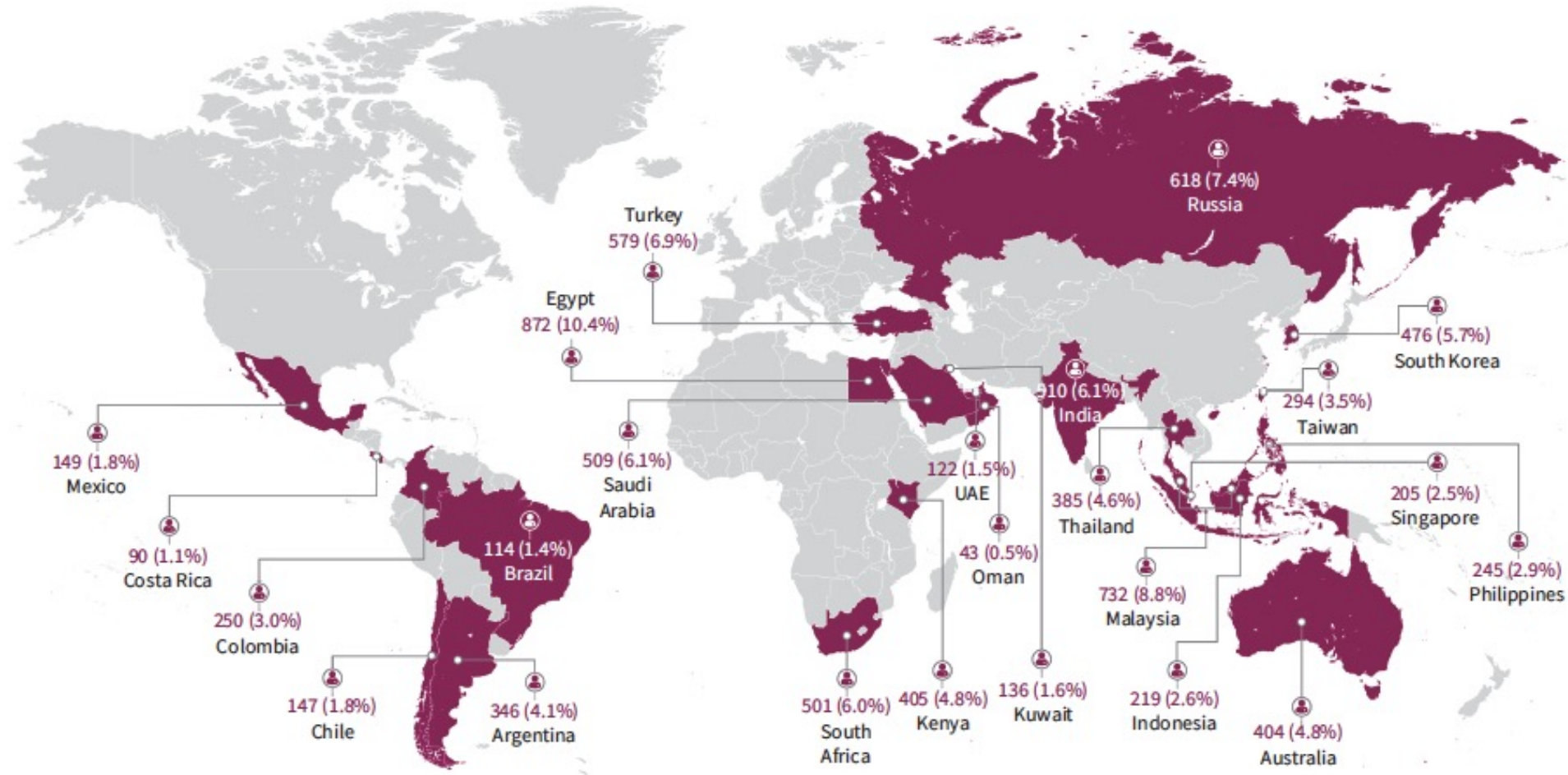
- Asthma-related and other causes

TABLE 3 Cause of death among asthma patients by use of short-acting  $\beta_2$ -agonists (SABA) during baseline year

	SABA canisters collected during the baseline year n			
	0-2	3-5	6-10	$\geq 11$
<b>Subjects</b>	254 500	76 619	27 065	7 140
<b>Vital status</b>				
Alive	253 135 (99.5)	76 011 (99.2)	26 690 (98.6)	6 924 (97.0)
Dead	1 365 (0.5)	608 (0.8)	375 (1.4)	216 (3.0)
<b>Cause of death</b>				
Suicide	199 (14.6)	82 (13.5)	48 (12.8)	19 (8.8)
Cardiovascular related	178 (13.1)	91 (15.0)	50 (13.3)	28 (13.0)
Poisoning by accident	131 (9.6)	52 (8.6)	42 (11.2)	18 (8.3)
Respiratory related	43 (3.2)	19 (3.1)	20 (5.3)	18 (8.3)
Asthma related	7 (0.5)	4 (0.7)	5 (1.3)	12 (5.6)
Malignancy related	196 (14.4)	68 (11.2)	28 (7.5)	18 (8.3)
Other	618 (45.3)	296 (48.7)	187 (49.9)	115 (53.2)

Data are presented as n or n (%).

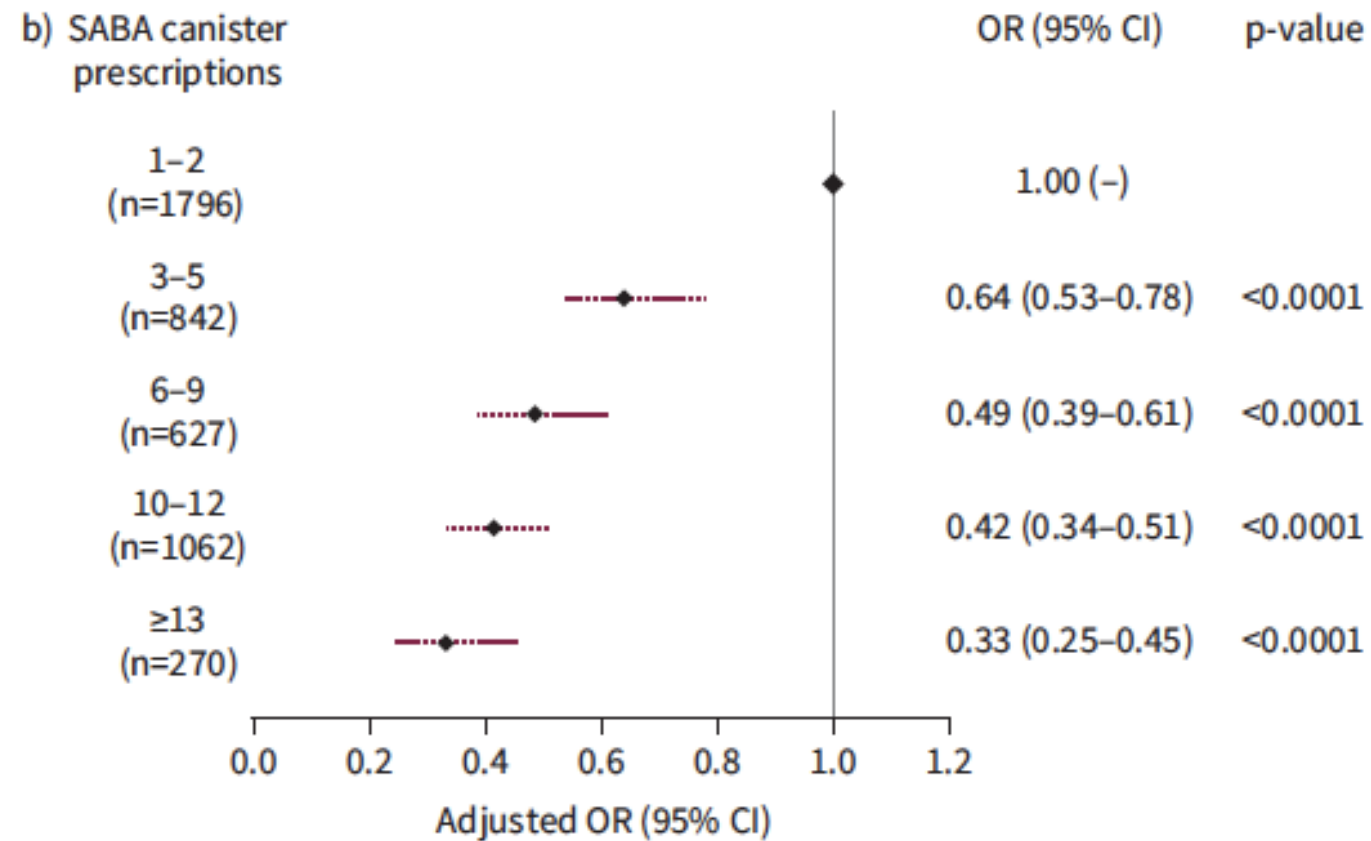
# SABINA III (SABA use IN Asthma)



**FIGURE 1** Patient enrolment across countries in SABINA III. UAE: United Arab Emirates.

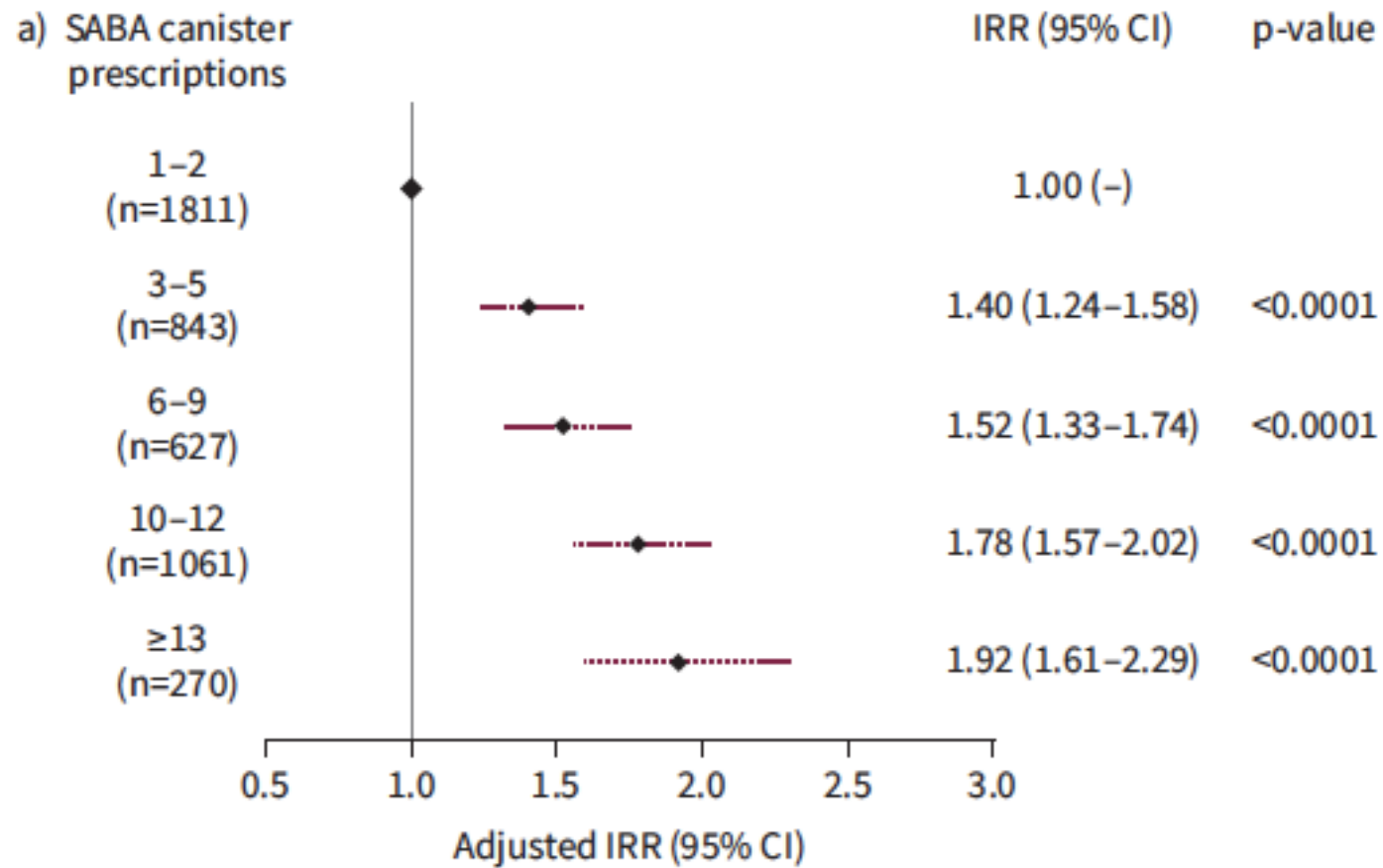


# SABA and symptom control





# SABA and exacerbations



“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**”

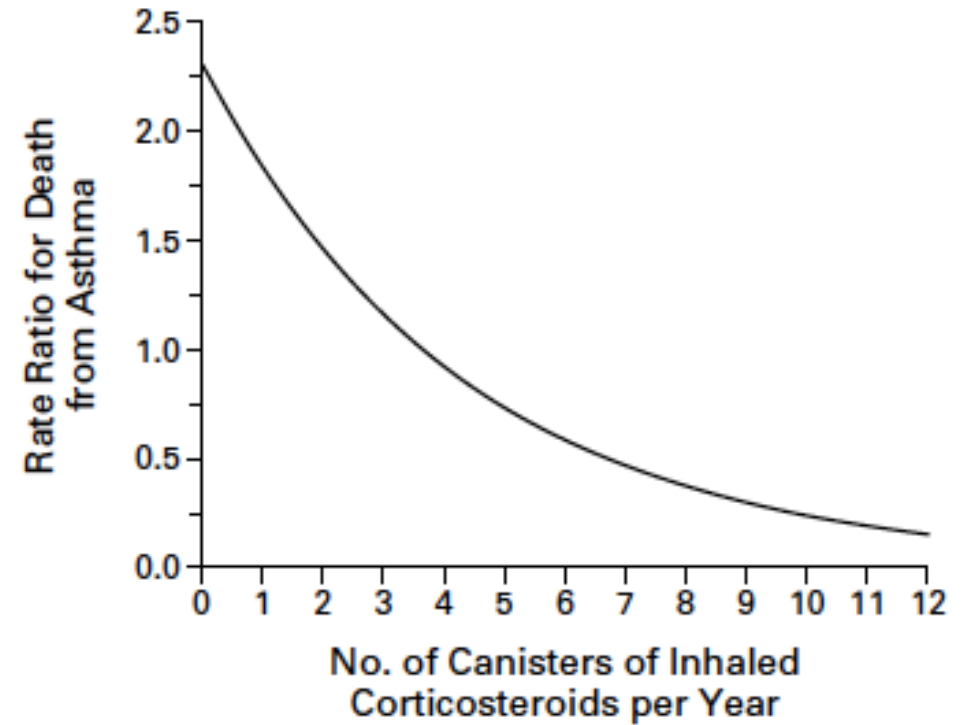
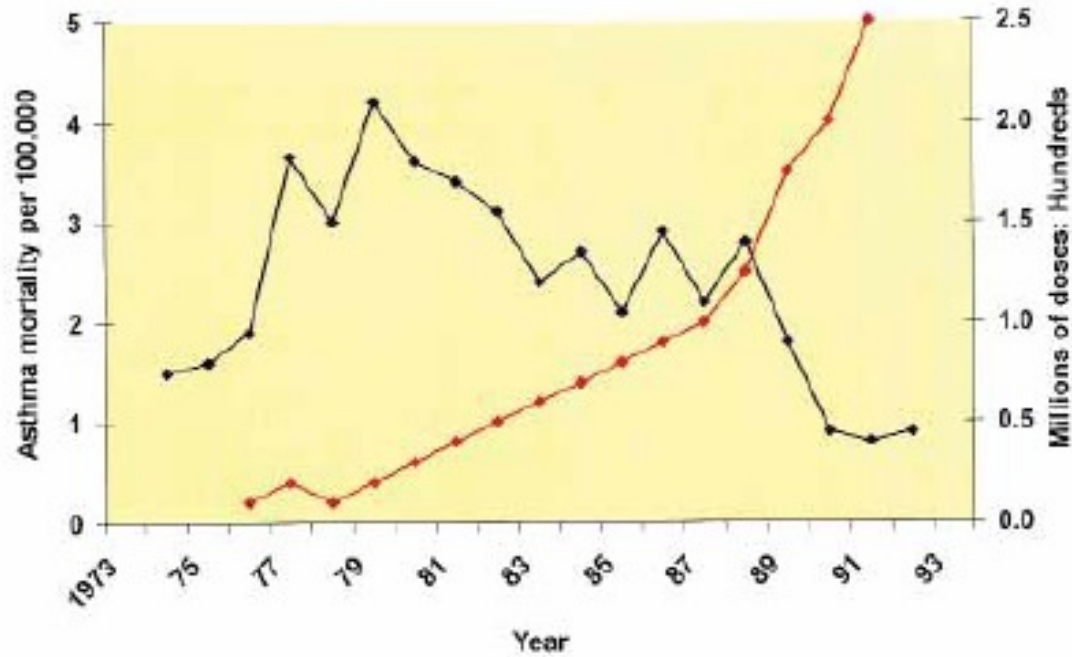






# Part III: Benefits of AIR

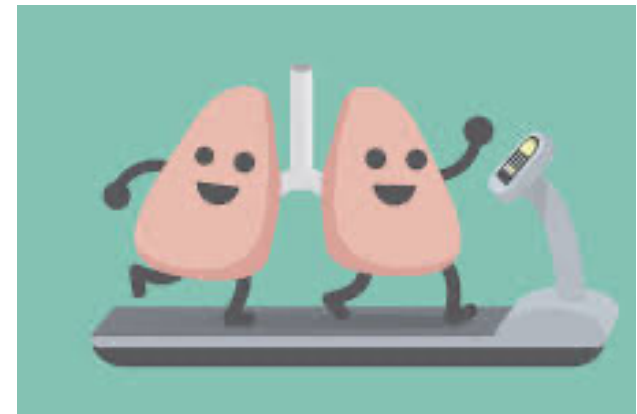
# ICS and asthma mortality





# 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



# Adherence

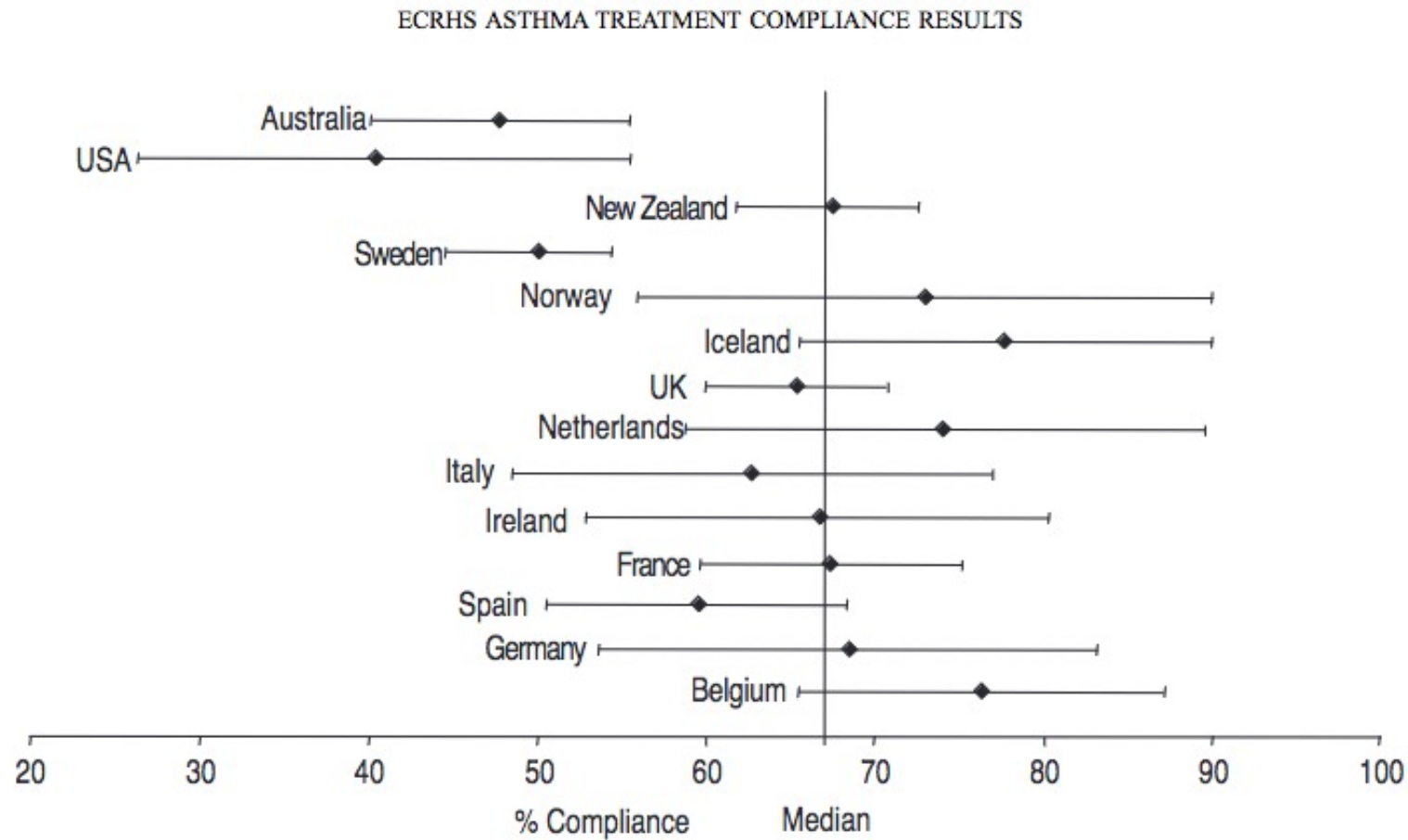
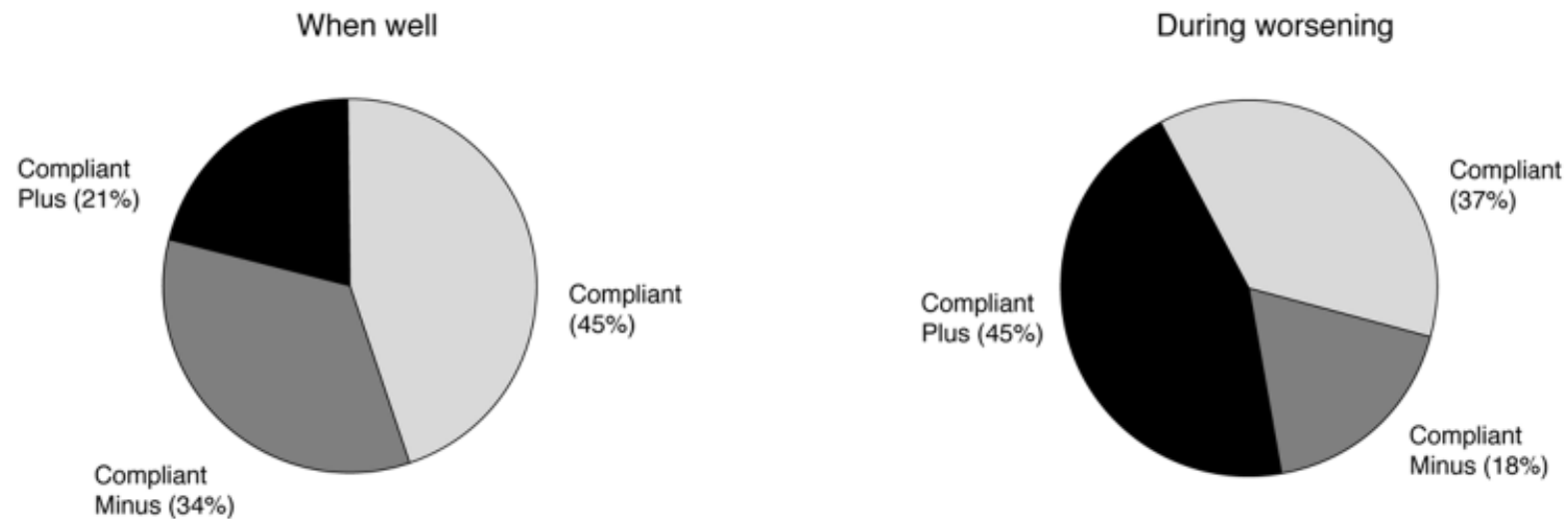


Fig. 2. – Prevalence (%) (◆) (95% confidence intervals (CI)) (—) of compliance between subjects with indications for treatment by country. A prevalence significantly different from the median is present when the 95% CI does not fit the vertical line of the median value.

# Patient behavior: INSPIRE study



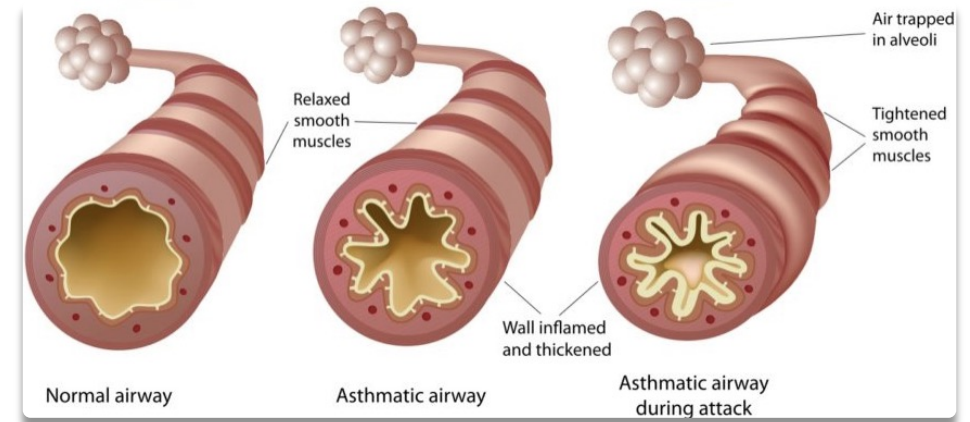
n=3415

#### 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: inflammatory, intermittent

- Triggers are unpredictable
  - Viruses
  - Pollens
  - Pollution
- Oral steroids: ~ 4–5 lifetime courses
  - ↑ risk osteoporosis, diabetes, cataract





# An analogy



ICS



FABA

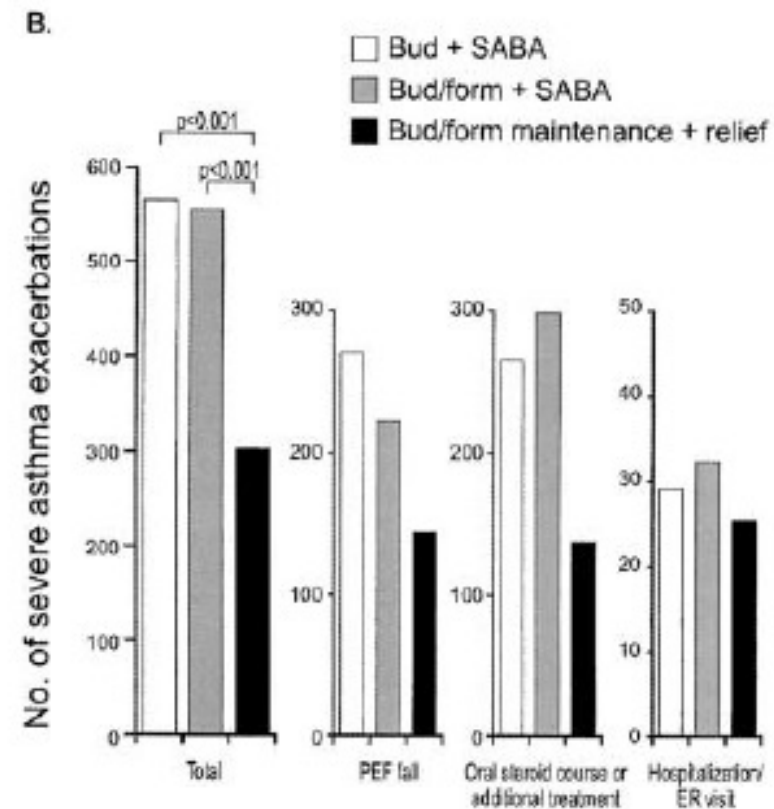
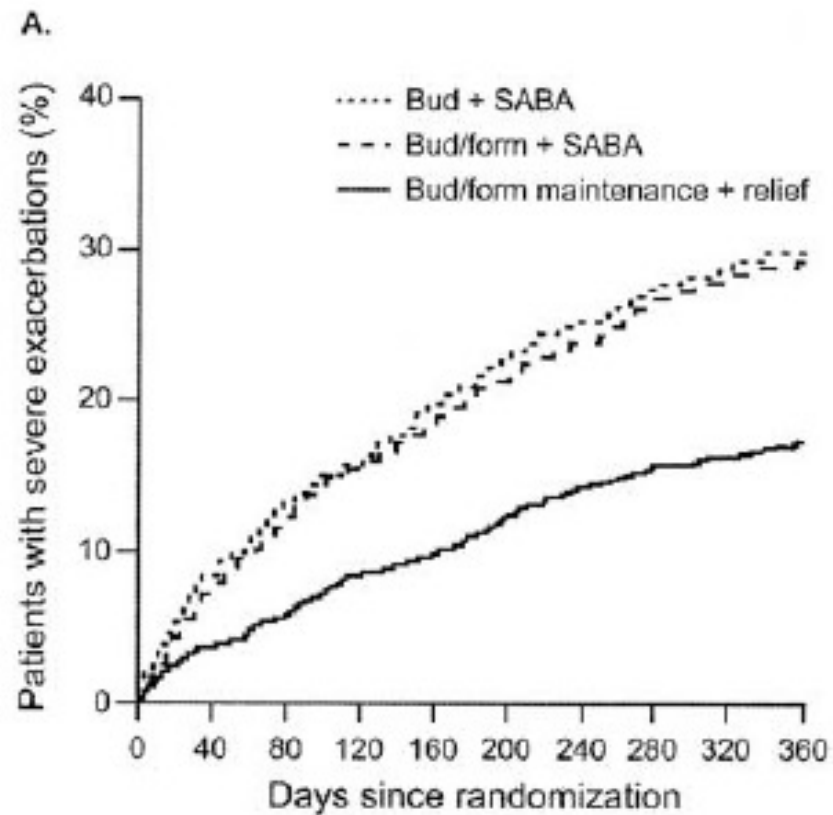
Solution: Give them at the same time!

**SMART!**

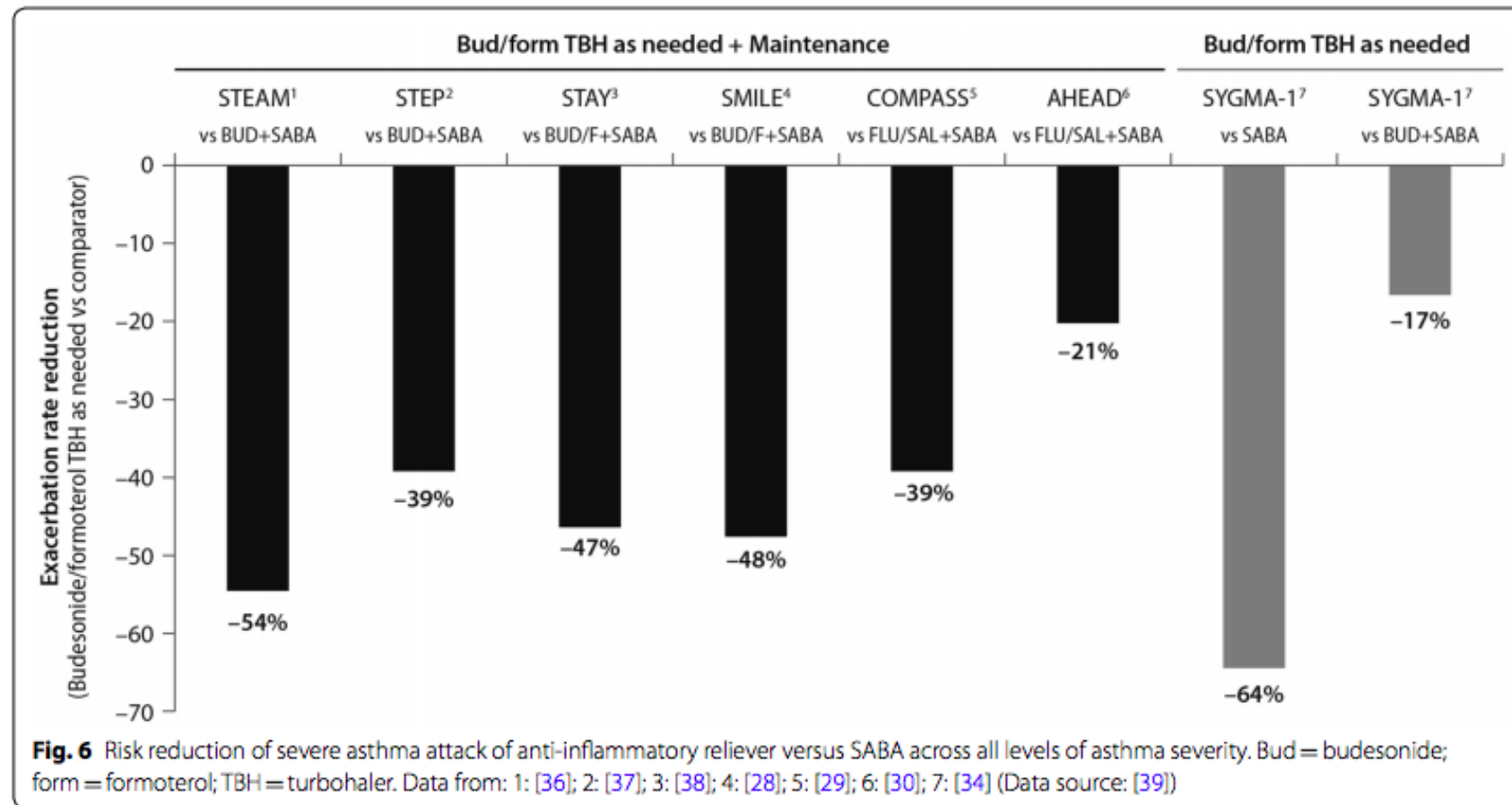


ICS/FABA  
(ICS/SABA or ICS/LABA)

# SMART approach: persistent asthma



# SMART vs various therapies, all SABA as reliever



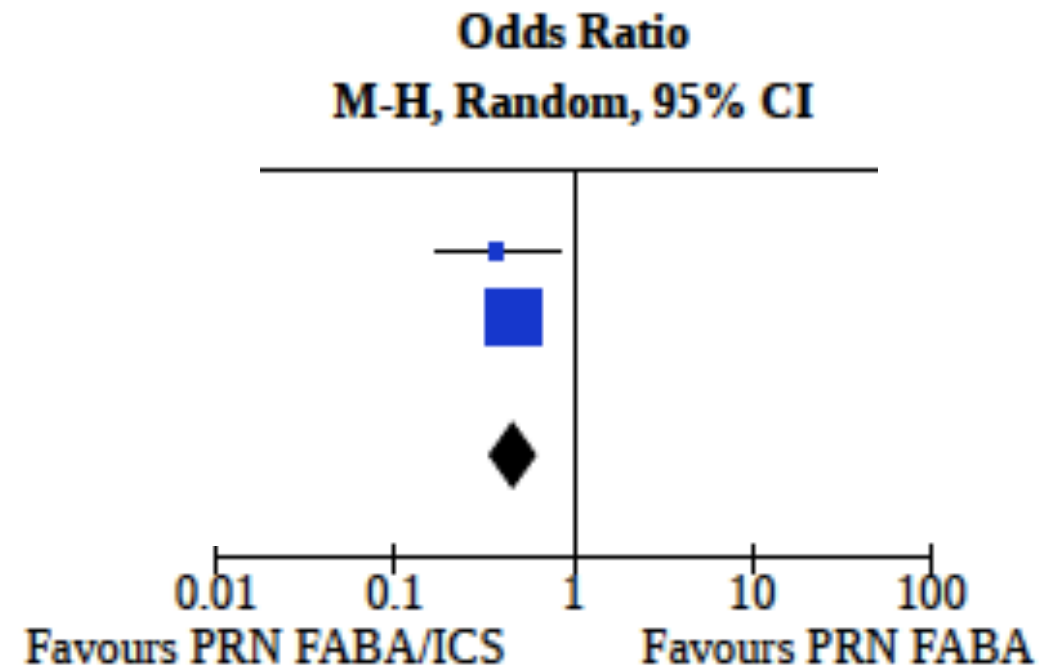
JAMA | Original Investigation

## Association of Inhaled Corticosteroids and Long-Acting $\beta$ -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

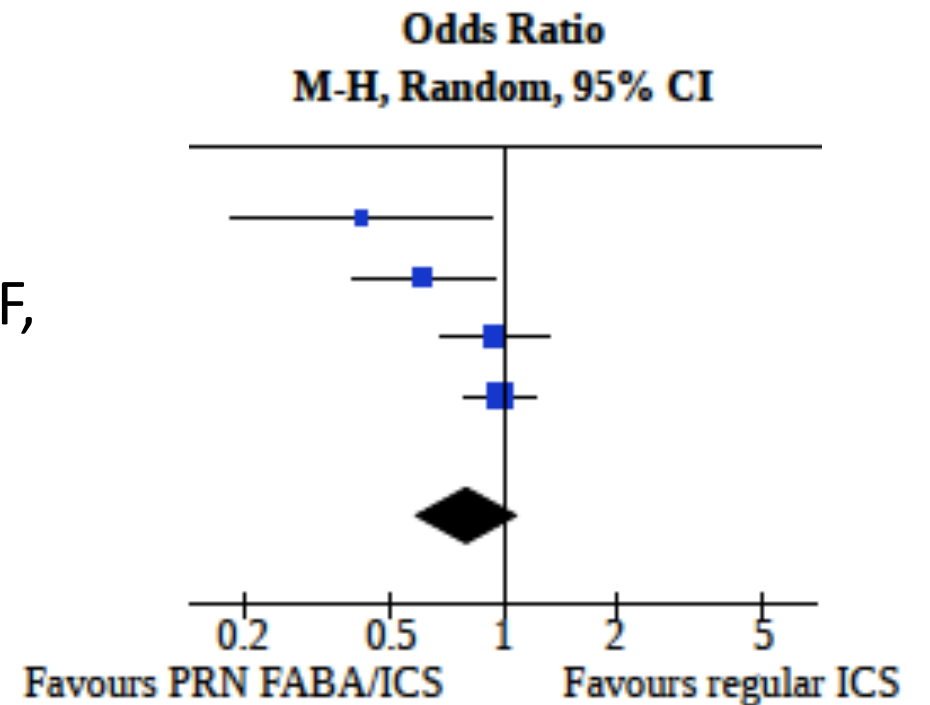
# Mild asthma: ICS/LABA prn vs SABA alone

- 6 studies included, ~10,000 participants
  - SYGMA 1+ 2, PRACTICAL, NovelSTART
- FABA prn vs ICS/FABA prn
  - **Reduced exacerbations by 50%** (high certainty)
  - Reduced ED/UC/hospital admissions (lower certainty)
  - May reduce total systemic steroid dose
  - No difference: symptoms, spirometry, QOL, mortality



# Mild: ICS bid vs ICS/FABA prn

- ICS + prn FABA vs ICS/FABA prn
  - **No clear difference in exacerbations**
  - Possibly lower ED/UC/hospital admission
  - **Reduced average daily steroid exposure**
  - No difference: symptom control, spirometry, PF, QOL, total systemic steroid dose





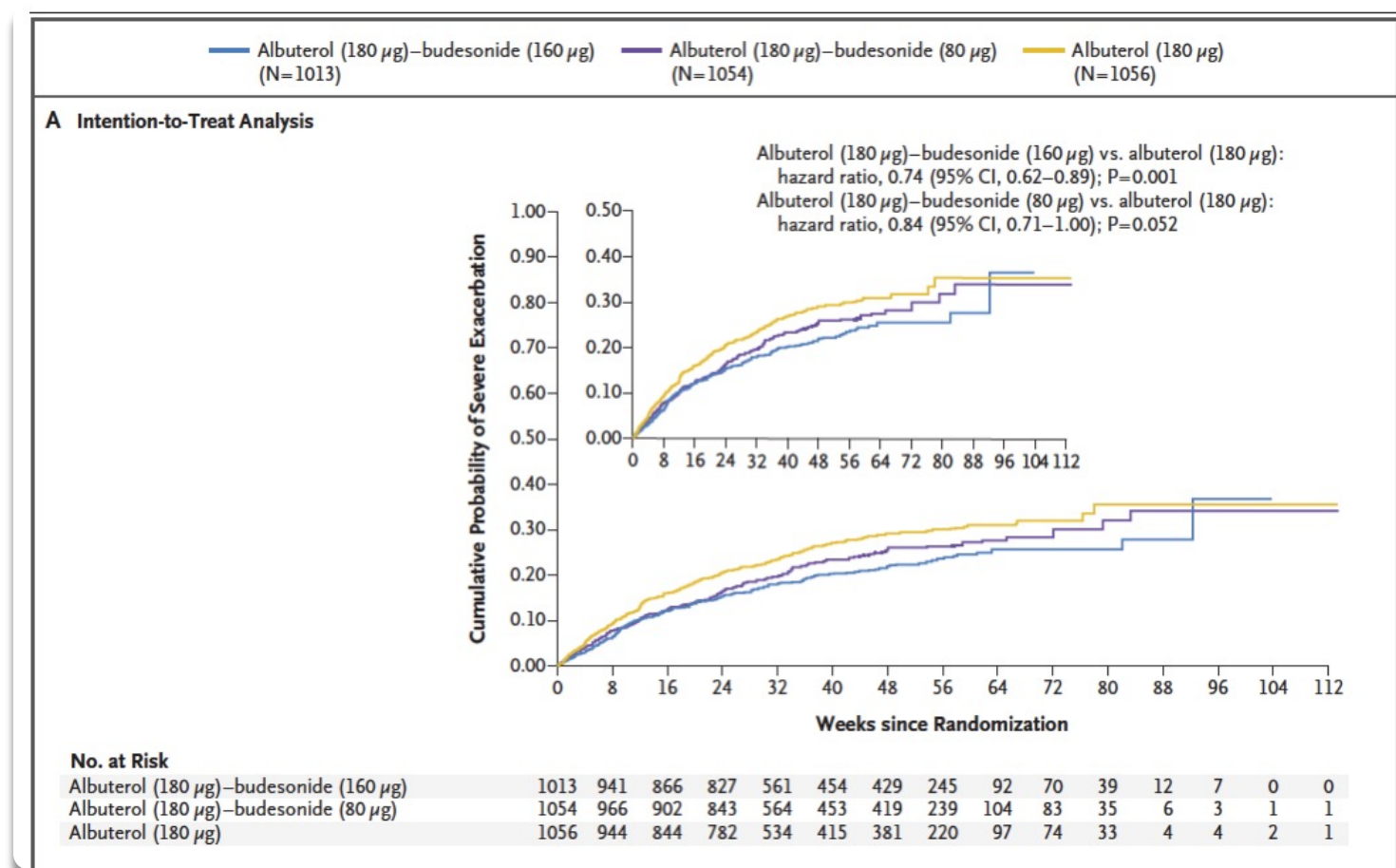
# Barriers to SMART or ICS/LABA prn approach

- Must be ICS-formoterol



# MANDALA trial

- ICS/SABA vs SABA as rescue
- Decreased exacerbations
- Annual dose of systemic steroids 50% higher in SABA alone group



*Airsupra (PT027) approved in the US for asthma*

**albuterol/budesonide (160mcg)**

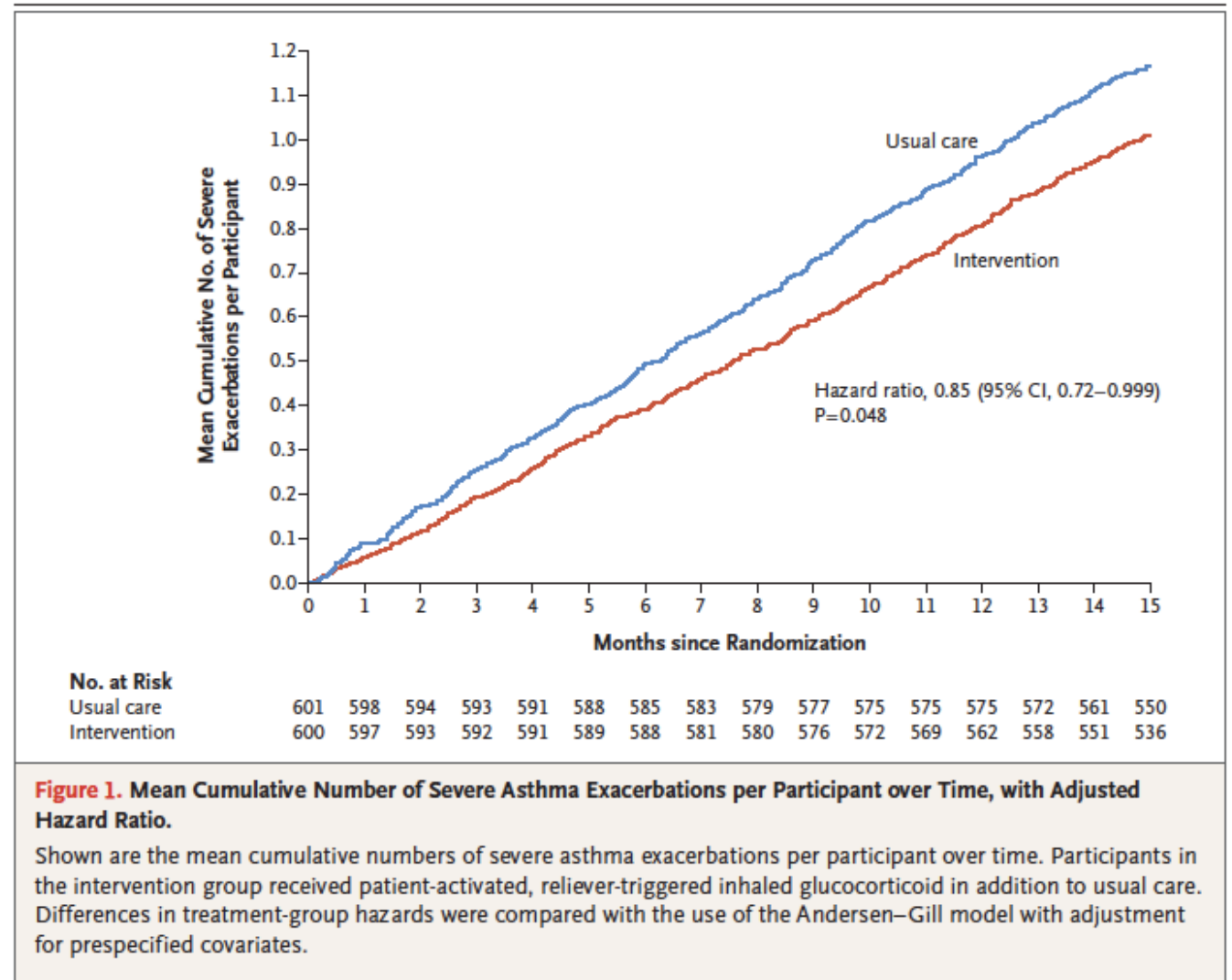
PUBLISHED

11 January 2023

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

# PREPARE: PeRson EmPowered Asthma RElief trial

- Rescue:
  - SABA vs ICS at time of SABA (MDI or neb)
- Decreased exacerbation rates
- Improved asthma control
- Fewer lost work / school days
- Less overall use of rescue medication



# MANDALA and PREPARE trials: What do they add?

- Have a new FDA – approved reliever inhaler (ICS/SABA)
- No need to change baseline controller medication
- Not required to have ICS-formoterol to implement “AIR”
- Can be used for patients who prefer nebulized therapy
  - not included in prior trials
- Easy to implement
  - 1 time instructional meeting was effective
- Shown to be beneficial in groups disproportionately burdened with asthma morbidity



# \*\*\*Principle is the same: BROWNIES!\*\*\*

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

- SMART: Single Maintenance And Reliever Therapy
  - simpler since one overall inhaler
  - BUT restricted to formoterol-containing
    - financial, insurance coverage, change of controller regimen
- 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
- PREPARE:
  - **improved flexibility**, use additional ICS when you need a nebulizer OR MDI for rescue
  - BUT 2 different medications for rescue along with controller



# OTC ICS/LABA

- Model of OTC budesonide-formoterol as rescue vs OTC epinephrine vs no OTC options
- 12,495 fewer deaths
- 14 million severe exacerbations
- \$68 billion saved

**Primatene Mist Epinephrine Inhalation Aerosol, 0.125mg per spray**

★★★★★ 5.0 (314)



**\$32.49**

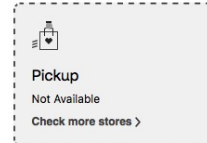
\$64.98 / oz.

Prices may vary from online to in store

Stock at my store

[Check more stores >](#)

How to get it



Eligible for 1 to 4 day shipping. Ships **Free** with \$35+ orders

[Shipping details >](#)

Limit 15 per order

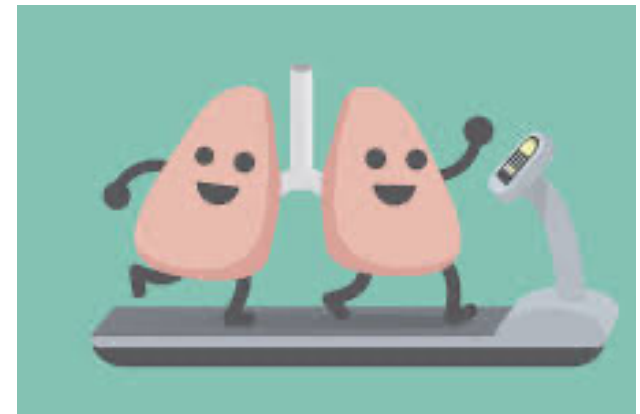
Quantity

1

**Add for shipping**

# Goals of asthma treatment

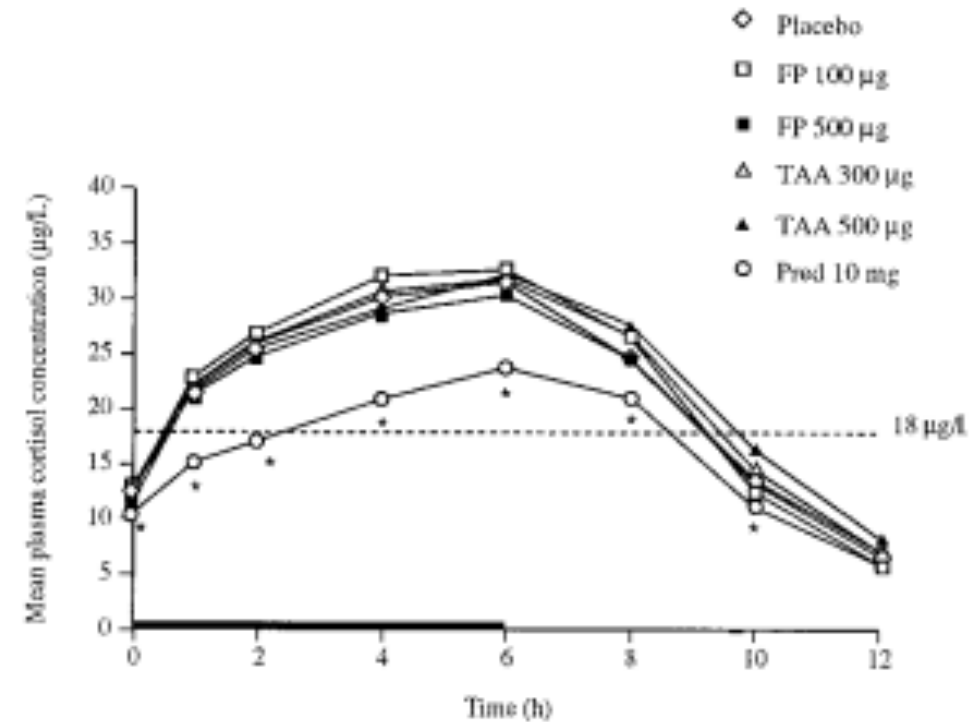
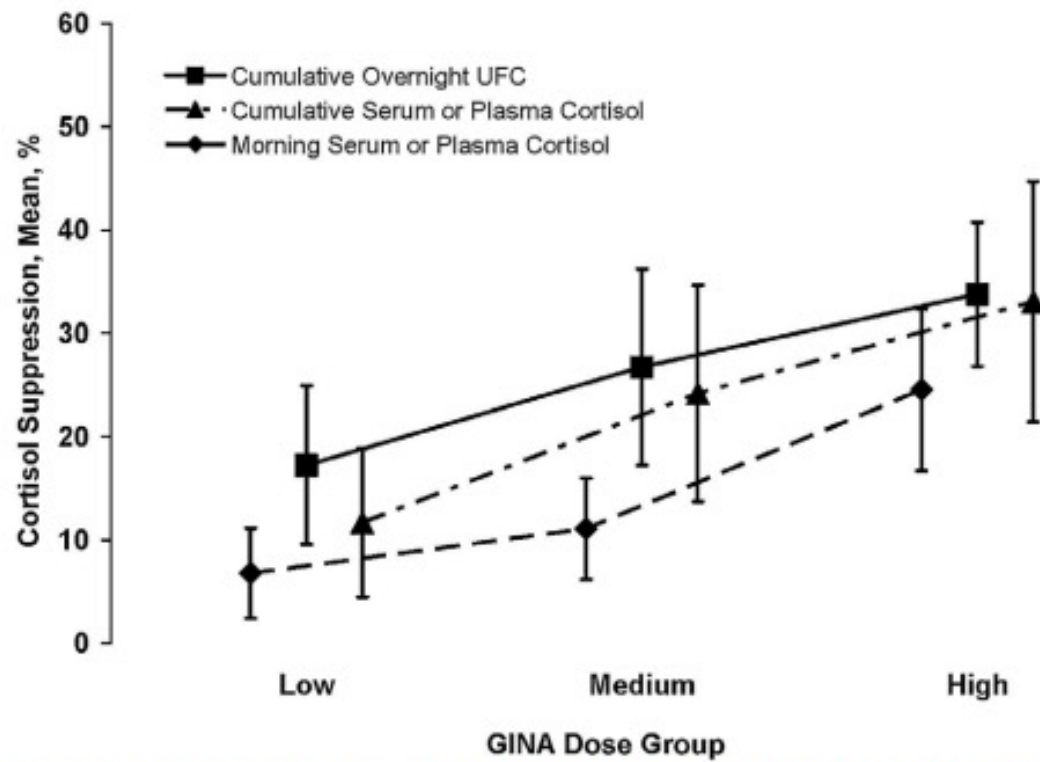
- ✓ • Reduce mortality
- ✓ • Reduce exacerbations:
  - hospitalizations / ED / UC / systemic steroids
- ✓ • Reduce symptoms, interference with normal life / activity
  - Improve quality of life
- ✓ • Minimize side effects of treatment



# Part IV: Disadvantages of AIR



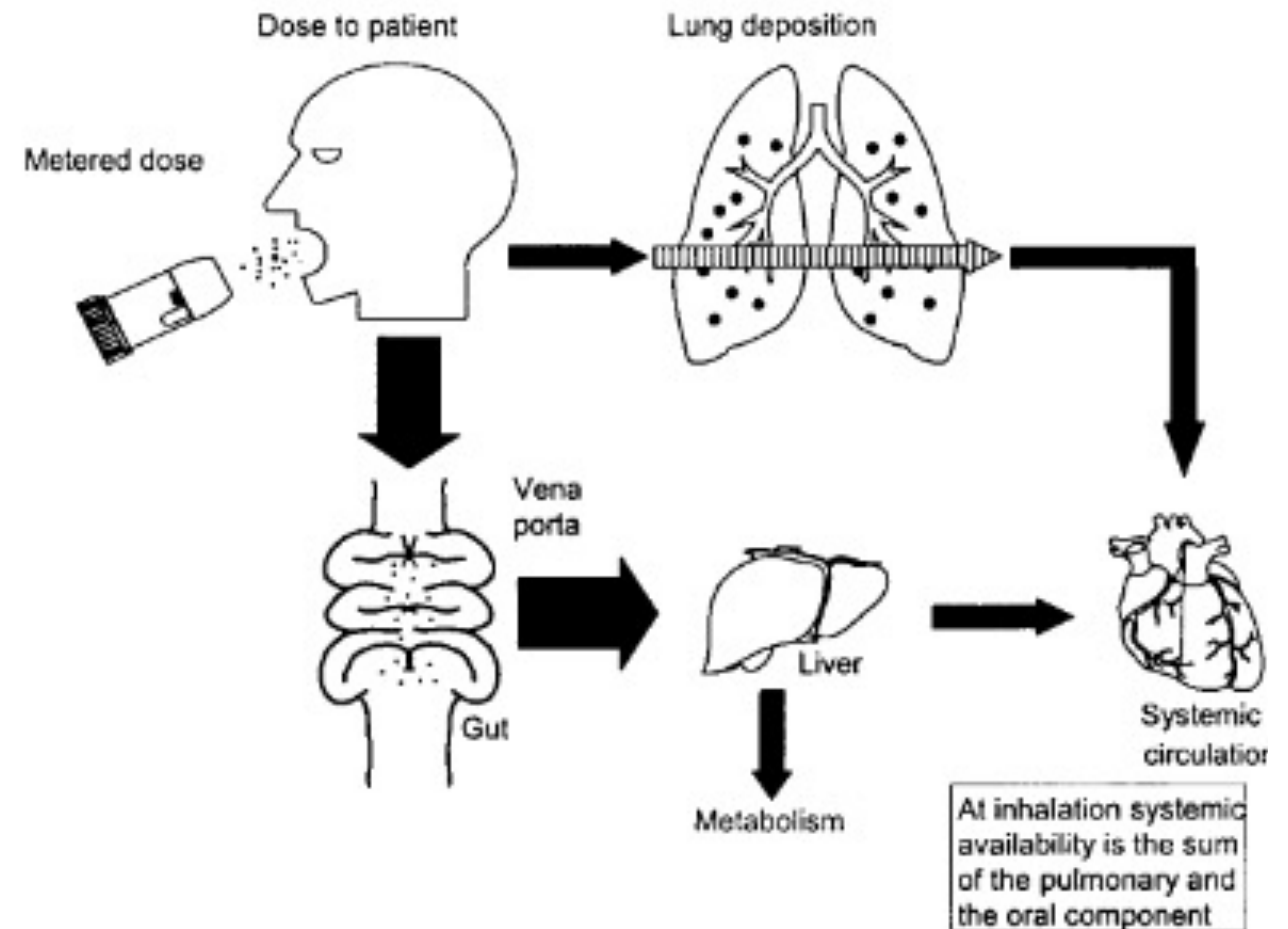
# HPA suppression by ICS



**FIG. 2.** Effect of placebo, fluticasone propionate (FP; 100 and 500 µg twice daily), triamcinolone acetonide (TAA; 300 and 500 µg twice daily), and prednisone (Pred; 10 mg daily) on plasma cortisol levels in asthma patients (data on file, Glaxo Wellcome).

# ICS risks

- Infection (pneumonia)
- Oral thrush
- Hoarseness
- Cost ..?
- Growth in children
- HPA suppression

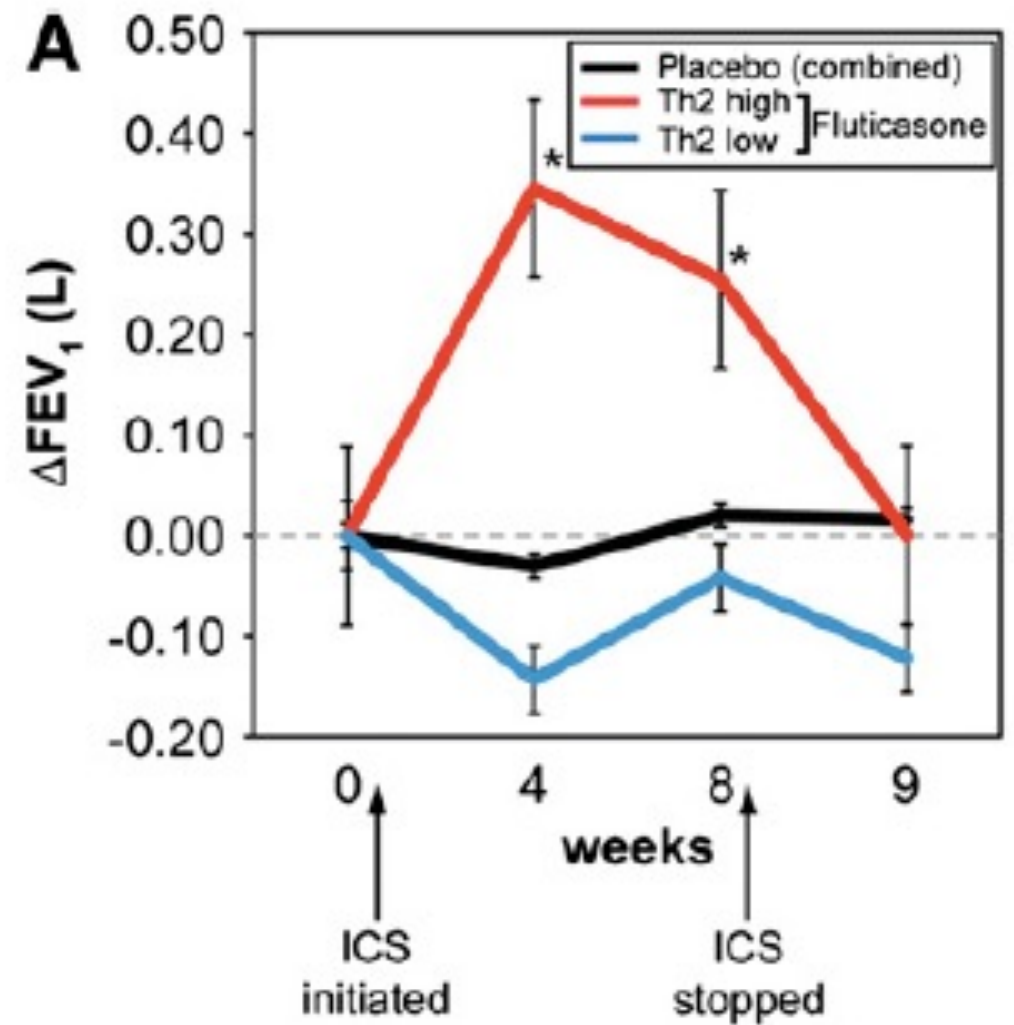




# Non “type 2 high” asthma and ICS

	Eos <3%	Eos ≥3%
Number	9	14
Age (years)	53	45
Male	5	11
Atopy	2	8
Current smoker	3	1
ΔFEV <sub>1</sub> (mL)	100 (-193 to 394)	142 (-5 to 289)
ΔSymptom VAS (mm)	-0.7 (15.4 to -16.8)	-24.4 (-12.5 to -36.3)
ΔPEF amplitude % mean	-3.2 (4.3 to -10.7)	-7.0 (-2.5 to -11.6)
ΔPC <sub>20</sub> (doubling doses)	0 (-1.2 to 1.2)	2.1 (1.3 to 3.0)
Decrease sputum eos (fold)	1.6 (0.98 to 2.7)	7.1 (3.7 to 13.5)

**Patient details with mean (95% CI) change in measures after treatment with budesonide in those stratified according to sputum eosinophil (eos) count**

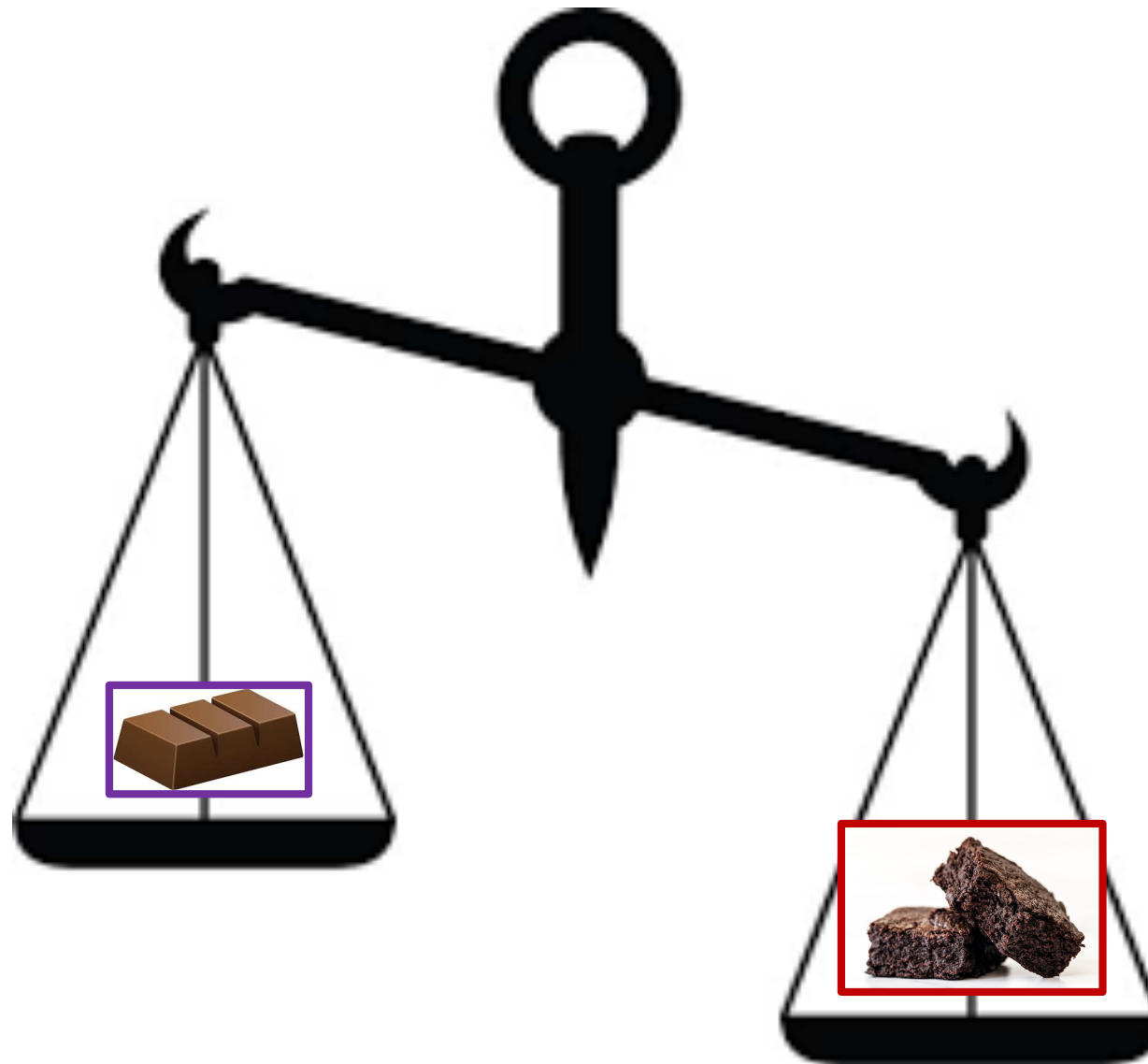


Pavord Lancet 1999

Woodruff AJRCCM 2009



SABA



AIR:

ICS/LABA

ICS/SABA

ICS at time of SABA

Decreased

- Exacerbations
- Overall steroid dose
- Symptoms

Thank You!

