# Recent Evidence about Anti-inflammatory Reliever (AIR)

HWANG KIEUN

Department of internal medicine, Wonkwang university school of medicine

원광대학교병원
WONKWANG UNIVERSITY HOSPITAL

- Anti-inflammatory Reliever (AIR)
  - Terminology
- 2023 GINA update
- Asthma management
  - Track 1
  - Track 2

# Terminology

- Reliever
  - For symptom relief, or before exercise or allergen exposure
- Controller
  - Function: targets both domains of asthma control (symptom control and future risk)
  - Mostly used for ICS-containing treatment
- Maintenance treatment
  - Frequency: regularly scheduled, e.g. twice daily

ICS: inhaled corticosteroid; SABA: short-acting beta$_2$-agonist

# The risks of ‘mild’ asthma

- Patients with apparently mild asthma are still at risk of serious adverse events
  - 30–37% of adults with acute asthma
  - 16% of patients with near-fatal asthma
  - 15–27% of adults dying of asthma

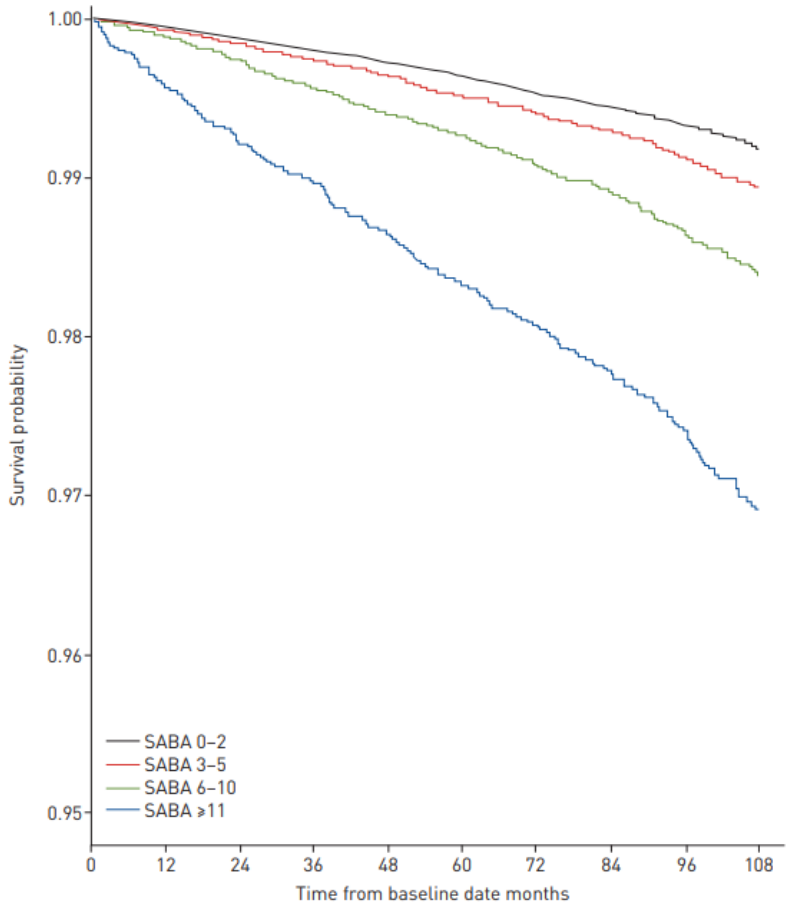
  } had symptoms less than weekly in previous 3 months *(Dusser, Allergy 2007; Bergstrom, 2008)*

- Exacerbation triggers are unpredictable (viruses, pollens, pollution, poor adherence)
- Even 4–5 lifetime OCS courses increase the risk of osteoporosis, diabetes, cataract *(Price et al, J Asthma Allerg 2018)*

SABA: short-acting beta$_2$-agonist

# Why not treat with SABA alone?

- Inhaled SABA has been first-line treatment for asthma for 50 years
  - Asthma was thought to be a disease of bronchoconstriction
  - Role of SABA reinforced by rapid relief of symptoms and low cost
- Regular use of SABA, even for 1–2 weeks, is associated with increased AHR, reduced bronchodilator effect, increased allergic response, increased eosinophils *(e.g. Hancox, 2000; Aldridge, 2000)*
  - Can lead to a vicious cycle encouraging overuse
  - Over-use of SABA associated with ↑ exacerbations and ↑ mortality *(e.g. Suissa 1994, Nwaru 2020)*




| 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 $\beta_2$-agonist (SABA) use.

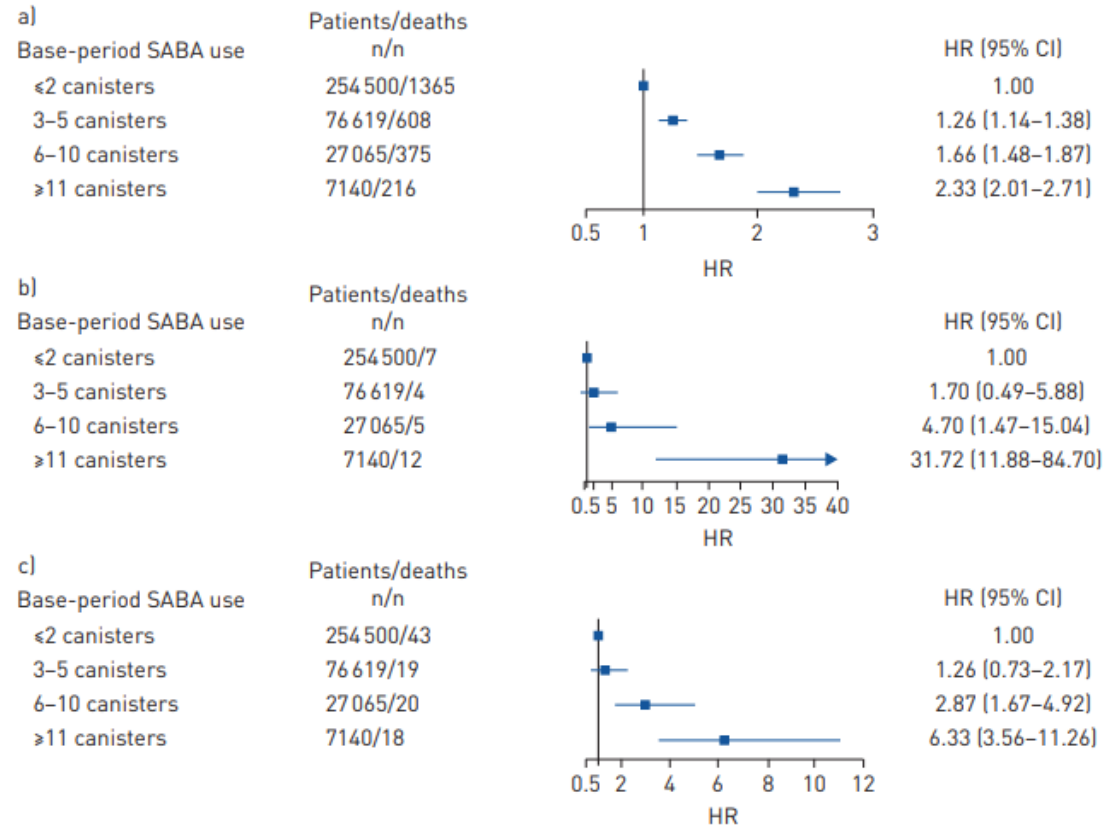



FIGURE 5 Association between baseline short-acting $\beta_2$-agonist (SABA) use and risk of mortality. a) Overall mortality; b) asthma-related mortality; c) respiratory-related mortality. Adjusted for treatment step, Charlson Comorbidity Index, sex and age. ⩽2 canisters: patients collecting two or fewer SABA canisters during the baseline year; ⩾3 canisters: patients collecting three or more SABA canisters during the baseline year; HR: hazard ratio.

*Eur Respir J. 2020 Apr 16;55(4):1901872*

# Why not treat with SABA alone?

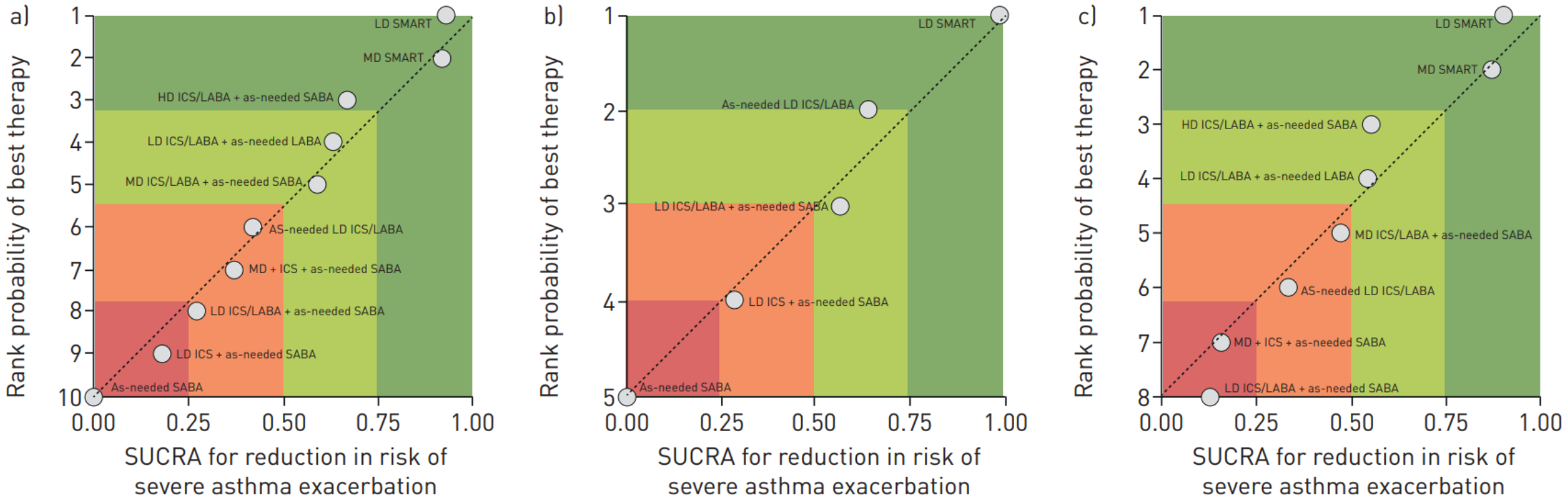
- Starting treatment with SABA trains the patient to regard it as their primary asthma treatment
- The only previous option was daily ICS even when no symptoms, but adherence is extremely poor
- GINA changed its recommendation once evidence for a safe and effective alternative was available

**TABLE I.** Risk of severe asthma exacerbations with ICS/formoterol reliever vs SABA reliever according to maintenance treatment

| | |
|---|---|
| ICS/formoterol alone vs SABA alone[14] | OR, 0.45; 95% CI, 0.34- 0.60 |
| ICS/formoterol alone vs low-dose ICS plus SABA[14] | OR, 0.79; 95% CI, 0.59- 1.07 |
| ICS/formoterol SMART vs same-dose ICS plus SABA[13] | RR, 0.64; 95% CI, 0.53- 0.78 |
| ICS/formoterol SMART vs 2× dose ICS plus SABA[13] | RR, 0.59; 95% CI, 0.49- 0.71 |
| ICS/formoterol SMART vs same-dose ICS/LABA plus SABA[13] | RR, 0.68; 95% CI, 0.58- 0.80 |
| ICS/formoterol SMART vs 2× dose ICS/LABA plus SABA[13] | RR, 0.77; 95% CI, 0.60- 0.98 |

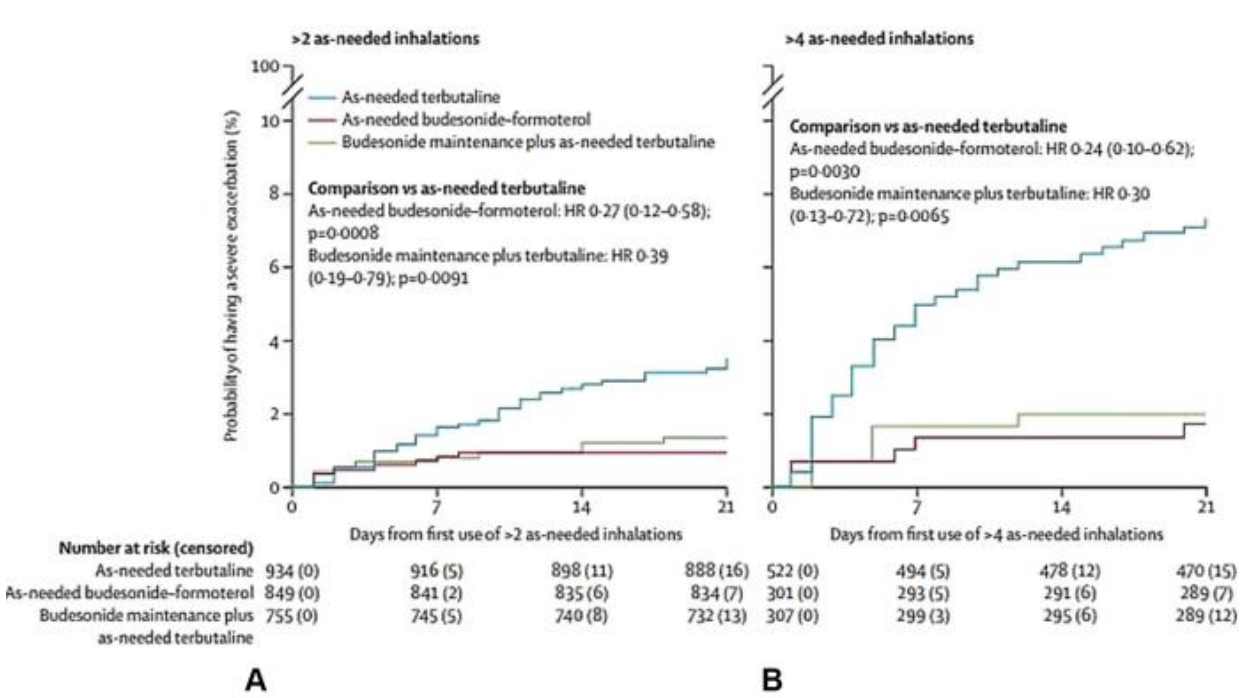
*OR*, Odds ratio; *RR*, risk ratio.

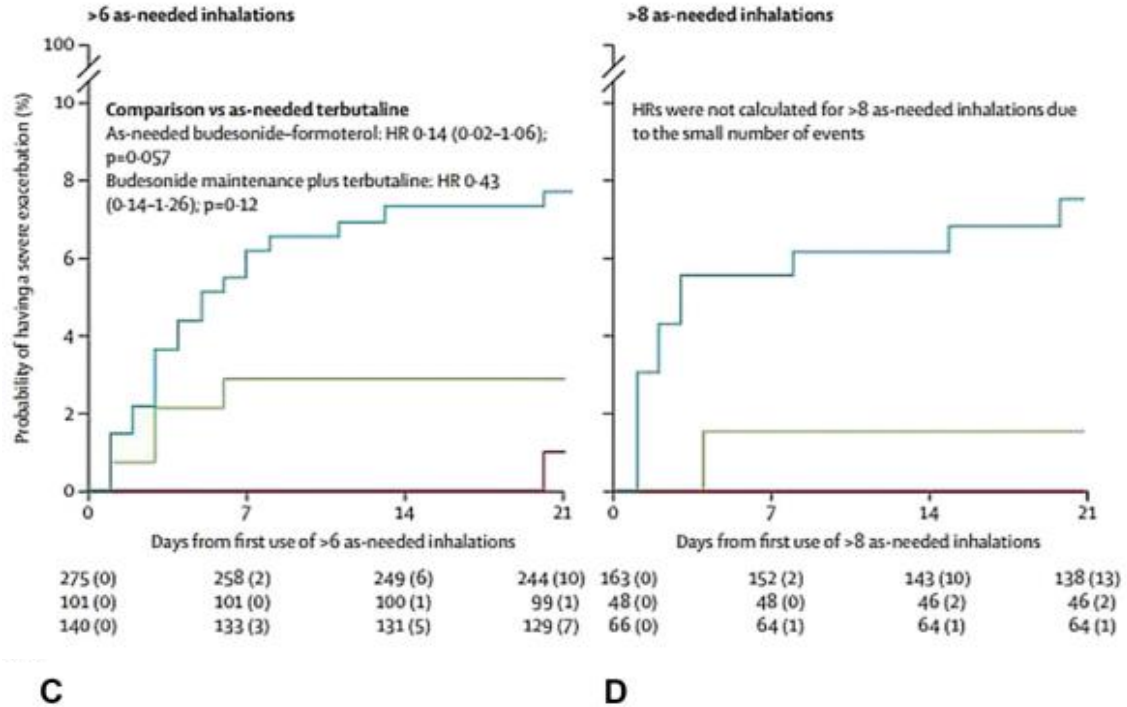
*J Allergy Clin Immunol Pract. 2023 Mar;11(3):762-772.e1*




Overall ranking plot displaying the efficacy of as-needed therapies in preventing the risk of severe exacerbation in asthmatic patients (a) and subset analyses on adult mild-to-moderate (b) and moderate-to-severe (c) asthmatic patients.

*Eur Respir J. 2020 Sep 10;56(3):2000625*




*J Allergy Clin Immunol Pract. 2023 Mar;11(3):762-772.e1*

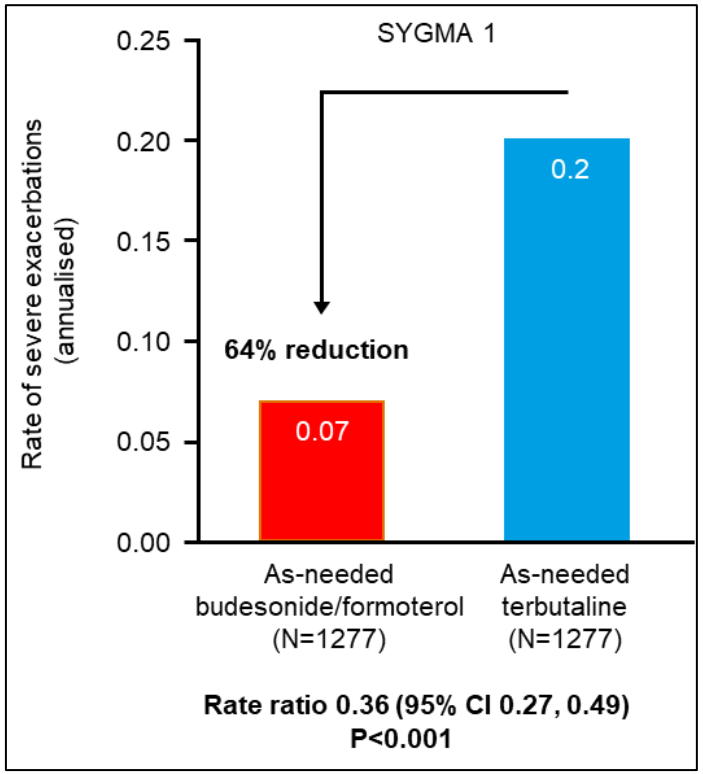
# As-needed low dose ICS-formoterol in mild asthma (n=9,565)

## COMPARED WITH AS-NEEDED SABA

- The risk of severe exacerbations was reduced by 60–64% (SYGMA 1, Novel START)

## COMPARED WITH MAINTENANCE LOW DOSE ICS

- The risk of severe exacerbations was similar (SYGMA 1 & 2), or lower (Novel START, PRACTICAL)
- Small differences in other asthma outcomes, favoring maintenance ICS, but all were less than the minimal clinically important difference
  - ACQ-5 mean difference 0.15 (MCID 0.5)
  - $FEV_1$ mean difference ~54 mL
  - FeNO mean difference ~10ppb (Novel START, PRACTICAL)
  - No evidence of progressive worsening over 12 months
- In Novel START and PRACTICAL, outcomes were independent of baseline features including blood eosinophils, FeNO, lung function, and exacerbation history
- Average ICS dose was ~50–100mcg budesonide/day




*O'Byrne et al, NEJM 2018*

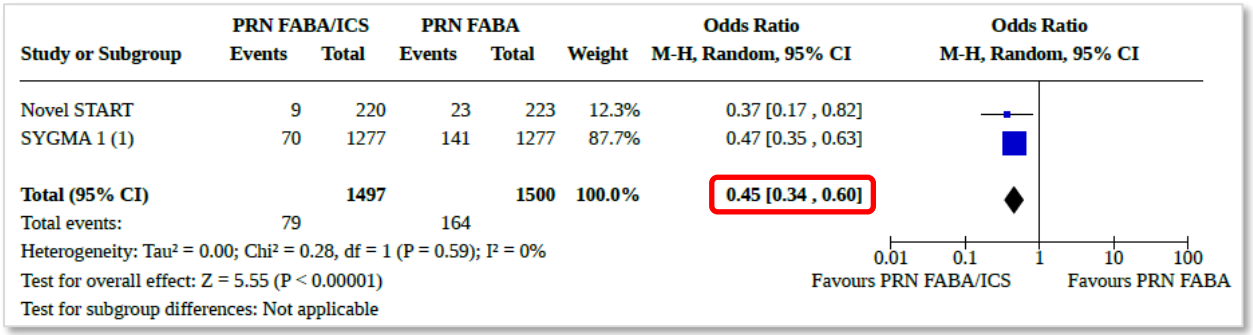
*Budesonide-formoterol 200/6 mcg, 1 inhalation as needed for symptom relief

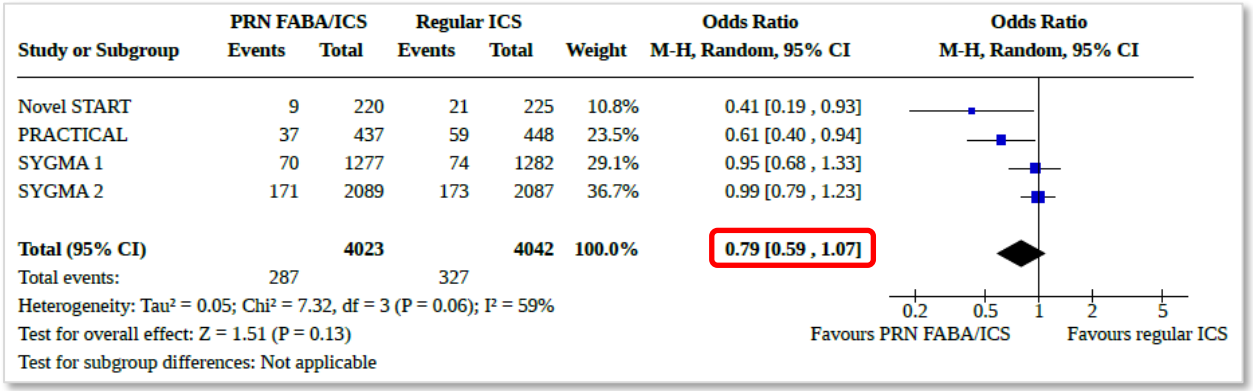
# New evidence for as-needed ICS-formoterol in mild asthma

- Meta-analysis of all four RCTs, n=9,565

  *(Crossingham, Cochrane 2021)*

  - 55% reduction in severe exacerbations compared with SABA alone
  - Similar risk of severe exacerbations as with daily ICS + as-needed SABA



# New evidence for as-needed ICS-formoterol in mild asthma

- Meta-analysis of four all RCTs, n=9,565

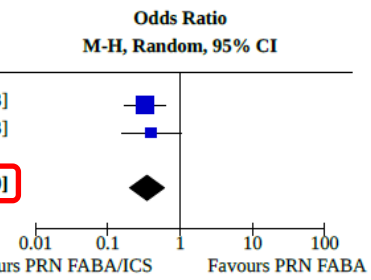
  *(Crossingham, Cochrane 2021)*

  - ED visits or hospitalizations
    - 65% lower than with SABA alone
    - 37% lower than with daily ICS

**Analysis 1.3. Comparison 1: As required fixed dose combination inhaler versus as required short acting beta agonist, Outcome 3: Exacerbations requiring hospital admission or emergency department / urgent care visit**

| Study or Subgroup | PRN FABA/ICS Events | PRN FABA/ICS Total | PRN FABA Events | PRN FABA Total | Weight | Odds Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Novel START (1) | 13 | 220 | 36 | 223 | 67.2% | 0.33 [0.17 , 0.63] |
| SYGMA 1 | 6 | 1277 | 15 | 1277 | 32.8% | 0.40 [0.15 , 1.03] |
| **Total (95% CI)** | | **1497** | | **1500** | **100.0%** | **0.35 [0.20 , 0.60]** |
| Total events: | 19 | | 51 | | | |

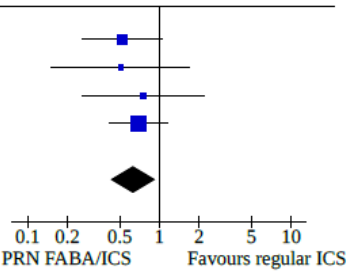
Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 1 (P = 0.74); I² = 0%
Test for overall effect: Z = 3.80 (P = 0.0001)
Test for subgroup differences: Not applicable




**Analysis 2.3. Comparison 2: Fixed dose combination inhaler as required versus regular inhaled steroid plus as required short acting beta agonist, Outcome 3: Exacerbations requiring hospital admission or emergency department / urgent care visit**

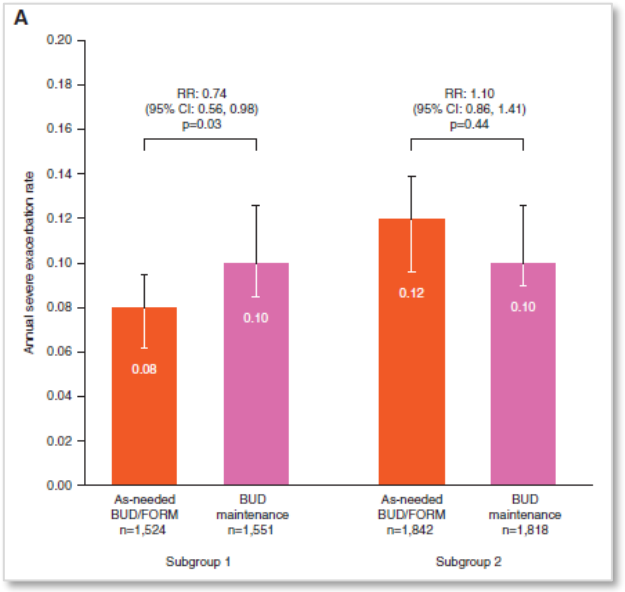
| Study or Subgroup | PRN FABA/ICS Events | PRN FABA/ICS Total | Regular ICS Events | Regular ICS Total | Weight | Odds Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Novel START | 13 | 220 | 24 | 225 | 27.4% | 0.53 [0.26 , 1.06] |
| PRACTICAL | 4 | 437 | 8 | 448 | 9.3% | 0.51 [0.15 , 1.70] |
| SYGMA 1 | 6 | 1277 | 8 | 1282 | 12.0% | 0.75 [0.26 , 2.17] |
| SYGMA 2 | 25 | 2089 | 36 | 2087 | 51.3% | 0.69 [0.41 , 1.15] |
| **Total (95% CI)** | | **4023** | | **4042** | **100.0%** | **0.63 [0.44 , 0.91]** |
| Total events: | 48 | | 76 | | | |

Heterogeneity: Tau² = 0.00; Chi² = 0.60, df = 3 (P = 0.90); I² = 0%
Test for overall effect: Z = 2.47 (P = 0.01)
Test for subgroup differences: Not applicable

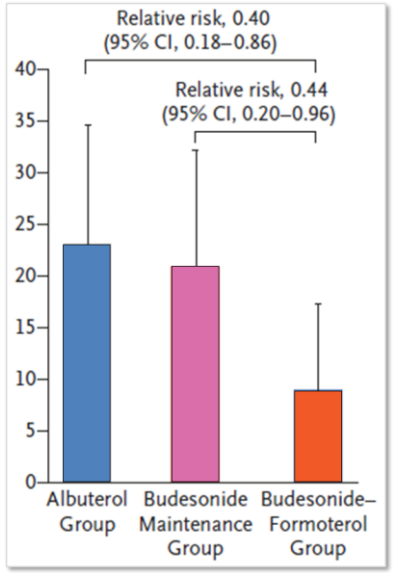


# New evidence for as-needed ICS-formoterol in mild asthma

- Analysis by previous treatment
  - Patients taking SABA alone had lower risk of severe exacerbations with as-needed ICS-formoterol compared with daily ICS + as-needed SABA *(Bateman, Annals ATS 2021; Beasley, NEJMed 2019)*




*Bateman 2021*




*Beasley 2019*

**Box 3-4. Terminology for asthma medications**

| Term | Definition | Notes |
|---|---|---|
| **Maintenance treatment** | Asthma treatment that is prescribed for use every day (or on a regularly scheduled basis) | Medications intended to be used continuously, even when the person does not have asthma symptoms. Examples include ICS-containing medications (ICS, ICS-LABA, ICS-LABA-LAMA), as well as LTRA and biologic therapy.<br>The term 'maintenance' describes the prescribed frequency of administration, not a particular class of asthma medicine. |
| **Controller** | Medication targeting both domains of asthma control (symptom control and future risk) | In the past, 'controller' was largely used for ICS-containing medications prescribed for regular daily treatment, so 'controller' and 'maintenance' became almost synonymous. However, this became confusing after the introduction of combination ICS-containing relievers for as-needed use.<br>To avoid confusion, 'ICS-containing treatment' and 'maintenance treatment' have been substituted as appropriate where the intended meaning was unclear. |
| **Reliever** | Asthma inhaler taken as needed, for quick relief of asthma symptoms | Sometimes called rescue inhalers. As well as being used for symptom relief, reliever inhalers can also be used before exercise, to prevent exercise-induced asthma symptoms.<br>Includes SABAs (e.g., salbutamol [albuterol], terbutaline, ICS-salbutamol), as-needed ICS-formoterol, and as-needed ICS-SABA.<br>SABA-containing relievers are not intended for regular maintenance use, or to be taken when the person does not have asthma symptoms (except before exercise). |
| **Anti-inflammatory reliever (AIR)** | Reliever inhaler that contains both a low-dose ICS and a rapid-acting bronchodilator | Includes budesonide-formoterol, beclometasone-formoterol and ICS-salbutamol combinations. Patients can also use them as needed before exercise or allergen exposure to prevent asthma symptoms and bronchoconstriction. Non-formoterol LABAs in combination with ICS cannot be used as relievers.<br>The anti-inflammatory effect of as-needed ICS-formoterol was demonstrated by reduction in FeNO in several studies.[171,172,195]<br>Some anti-inflammatory relievers can be used as-needed at Steps 1–2 as the person's sole asthma treatment, without a maintenance treatment ('**AIR-only**' treatment). Almost all evidence for this is with ICS-formoterol. Some ICS-formoterol combinations can be used as both maintenance treatment and reliever treatment at Steps 3–5 (see **MART**, below). For medications and doses see Box 3-15, p.80. |
| **Maintenance-and-reliever therapy (MART)** | Treatment regimen in which the patient uses an ICS-formoterol inhaler every day (maintenance dose), and also uses the same medication as needed for relief of asthma symptoms (reliever doses) | MART (**M**aintenance **A**nd **R**eliever **T**herapy) can be used only with combination ICS-formoterol inhalers such as budesonide-formoterol and beclometasone-formoterol. Other ICS-formoterol inhalers can also potentially be used, but combinations of ICS with non-formoterol LABAs, or ICS-SABA, cannot be used for MART. MART is also sometimes called SMART (single-inhaler maintenance and reliever therapy); the meaning is the same. For medications and doses see Box 3-15, p.80. |

See list of abbreviations (p.10).

# Terminology

- **A**nti-**I**nflammatory **R**eliever = **AIR**
  - e.g. ICS-formoterol, ICS-SABA
  - Provides rapid symptom relief, plus a small dose of ICS
  - Reduces the risk of exacerbations, compared with using a SABA reliever

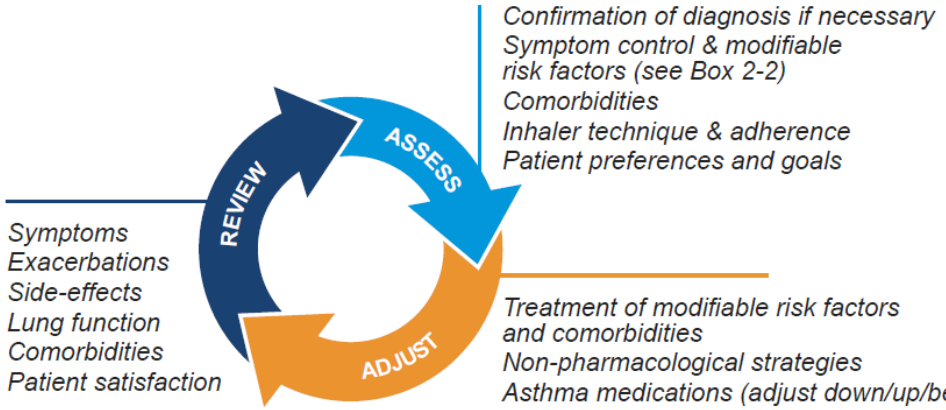
## Regimens with ICS-formoterol anti-inflammatory reliever

- As-needed-only ICS-formoterol = **AIR-only**
  - The patient takes low-dose ICS-formoterol whenever needed for symptom relief
- **M**aintenance **A**nd **R**eliever **T**herapy with ICS-formoterol = **MART**
  - A low dose of ICS-formoterol is used as the patient's maintenance treatment, plus whenever needed for symptom relief
- ICS-formoterol can also be used before exercise or allergen exposure

ICS: inhaled corticosteroid: SABA: short-acting beta$_2$-agonist; MART is sometimes also called SMART

# GINA 2023 – Adults & adolescents 12+ years

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




**TRACK 1: PREFERRED CONTROLLER and RELIEVER**
Using ICS-formoterol as the reliever* reduces the risk of exacerbations compared with using a SABA reliever, and is a simpler regimen

| STEPS 1 – 2 | STEP 3 | STEP 4 | STEP 5 |
|---|---|---|---|
| As-needed-only low dose ICS-formoterol | Low dose maintenance ICS-formoterol | Medium dose maintenance ICS-formoterol | Add-on LAMA<br>Refer for assessment of phenotype. Consider high dose maintenance ICS-formoterol, ± anti-IgE, anti-IL5/5R, anti-IL4Rα, anti-TSLP |
| RELIEVER: As-needed low-dose ICS-formoterol* | | | |

*See GINA severe asthma guide*

**TRACK 2: Alternative CONTROLLER and RELIEVER**
Before considering a regimen with SABA reliever, check if the patient is likely to adhere to daily controller treatment

| STEP 1 | STEP 2 | STEP 3 | STEP 4 | STEP 5 |
|---|---|---|---|---|
| Take ICS whenever SABA taken* | Low dose maintenance ICS | Low dose maintenance ICS-LABA | Medium/high dose maintenance ICS-LABA | Add-on LAMA<br>Refer for assessment of phenotype. Consider high dose maintenance ICS-LABA, ± anti-IgE, anti-IL5/5R, anti-IL4Rα, anti-TSLP |
| RELIEVER: as-needed ICS-SABA*, or as-needed SABA | | | | |

| | | | | |
|---|---|---|---|---|
| *Other controller options (limited indications, or less evidence for efficacy or safety – see text)* | *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* |

*Anti-inflammatory reliever (AIR)

# GINA 2023 – Adults and adolescents
# Track 1

Maintenance and reliever therapy (MART) with ICS-formoterol

As-needed-only ICS-formoterol ('AIR-only')

**TRACK 1: PREFERRED CONTROLLER and RELIEVER**
Using ICS-formoterol as the reliever* reduces the risk of exacerbations compared with using a SABA reliever, and is a simpler regimen

**STEPS 1 – 2**
As-needed-only low dose ICS-formoterol*

**STEP 3**
Low dose maintenance ICS-formoterol*

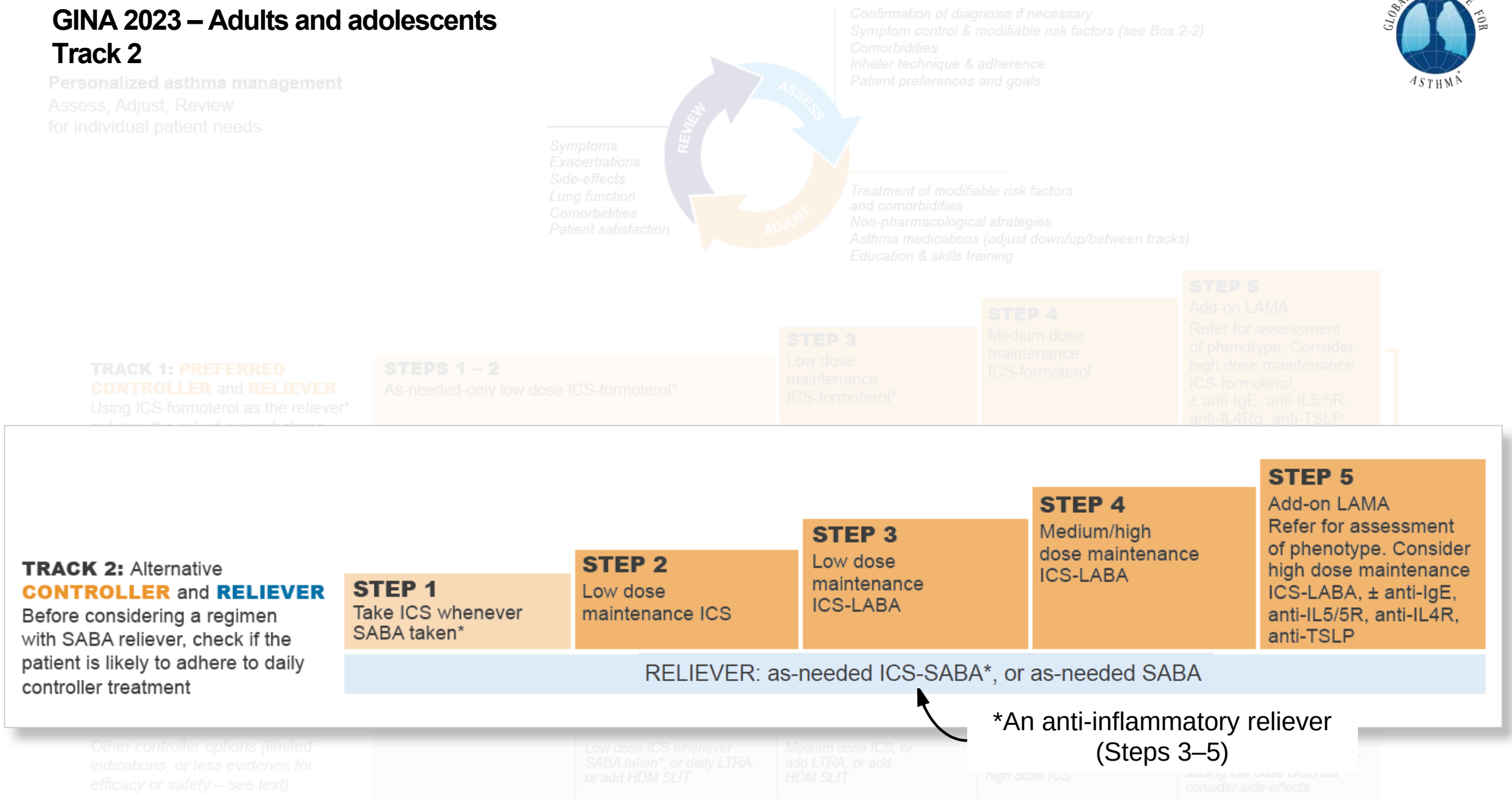
**STEP 4**
Medium dose maintenance ICS-formoterol

**STEP 5**
Add-on LAMA
Refer for assessment of phenotype. Consider high dose maintenance ICS-formoterol, ± anti-IgE, anti-IL5/5R, anti-IL4Rα, anti-TSLP

RELIEVER: As-needed low-dose ICS-formoterol*

*An anti-inflammatory reliever (AIR)

# GINA 2023 – Adults and adolescents
# Track 2



# Step 1:  low-dose combination ICS-formoterol, taken as needed for relief of symptoms, and, if needed, before exercise (Track 1)

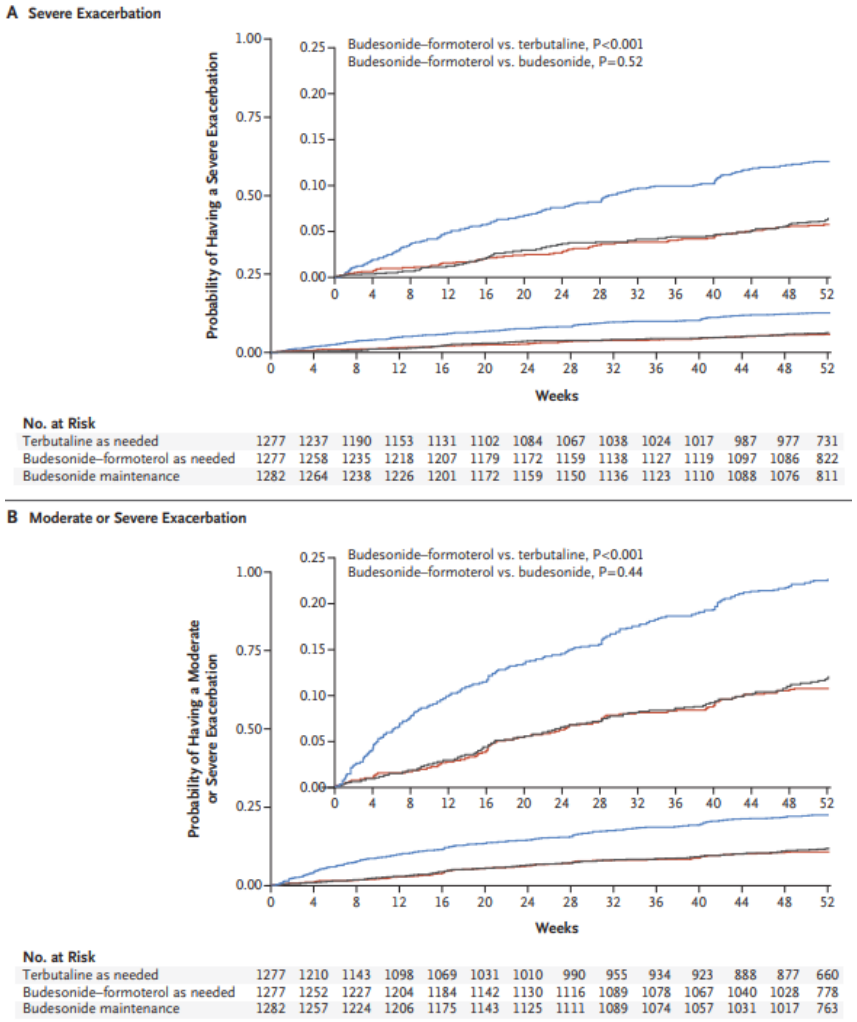
Population: GINA step 1 recommendations are for:

- Initial asthma treatment in patients with symptoms less than twice a month and no exacerbation risk factors, a group that is rarely studied
- Step-down treatment for patients whose asthma is well controlled on regular ICS or LTRA

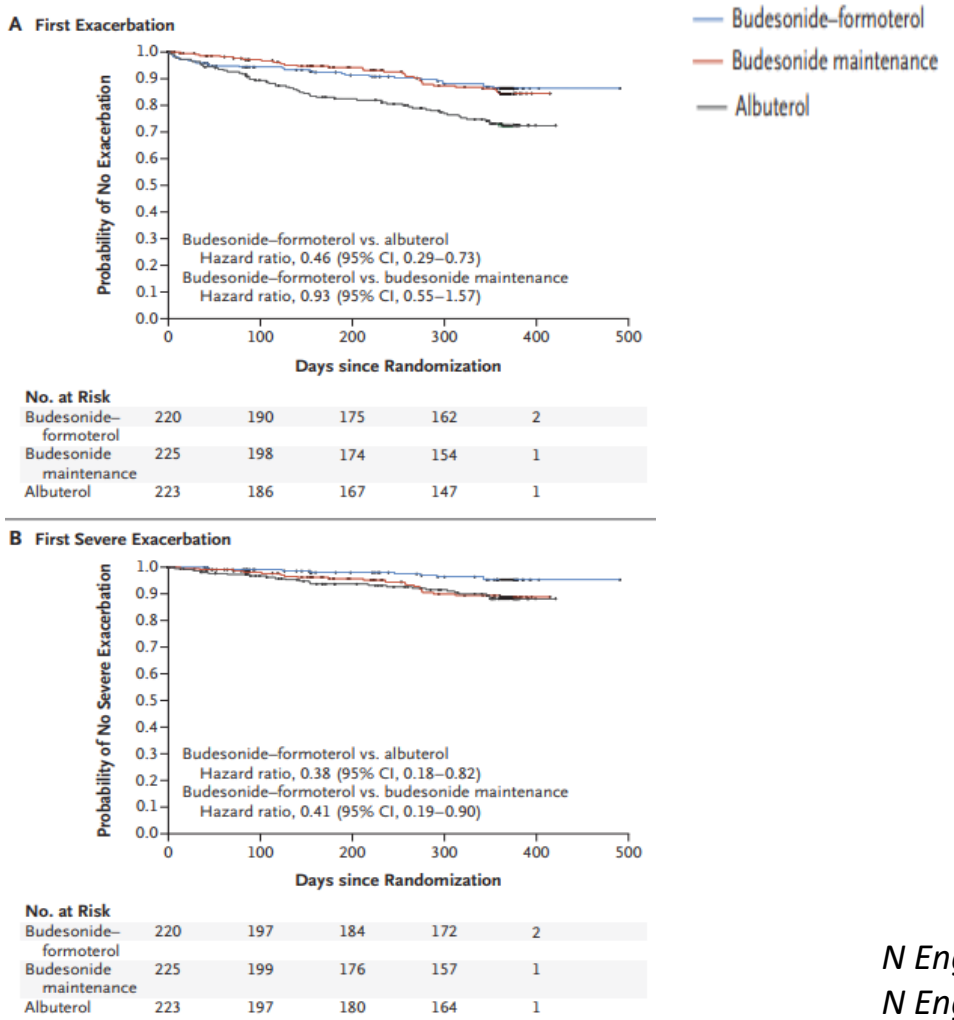
<u>In track 1, the preferred treatment (as-needed ICS-formoterol) is the same for Step 1 and 2.</u>

# Step 1: low-dose combination ICS-formoterol, taken as needed for relief of symptoms, and, if needed, before exercise (Track 1)

## SYGMA 1



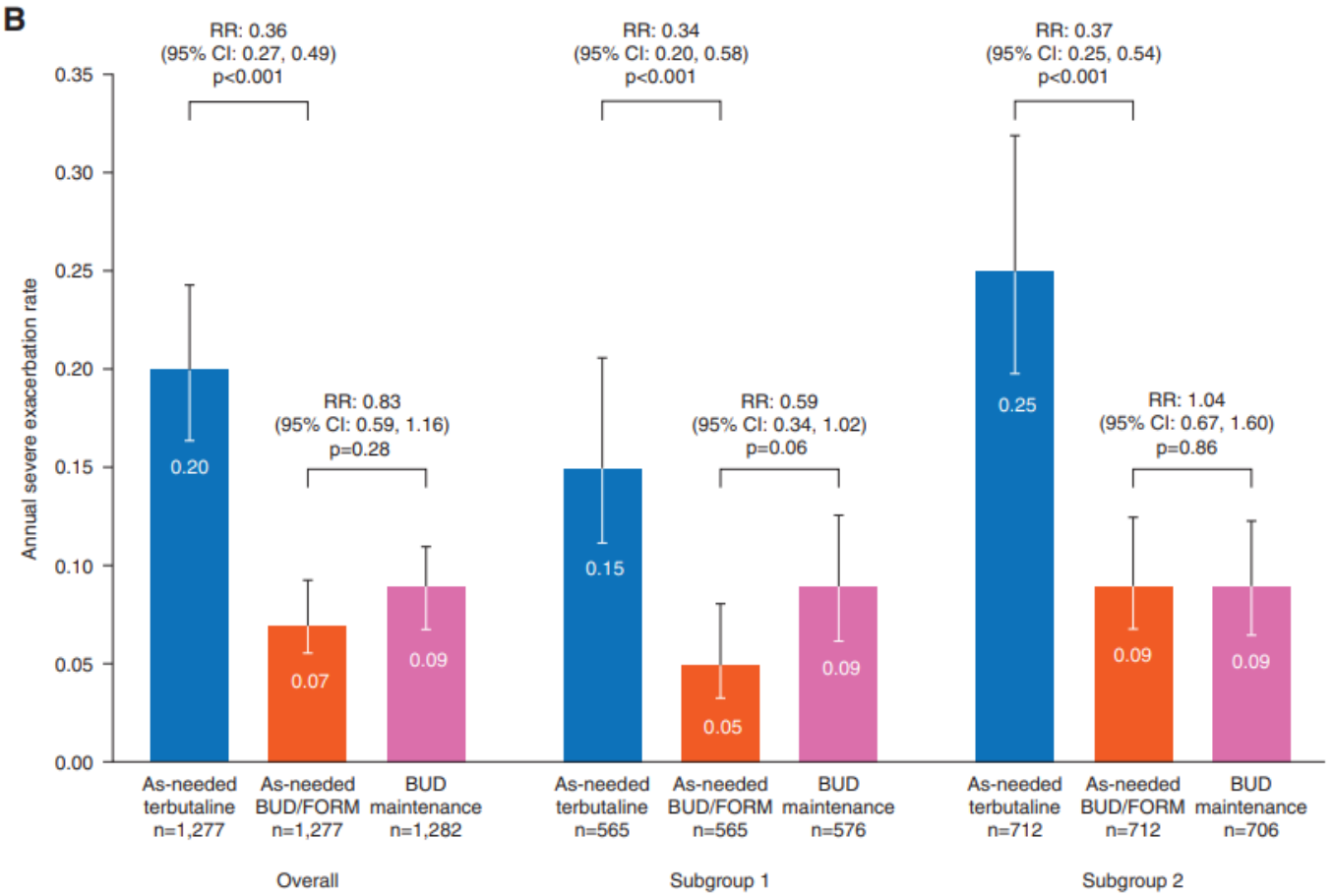

## Novel START Study




*N Engl J Med 2018;378:1865-76*
*N Engl J Med 2019;380:2020-30*

# Step 1: low-dose combination ICS-formoterol, taken as needed for relief of symptoms, and, if needed, before exercise (Track 1)

**Pooled Analysis of SYGMA 1 and 2**




*Ann Am Thorac Soc. 2021 Dec;18(12):2007-2017*

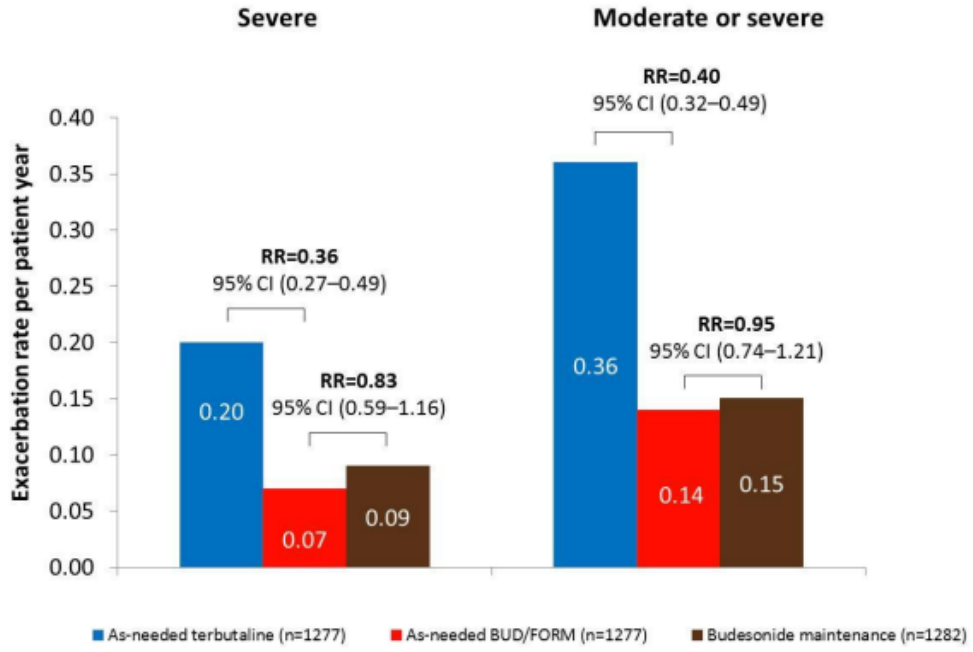
# Step 2:  low-dose combination ICS-formoterol, taken as needed for relief of symptoms, and, if needed, before exercise (Track 1)

- Population: patients enrolled in these studies were considered by their physicians to have mild asthma, with symptoms or SABA use up to twice a day on SABA alone or regular ICS or LTRA plus as-needed SABA
- The current evidence for this treatment in step 2 is with low-dose budesonide-formoterol.

# Step 2: low-dose combination ICS-formoterol, taken as needed for relief of symptoms, and, if needed, before exercise (Track 1)

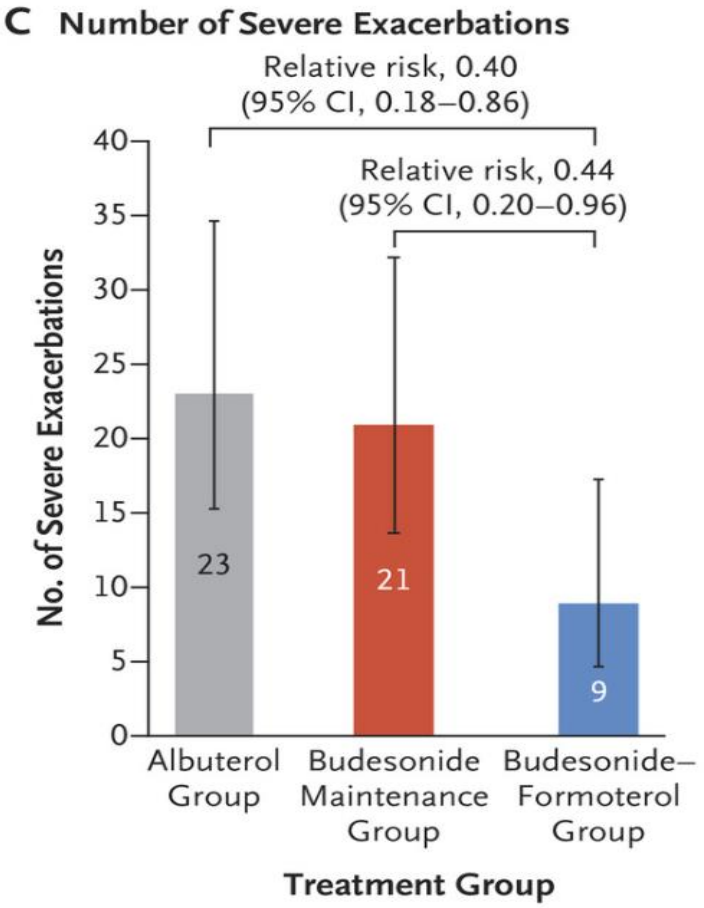
**SYGMA 1**

**Figure S4. Annualized Exacerbation Rate**




BUD/FORM, budesonide/formoterol; CI, confidence interval; RR, rate ratio.

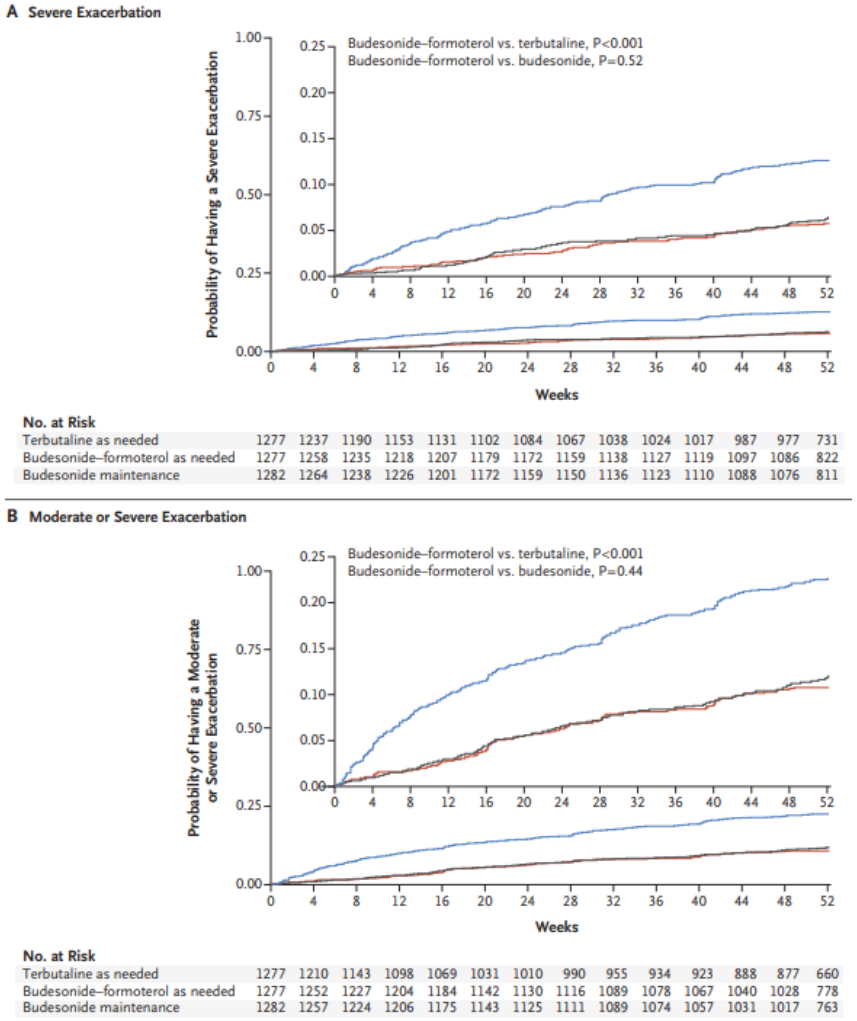
**Novel START Study**



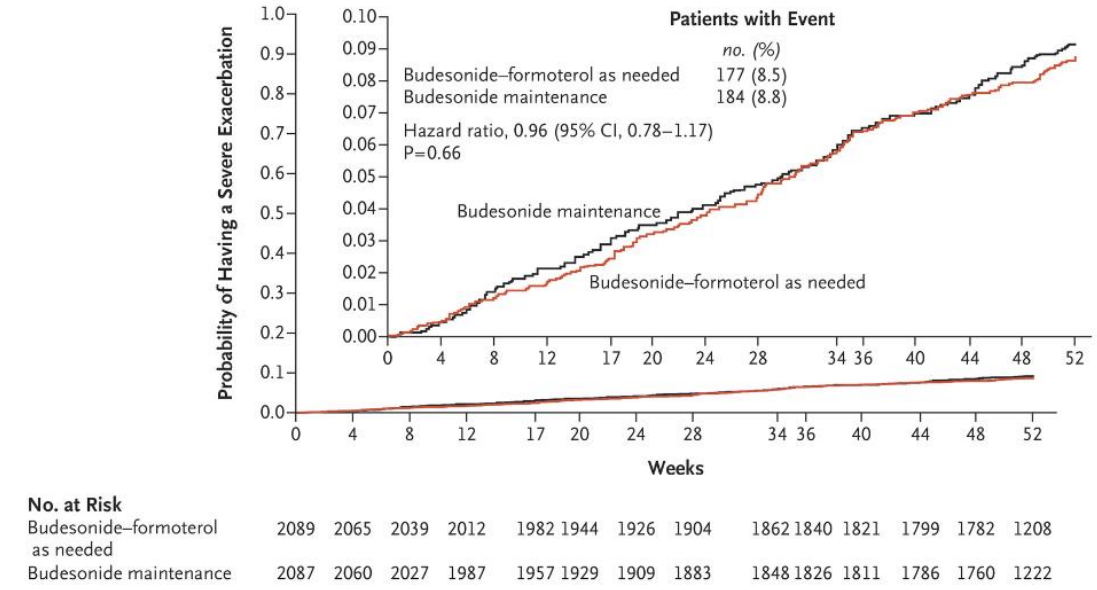

*N Engl J Med 2018;378:1865-76*
*N Engl J Med 2019;380:2020-30*

# Step 2: low-dose combination ICS-formoterol, taken as needed for relief of symptoms, and, if needed, before exercise (Track 1)

## SYGMA 1



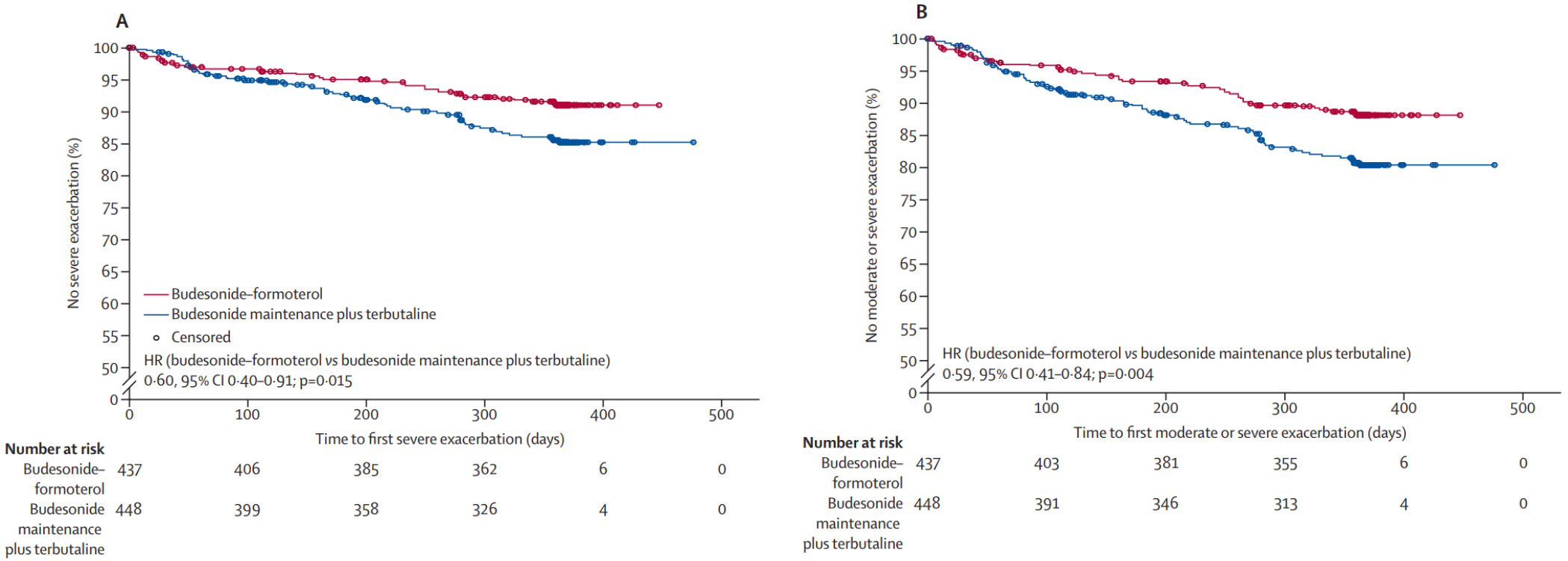

## SYGMA 2




*N Engl J Med 2018;378:1865-76*
*N Engl J Med 2018;378:1877-87*

# Step 2: low-dose combination ICS-formoterol, taken as needed for relief of symptoms, and, if needed, before exercise (Track 1)

**PRACTICAL: a 52-week, open-label, multicentre, superiority, randomised controlled trial**




(A) time to first severe exacerbation and (B) time to first moderate or severe exacerbation.

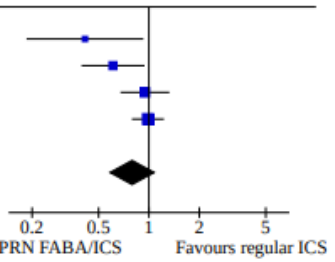
*Lancet. 2019 Sep 14;394(10202):919-928*

# Step 2: low-dose combination ICS-formoterol, taken as needed for relief of symptoms, and, if needed, before exercise (Track 1)

**Analysis 2.1. Comparison 2: Fixed dose combination inhaler as required versus regular inhaled steroid plus as required short acting beta agonist, Outcome 1: Number of exacerbations requiring systemic steroid**

| Study or Subgroup | PRN FABA/ICS Events | PRN FABA/ICS Total | Regular ICS Events | Regular ICS Total | Weight | Odds Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Novel START | 9 | 220 | 21 | 225 | 10.8% | 0.41 [0.19 , 0.93] |
| PRACTICAL | 37 | 437 | 59 | 448 | 23.5% | 0.61 [0.40 , 0.94] |
| SYGMA 1 | 70 | 1277 | 74 | 1282 | 29.1% | 0.95 [0.68 , 1.33] |
| SYGMA 2 | 171 | 2089 | 173 | 2087 | 36.7% | 0.99 [0.79 , 1.23] |
| **Total (95% CI)** | | **4023** | | **4042** | **100.0%** | **0.79 [0.59 , 1.07]** |
| Total events: | 287 | | 327 | | | |

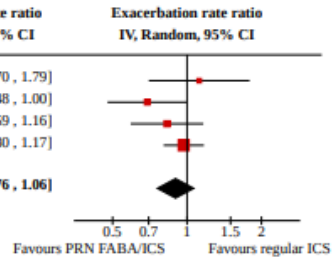
Heterogeneity: Tau² = 0.05; Chi² = 7.32, df = 3 (P = 0.06); I² = 59%
Test for overall effect: Z = 1.51 (P = 0.13)
Test for subgroup differences: Not applicable




**Analysis 2.2. Comparison 2: Fixed dose combination inhaler as required versus regular inhaled steroid plus as required short acting beta agonist, Outcome 2: Annual severe exacerbation rate**

| Study or Subgroup | log[Exacerbation rate ratio] | SE | PRN FABA/ICS Total | Regular ICS Total | Weight | Exacerbation rate ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Novel START | 0.113329 | 0.239517 | 220 | 225 | 11.7% | 1.12 [0.70 , 1.79] |
| PRACTICAL | -0.371064 | 0.188492 | 437 | 448 | 17.8% | 0.69 [0.48 , 1.00] |
| SYGMA 1 | -0.18633 | 0.172466 | 1277 | 1282 | 20.8% | 0.83 [0.59 , 1.16] |
| SYGMA 2 | -0.030459 | 0.095591 | 2089 | 2087 | 49.7% | 0.97 [0.80 , 1.17] |
| **Total (95% CI)** | | | **4023** | **4042** | **100.0%** | **0.90 [0.76 , 1.06]** |

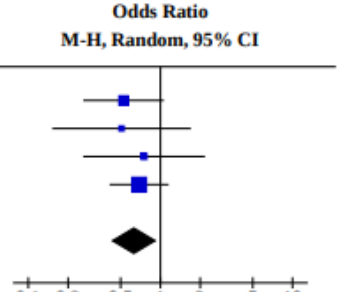
Heterogeneity: Tau² = 0.01; Chi² = 3.64, df = 3 (P = 0.30); I² = 18%
Test for overall effect: Z = 1.25 (P = 0.21)
Test for subgroup differences: Not applicable




**Analysis 2.3. Comparison 2: Fixed dose combination inhaler as required versus regular inhaled steroid plus as required short acting beta agonist, Outcome 3: Exacerbations requiring hospital admission or emergency department / urgent care visit**

| Study or Subgroup | PRN FABA/ICS Events | PRN FABA/ICS Total | Regular ICS Events | Regular ICS Total | Weight | Odds Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Novel START | 13 | 220 | 24 | 225 | 27.4% | 0.53 [0.26 , 1.06] |
| PRACTICAL | 4 | 437 | 8 | 448 | 9.3% | 0.51 [0.15 , 1.70] |
| SYGMA 1 | 6 | 1277 | 8 | 1282 | 12.0% | 0.75 [0.26 , 2.17] |
| SYGMA 2 | 25 | 2089 | 36 | 2087 | 51.3% | 0.69 [0.41 , 1.15] |
| **Total (95% CI)** | | **4023** | | **4042** | **100.0%** | **0.63 [0.44 , 0.91]** |
| Total events: | 48 | | 76 | | | |

Heterogeneity: Tau² = 0.00; Chi² = 0.60, df = 3 (P = 0.90); I² = 0%
Test for overall effect: Z = 2.47 (P = 0.01)
Test for subgroup differences: Not applicable




*Cochrane Database Syst Rev. 2021 May 4;5(5):CD013518*

# Step 2: low-dose combination ICS-formoterol, taken as needed for relief of symptoms, and, if needed, before exercise (Track 1)

**post-hoc analysis of the SYGMA 1 study**

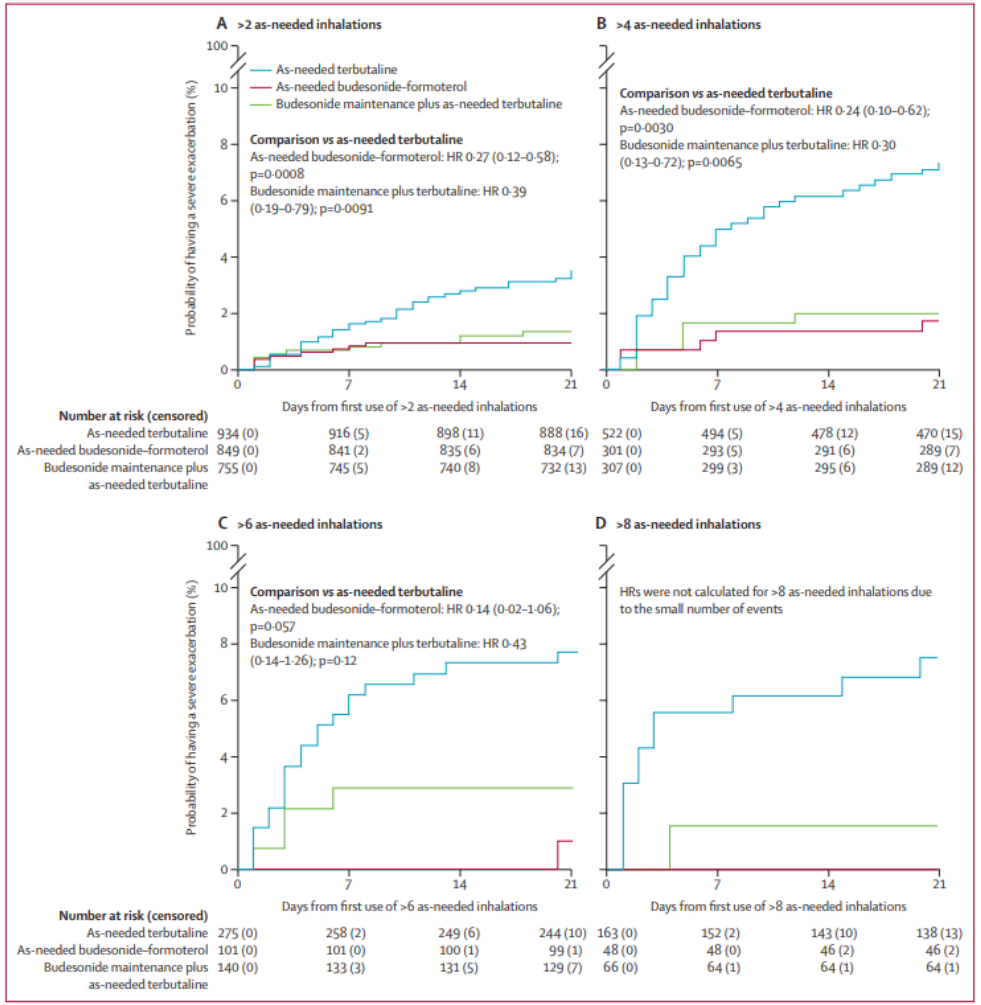



*Figure 3:* **Probability of a severe exacerbation during the 21 days after the first day with more than two (A), more than four (B), more than six (C), and more than eight (D) as-needed inhalations**

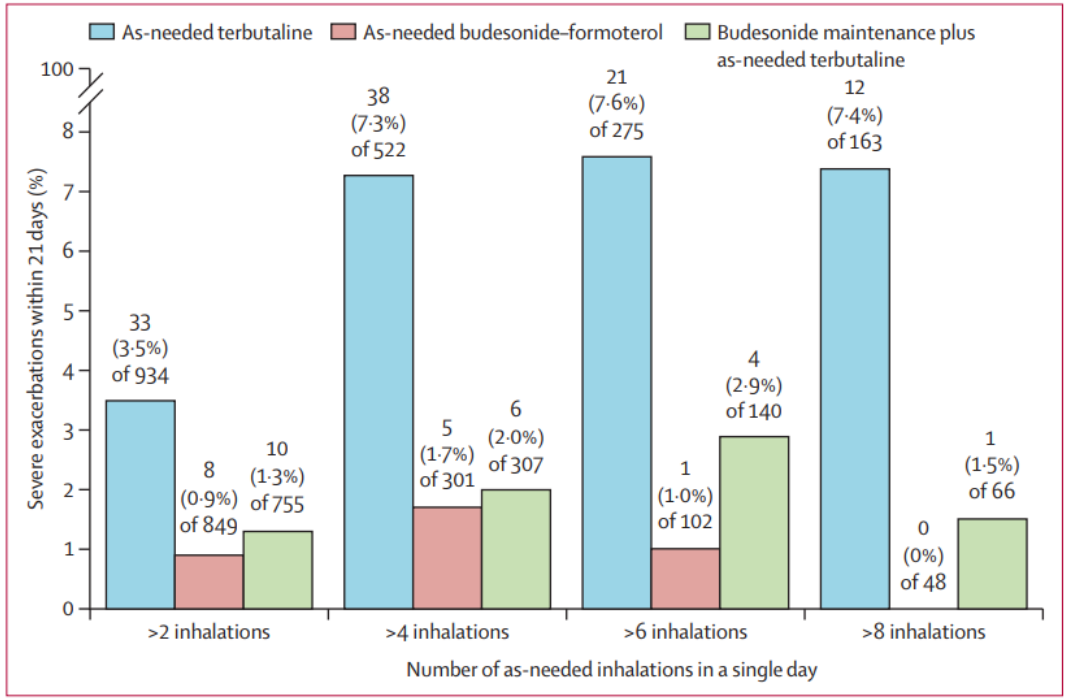



*Figure 2:* **Proportion of patients with a severe exacerbation within 21 days after the first day with more than two, four, six, or eight as-needed inhalations**

This study suggest that timing of use of ICS-formoterol is important.

*Lancet Respir Med. 2021 Feb;9(2):149-158*

# Step 3: low-dose ICS-formoterol maintenance and reliever therapy (Track 1)

- For adults and adolescents, the ‘preferred’ Step 3 option is low- dose ICS-formoterol as both maintenance and reliever treatment (MART).
- In this regimen, low-dose ICS-formoterol, either budesonide-formoterol or beclomethasone-formoterol, is used as both the daily maintenance treatment and as an anti-inflammatory reliever for symptom relief.

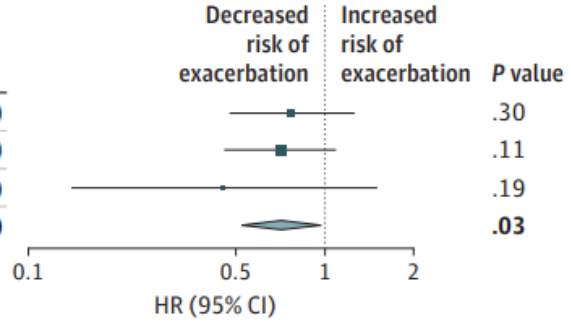
*JAMA Netw Open. 2022 Mar 1;5(3):e220615*

# Step 3: ICS-formoterol maintenance and reliever therapy (Track 1)

**Figure 2. Meta-analysis of the Association of Single Inhaler Maintenance and Reliever Therapy (SMART) vs Inhaled Corticosteroid–Long-acting $\beta_2$-Agonist (ICS-LABA) Maintenance Plus Short-acting $\beta_2$-Agonist (SABA) Reliever With Time to First Severe Exacerbation**

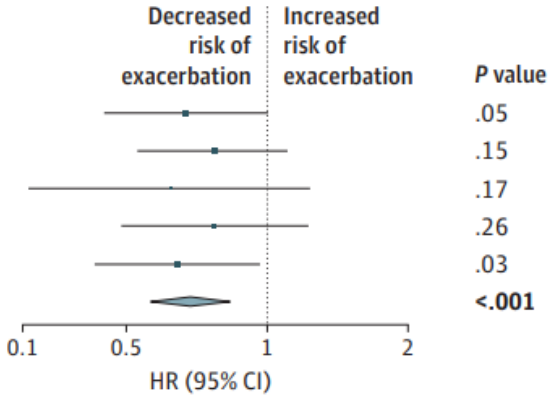
A SMART vs step up to GINA step 4

| Trial | No. exacerbation, No./total No. (%) SMART | GINA step 4 | HR (95% CI) | *P* value |
|---|---|---|---|---|
| AHEAD[10] | 29/371 (7.8) | 38/373 (10.2) | 0.77 (0.48-1.25) | .30 |
| COMPASS[8] | 29/372 (7.8) | 84/774 (10.9) | 0.71 (0.46-1.08) | .11 |
| Patel et al,[9] | 5/38 (13.2) | 6/22 (27.3) | 0.45 (0.14-1.49) | .19 |
| **Total** | **63/781 (8.1)** | **128/1169 (10.9)** | **0.71 (0.52-0.97)** | **.03** |




B SMART vs same GINA step 3 or 4

| Trial | No. exacerbation, No./total No. (%) SMART | GINA step 3 or 4 | HR (95% CI) | *P* value |
|---|---|---|---|---|
| AHEAD[10] | 40/327 (12.2) | 61/348 (17.5) | 0.67 (0.45-1.00) | .05 |
| COMPASS[8] | 41/333 (12.3) | 108/681 (15.9) | 0.77 (0.53-1.10) | .15 |
| Patel et al,[9] | 13/46 (28.3) | 21/48 (43.8) | 0.62 (0.31-1.23) | .17 |
| SAKURA[12] | 35/251 (13.9) | 38/215 (17.7) | 0.77 (0.49-1.22) | .26 |
| SMILE[11] | 42/339 (12.4) | 58/325 (17.8) | 0.64 (0.43-0.96) | .03 |
| **Total** | **171/1296 (13.2)** | **286/1617 (17.7)** | **0.70 (0.58-0.85)** | **<.001** |




*JAMA Netw Open. 2022 Mar 1;5(3):e220615*

# Step 4: medium-dose ICS-formoterol maintenance and reliever therapy (Track 1)

- For adult and adolescent patients, combination ICS-formoterol as both maintenance and reliever treatment (MART) is more effective in reducing exacerbations than the same dose of maintenance ICS-LABA or higher doses of ICS.

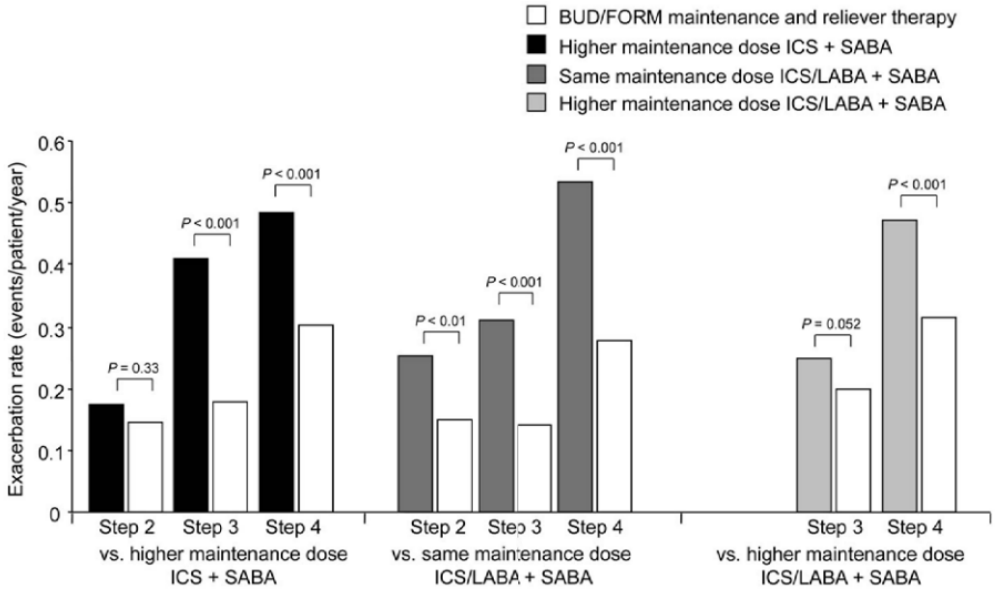


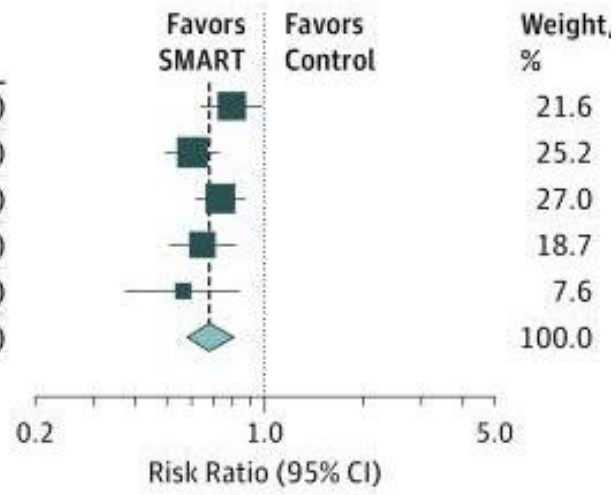

**Figure 3 Exacerbation rate by study treatment and GINA treatment step at study entry.**

*Respir Res. 2011 Apr 4;12(1):38*

# Step 4: medium-dose ICS-formoterol maintenance and reliever therapy (Track 1)

| Source | SMART Group | | Control Group | | Absolute Risk Difference (95% CI), % | Risk Ratio (95% CI) |
|---|---|---|---|---|---|---|
| | Total No. of Participants | No. With Event | Total No. of Participants | No. With Event | | |
| Vogelmeier et al,[23] 2012 | 1067 | 132 | 1076 | 167 | -3.1 (-6.1 to -0.2) | 0.80 (0.64 to 0.99) |
| Rabe et al,[25] 2006 | 1107 | 143 | 1138 | 245 | -8.6 (-11.7 to -5.5) | 0.60 (0.50 to 0.72) |
| Atienza et al,[24] 2013 | 1049 | 170 | 1042 | 229 | -5.8 (-9.1 to -2.4) | 0.74 (0.62 to 0.88) |
| Papi et al,[26] 2013 | 852 | 99 | 849 | 152 | -6.3 (-9.6 to -2.9) | 0.65 (0.51 to 0.82) |
| Patel et al,[27] 2013 | 151 | 28 | 152 | 50 | -14.4 (-24.1 to -4.6) | 0.56 (0.38 to 0.84) |
| Overall (random-effects model) | 4226 | 572 | 4257 | 843 | -6.4 (-10.2 to -2.6) | 0.68 (0.58 to 0.80) |

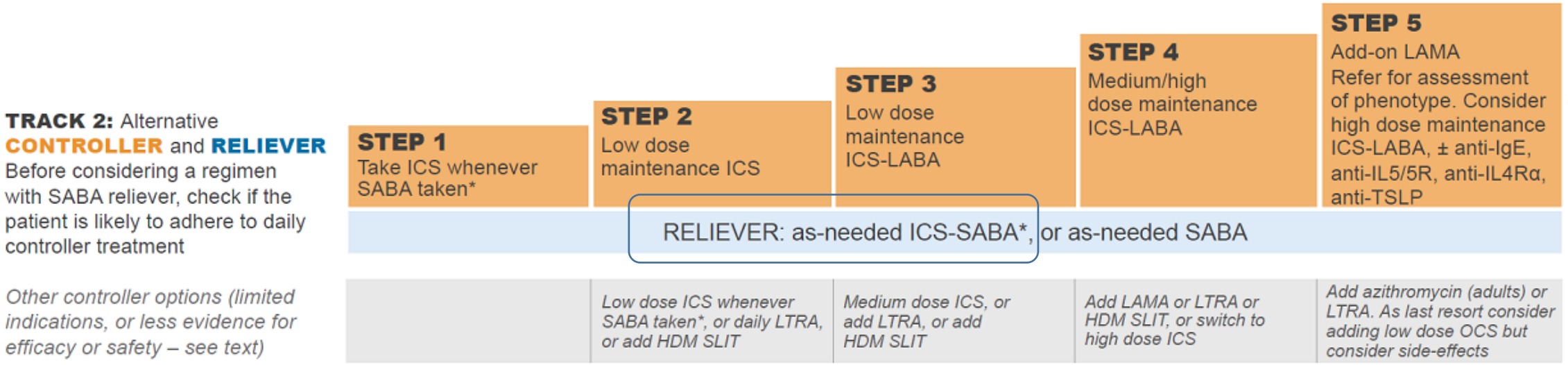
Heterogeneity: $I^2 = 29\%$, $P = .23$
Test for overall effect: $t_4 = -6.44$, $P < .001$




Association of SMART With Exacerbations Requiring Systemic Corticosteroids, Hospitalization, or ED Visits Among Patients Aged 12 Years or Older vs the Same Dose of Inhaled Corticosteroids and LABA Controller Therapy

*JAMA. 2018 Apr 10;319(14):1485-1496*

# Step 3-5:  maintenance ICS-LABA plus as-needed SABA or plus as-needed combination ICS-SABA (Track 2)
# : Maintenance ICS-LABA plus as-needed combination ICS-SABA

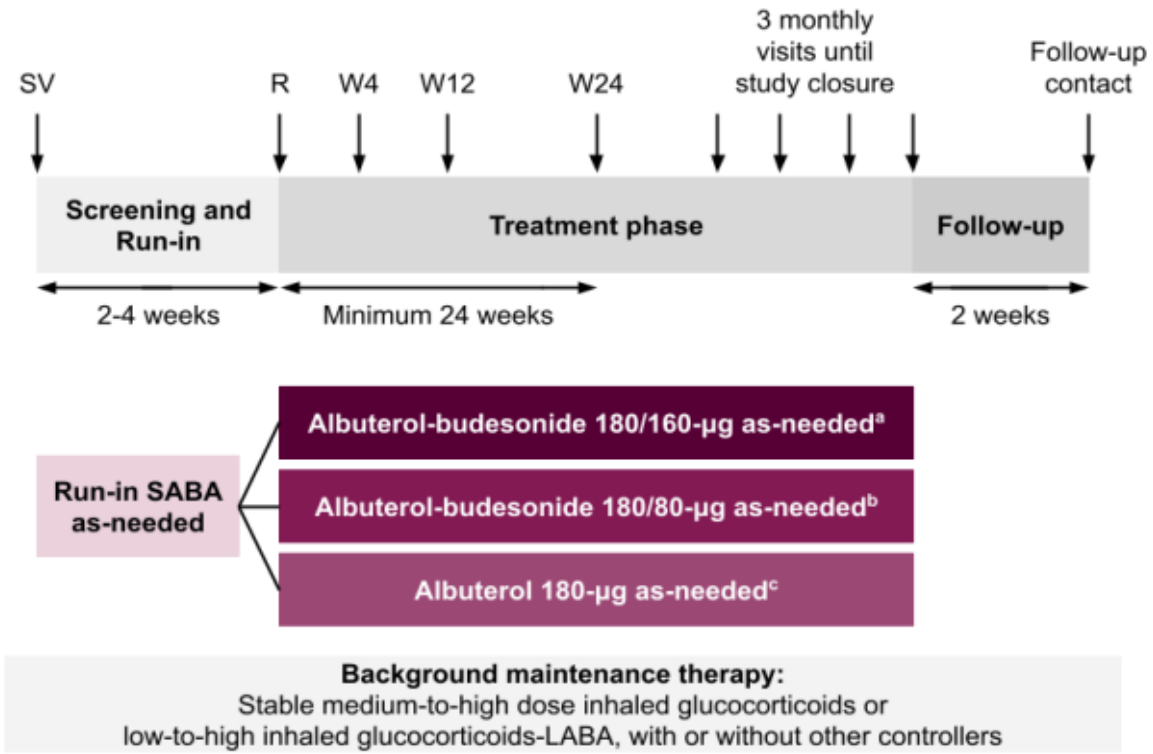


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 2, 2022 VOL. 386 NO. 22

# Albuterol–Budesonide Fixed-Dose Combination Rescue Inhaler for Asthma


Multinational, phase 3, double-blind, randomized, parallel-group, event-driven trial with a minimum duration of 24 weeks




Primary efficacy end point

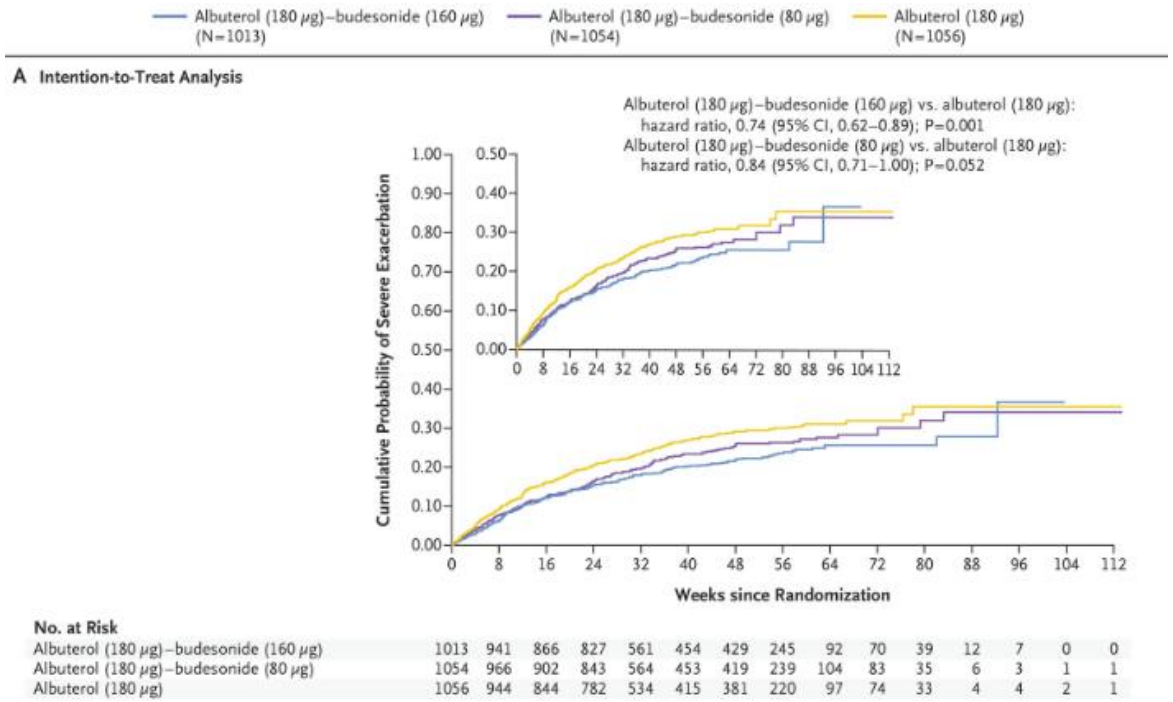
- First event of severe asthma exacerbation in a time-to-event analysis

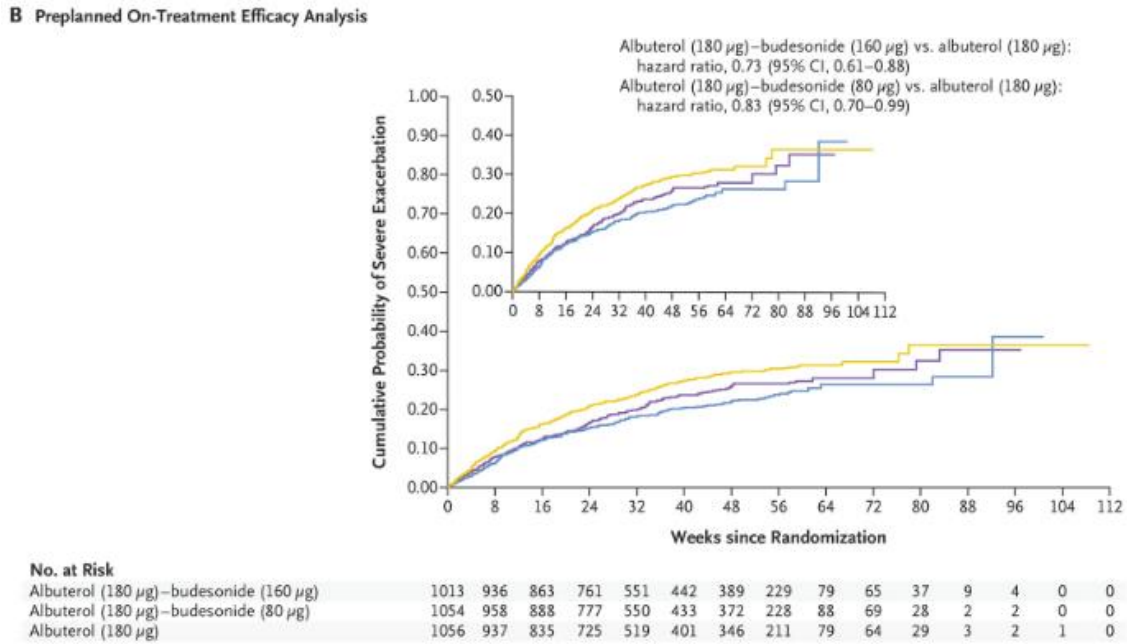
Secondary efficacy end points:

- Annualized rate of severe asthma exacerbations
- Total systemic glucocorticoid exposure for asthma during the treatment period
- “Response” at week 24 on the ACQ-5 (validated for persons ≥6 years of age)
- Asthma Quality of Life Questionnaire
- Pediatric Asthma Quality of Life Questionnaire

*N Engl J Med. 2022 Jun 2;386(22):2071-2083*

# Primary end point



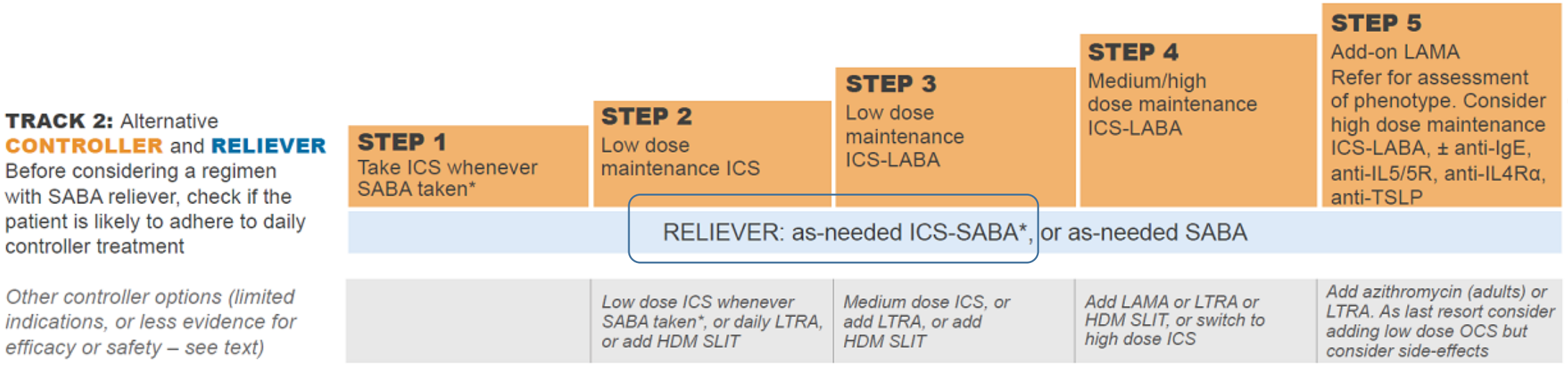




CONCLUSIONS

The risk of severe asthma exacerbation was significantly lower with as-needed use of a fixed-dose combination of 180 µg of albuterol and 160 µg of budesonide than with as-needed use of albuterol alone among patients with uncontrolled moderate-to-severe asthma who were receiving a wide range of inhaled glucocorticoid-containing maintenance therapies.

*N Engl J Med. 2022 Jun 2;386(22):2071-2083*

# Step 3-5: maintenance ICS-LABA plus as-needed SABA or plus as-needed combination ICS-SABA (Track 2)
# : Maintenance ICS-LABA plus as-needed combination ICS-SABA




Despite the addition of ICS-SABA reliever in Track 2, GINA track 1 with as-needed ICS-formoterol remains the preferred treatment approach for adults and adolescents.

# Why is GINA Track 1 with ICS-formoterol preferred?

- **Steps 1–2**: weight of evidence for effectiveness and safety compared with SABA alone, or low-dose ICS plus as-needed SABA (4x12 month studies, n~10,000) *(Crossingham et al, Cochrane 2021)*
  - As-needed ICS-SABA: only one 6-month RCT (n=455) *(Papi et al, NEJMed 2007)*
- **Steps 3–5**: weight of evidence for effectiveness and safety of MART versus regimens with as-needed SABA (n~30,000) *(Sobieraj et al, JAMA 2018; Cates et al, Cochrane 2013)*
  - As-needed ICS-SABA: only one RCT (n=3,132) vs as-needed SABA *(Papi et al, NEJMed 2022);* cannot be used for maintenance and reliever therapy
- Both the ICS and the formoterol contribute to reduction in severe exacerbations *(Tattersfield et al, Lancet 2001; Pauwels et al, ERJ 2003; Rabe et al, Lancet 2006)*
  - Safety established up to total 12 inhalations in any day, in large studies
- **Simplicity of approach** for patients and clinicians
  - A single medication for both symptom relief and maintenance treatment (if needed) from diagnosis
  - Avoids confusion about inhaler technique with different devices
  - Short-term increase in symptoms → patient increases the number of **as-needed** doses
  - Step treatment down or up by changing the number of maintenance doses

| Step | Age (years) | Medication and device (check patient can use inhaler) | Metered dose (mcg/inhalation) | Delivered dose (mcg/inhalation) | Dosage |
|---|---|---|---|---|---|
| **Steps 1–2 (AIR-only)** | 6–11 | (No evidence) | - | - | - |
| | 12–17<br>≥18 | Budesonide-formoterol DPI | 200/6 | 160/4.5 | **1 inhalation whenever needed** |
| **Step 3 MART** | 6–11 | Budesonide-formoterol DPI | 100/6 | 80/4.5 | **1 inhalation once daily**,<br>PLUS 1 inhalation whenever needed |
| | 12–17<br>≥18 | Budesonide-formoterol DPI | 200/6 | 160/4.5 | **1 inhalation once or twice daily,**<br>PLUS 1 inhalation whenever needed |
| | ≥18 | BDP-formoterol pMDI | 100/6 | 84.6/5.0 | |
| **Step 4 MART** | 6–11 | Budesonide-formoterol DPI | 100/6 | 80/4.5 | **1 inhalation twice daily**,<br>PLUS 1 inhalation whenever needed |
| | 12–17<br>≥18 | Budesonide-formoterol DPI | 200/6 | 160/4.5 | **2 inhalations twice daily**,<br>PLUS 1 inhalation whenever needed |
| | ≥18 | BDP-formoterol pMDI | 100/6 | 84.6/5.0 | |
| **Step 5 MART** | 6–11 | (No evidence) | - | - | - |
| | 12–17<br>≥18 | Budesonide-formoterol DPI | 200/6 | 160/4.5 | **2 inhalations twice daily**,<br>PLUS 1 inhalation whenever needed |
| | ≥18 | BDP-formoterol pMDI | 100/6 | 84.6/5.0 | |

*DPI: dry powder inhaler; pMDI: pressurized metered dose inhaler. For budesonide-formoterol pMDI with 3 mcg [2.25 mcg] formoterol, use double number of puffs*

# Asthma action plan

Special Article

## A Practical Guide to Implementing SMART in Asthma Management

Helen K. Reddel, MB, BS, PhD[a,*], Eric D. Bateman, MB, ChB, MD[b,*], Michael Schatz, MD, MS[c], Jerry A. Krishnan, MD, PhD[d], and Michelle M. Cloutier, MD[e] *Sydney, Australia; Cape Town, South Africa; San Diego, Calif; Chicago, Ill; and Farmington, Conn*

**TABLE I.** Recommended doses of budesonide-formoterol for single maintenance and reliever therapy (SMART) based on published studies and international use

| | | Step 3 | | Step 4 | | Step 3 or 4 |
|---|---|---|---|---|---|---|
| Age group | Budesonide-formoterol dose | Maintenance dose | As-needed dose | Maintenance dose | As-needed dose | Maximum total daily inhalations* |
| Adults and adolescents aged ≥12 y | 160/4.5 µg delivered dose (200/6 µg metered dose) | One inhalation twice daily or once daily | One inhalation as needed | Two inhalations twice daily | One inhalation as needed | 12 |
| Children 4-11 years† | 80/4.5 µg delivered dose (100/6 µg metered dose) | One inhalation once daily‡ | One inhalation as needed | One inhalation twice daily§ | One inhalation as needed | 8 |

*J Allergy Clin Immunol Pract. 2022 Jan;10(1S):S31-S38*

# Conclusion

- Anti-inflammatory reliever (AIR)
  - Reliever inhaler that contains both a low-dose ICS and a rapid-acting bronchodilator
  - Track 1
    - Step 1-2: AIR-only
    - Step 3-5: MART
  - Track 2
    - Step 3-5: as needed ICS-SABA